Essential Information

Indication: 1. Treatment of hepatocellular carcinoma. 2. Treatment of patients with advanced renal cell carcinoma who have failed prior interferonalpha or interleukin-2-based therapy or are considered poor candidates for chemotherapy. 3. Treatment of patients with advanced renal cell carcinoma who are poor candidates for chemotherapy. 4. Treatment of patients with advanced renal cell carcinoma who have failed prior interferonalpha or interleukin-2-based therapy or are considered poor candidates for chemotherapy.

Contraindications: previous sensitivity to sorafenib or to any of the following: warfarin, methotrexate, and interferon. Severe hypocalcaemia, severe liver disease, pregnancy, and breastfeeding.

Warnings and Precautions: 1. Do not adjust dose. 2. Use with caution in patients with a history of autoimmune disease, such as rheumatoid arthritis or lupus erythematosus. 3. Use with caution in patients with a history of cancer.

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Dear ILCA members, colleagues and friends,

This year’s meeting is very special as it marks the 10th Anniversary of ILCA. It has been 10 years that ILCA has been striving to advance research in the pathogenesis, prevention, and treatment of liver cancer.

This year again ILCA offers a programme with a multidisciplinary and transversal approach, with the objective to encourage and stimulate scientific debate and networking between liver cancer experts from all regions.

Distinguished international speakers from all related disciplines will enrich the scientific programme of ILCA 2016 featuring:

- **State-of-the-Art Lectures** delivered by renowned colleagues within the field
- **Symposia** focusing on cutting-edge advancements on research and treatments
- **General Sessions** and e-Poster Viewing Tours that will deliver the latest breaking research from among the abstracts submitted to the conference
- **Luncheon Workshops** offered by the most knowledgeable HCC experts in highly interactive sessions
- **Pre-Conference Workshop** on Pre-Clinical Models of HCC: From Target Identification to Clinical Trials

ILCA 2016 will also provide you with numerous opportunities to network and connect with colleagues and industry partners from all over the world during networking breaks, lunches and the welcome reception.

We are excited to welcome you in Vancouver for the 10th Annual Conference and hope you will enjoy many opportunities for learning, sharing, networking and advancing liver cancer science and care with us.

On behalf of the ILCA Governing Board

Richard Finn, MD
ILCA President

Jessica Zucman-Rossi, MD, PhD
ILCA Executive Secretary
### ILCA Pre-Conference Workshop on Pre-clinical Models of HCC: From Target Identification to Clinical Trials

**Chairs:** Xin-Wei Wang, PhD (USA), Jessica Zucman-Rossi, MD, PhD (France) and Eli Pikarsky, MD, PhD (Israel)

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<tr>
<th>Time</th>
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| 13:10 – 15:30 | • The Importance and Relevance of Pre-Clinical Models for Human HCC  
Xin-Wei Wang, PhD (USA)  
• Somatic Gene Mutations in Human HCC as Therapeutic Targets  
Jessica Zucman-Rossi, MD, PhD (France)  
• Mouse Models of Inflammation Induced HCC  
Eli Pikarsky, MD, PhD (Israel)  
• Identification of Novel Targets to Treat NASH and its Transition to HCC  
Mathias Heikenwälder, MD, PhD (Germany)  
• WNT/Beta-Catenin Activation in Mice Models  
Sabine Colnot, PhD (France)  
• Bridging the Gap between Emerging Biology and Drug Discovery to Enable Precision Medicine in HCC  
Klaus Hoeflich, PhD (USA) |
| 15:30 – 16:00 | Coffee & Networking Break |
| 16:00 - 18:50 | • Paradoxical Differences in Animal Models of Hepatocarcinogenesis  
Gen-Sheng Feng, PhD (USA)  
• Functional Target Discovery and Academic Drug Discovery in Hepatocellular Carcinoma  
Lars Zender, MD, PhD (Germany)  
• Xenografted Tumours: Mice as Human Avatar?  
Supriya Saha, MD (USA)  
• Which Model for Immune Therapy?  
Tim Greten, MD (USA)  
• In Cellulo Approaches to Test Drug Sensitivity  
Richard Finn, MD (USA) |
| 18:50 | Round Table Discussion  
Josep M. Llovet, MD (Spain/USA) and Valérie Paradis, MD, PhD (France) |
### Friday, 9 September 2016

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<tr>
<td>08:00 – 09:30</td>
<td><strong>ILCA Symposium 1: New Targets in Hepatocellular Carcinoma</strong></td>
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<td>Chairs: Richard Finn, MD (USA) and Peter R. Galle, MD, PhD (Germany)</td>
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<tr>
<td></td>
<td>• SIRT6 – An Epigenetic Player in Liver Differentiation and Cancer</td>
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<td></td>
<td>Peter R. Galle, MD, PhD (Germany)</td>
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<tr>
<td></td>
<td>• Beta-Catenin Mutations in HCC: Biological and Therapeutic Implications</td>
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<tr>
<td></td>
<td>Satdarshan (Paul) S. Monga, MD (USA)</td>
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<tr>
<td></td>
<td>• Hepatocellular Carcinoma – Liver Cancer Stem Cells</td>
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<tr>
<td></td>
<td>Irene Ng, MD, PhD (Hong Kong)</td>
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<tr>
<td></td>
<td>• Therapeutic Targeting of IGF2 in Liver Cancer</td>
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<td>Daniela Sia, PhD (Italy)</td>
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<tr>
<td>09:30 – 10:30</td>
<td><strong>State-of-the-Art Lecture 1: Immunology and Immunotherapy of Hepatocellular Carcinoma</strong></td>
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<td>Chair: Andrew X. Zhu, MD, PhD (USA)</td>
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<td>Speaker: Tim Greten, MD (USA)</td>
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<td>10:30 – 11:00</td>
<td>Coffee &amp; Networking Break</td>
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<td>11:00 – 11:15</td>
<td><strong>Welcome Address</strong></td>
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<td>Richard Finn, MD (USA), Jessica Zucman-Rossi, MD, PhD (France), Morris Sherman, MD, PhD (Canada) and Peter R. Galle, MD, PhD (Germany)</td>
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<td>11:15 – 12:45</td>
<td><strong>General Session 1: Molecular Pathogenesis</strong></td>
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<td>Chairs: Irene Ng, MD, PhD (Hong Kong) and Augusto Villanueva, MD, PhD (USA)</td>
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<td>12:45 – 13:00</td>
<td>Session Break</td>
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<td>13:00 – 14:30</td>
<td><strong>Bayer Lunch Symposium</strong></td>
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<td>14:30 – 14:45</td>
<td>Session Break</td>
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<td>14:45 – 16:15</td>
<td><strong>General Session 2: Molecular Pathology</strong></td>
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<td>Chairs: Jessica Zucman-Rossi, MD, PhD (France) and Valérie Paradis, MD, PhD (France)</td>
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<td>16:15 – 16:45</td>
<td>Coffee &amp; Networking Break</td>
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<td>16:45 – 18:15</td>
<td><strong>ILCA Symposium 2: Controversies in Liver Cancer (Pros and Cons Session)</strong></td>
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<td>Chairs: Masatoshi Kudo, MD, PhD (Japan) and Kwang-Hyub Han, MD (Republic of Korea)</td>
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<tr>
<td></td>
<td>• Y90 vs. TACE</td>
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<td>Bruno Sangro, MD, PhD (Spain) vs. Valérie Vilgrain, PhD (France)</td>
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<td>• What to Expect after Sorafenib?</td>
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<td>Ann-Lii Cheng, MD, PhD (Taiwan) vs. Jordi Bruix, MD, PhD (Spain)</td>
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<td>• Transplant beyond Milan</td>
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<td>Gonzalo Sapisochin, MD (Canada) vs. Francis Yao, MD (USA)</td>
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<td>• Assessment of Tumour Response after Treatment</td>
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<td>Richard Kinh Gian Do, MD, PhD (USA) vs. Haesun Choi, MD (USA)</td>
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# Programme at a Glance

## Saturday, 10 September 2016

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<td>08:30 – 10:00</td>
<td>General Session 3: Epidemiology and Diagnosis</td>
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<td>Chairs: Morris Sherman, MD, PhD (Canada) and Sheng-Long Ye, MD, PhD (P.R. China)</td>
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<tr>
<td>10:00 – 11:00</td>
<td>e-Poster Viewing Tour &amp; Networking Break</td>
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<td>11:00 – 12:30</td>
<td>Plenary Session</td>
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<td>Chairs: Richard Finn, MD (USA), Jessica Zucman-Rossi, MD, PhD (France), Morris Sherman, MD, PhD (Canada) and Peter Galle, MD, PhD (Germany)</td>
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<td>12:45 – 14:00</td>
<td>ILCA Special Interest Groups (SIGs) Luncheon Workshops</td>
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<td>SIG 1: Molecular Classification and Signalling Pathways</td>
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<td><em>Single Cell Genome in Liver Cancer</em></td>
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<td>Chairs: Xin Wei Wang, PhD (USA) and Keji Zhao, PhD (USA)</td>
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<td>SIG 2: Surveillance, Biomarkers and Molecular Pathology</td>
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<td></td>
<td><em>Biomarkers: A Review of the Present and a Glimpse of the Future</em></td>
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<td>Chair: Neehar Parikh, MD (USA)</td>
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<td>SIG 3: Imaging and Locoregional Therapies</td>
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<td><em>Methods of Response Assessment: Comparing Systemic and Locoregional Therapies</em></td>
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<td>Chairs: Riad Salem, MD (USA) and Bruno Sangro, MD, PhD (Spain)</td>
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<td>SIG 4: Target and Systemic Therapies</td>
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<td><em>Emerging Systemic Therapies on Advanced Hepatocellular Carcinoma</em></td>
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<td>Chairs: Joong-Won Park, MD, PhD (Republic of Korea) and Tim Meyer, MD, PhD (United Kingdom)</td>
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<td>SIG 5: Liver Surgery and Transplantation</td>
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<td><em>Liver Transplantation vs. Resection for Hepatocellular Carcinoma</em></td>
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<td>Chair: Katsuhiro Yanaga, MD, PhD (Japan)</td>
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<td>SIG 6: Non-HCC Hepatic Malignancies</td>
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<td><em>An Update on Risk Factors for Cholangiocarcinoma</em></td>
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<td>Chairs: Shahid A. Khan, MD, PhD (United Kingdom) and Lewis R. Roberts, PhD (USA)</td>
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<td>14:00 – 14:15</td>
<td>Session Break</td>
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<td>14:15 – 15:45</td>
<td>General Session 4: Staging and Curative Treatments</td>
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<td>Chairs: Bruno Sangro, MD, PhD (Spain) and Myron Schwartz, MD (USA)</td>
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<td>15:45 – 16:45</td>
<td>e-Poster Viewing Tour &amp; Networking Break</td>
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<td>16:45 – 18:15</td>
<td>ILCA Symposium 3: What is New in Adenoma?</td>
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<td>Chair: Peter Schirmacher, MD, PhD (Germany)</td>
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<td></td>
<td>• Molecular Classification of Hepatocellular Adenomas in Clinical Practice</td>
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<td>Jean-Charles Nault, MD (France)</td>
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<td>• What is New in Hepatocellular Adenoma Morphological Types?</td>
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<td>Valérie Paradis, MD, PhD (France)</td>
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<td>• Surgery, Resection or Ablation for Small Adenoma</td>
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<td>Thomas van Gulik, MD, PhD (Netherlands)</td>
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<td>• Imaging/Phenotype Correlations</td>
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<td>Alexander Kagen, MD (USA)</td>
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### Programme at a Glance

#### Sunday, 11 September 2016

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<td>07:30 – 08:30</td>
<td><strong>Bristol-Myers Squibb Symposium</strong></td>
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<tr>
<td>08:30 – 09:15</td>
<td><strong>ILCA General Assembly</strong></td>
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<td>09:15 – 09:45</td>
<td>Coffee &amp; Networking Break</td>
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| 09:45 – 10:45      | **State-of-the-Art Lecture 2: Assessing Hepatocellular Carcinoma Risk**  
Chair: Josep M. Llovet, MD (Spain/USA)  
Speaker: Morris Sherman, MD, PhD (Canada) |
| 10:45 – 12:15      | **General Session 5: From New Targets to Clinical Trials**  
Chairs: Sandrine Faivre, MD, PhD (France) and Thomas Yau, MD (USA) |
| 12:15 – 12:30      | **Closing Ceremony**                      |

ILCA is not responsible for topics and speakers selection of industry symposia, nor for the opinions and statements produced at the time of their celebration.
The International Liver Cancer Association Announces its 11th Annual Conference

ILCA 2017
15–17 September 2017
Seoul, South Korea

Conference Highlights:
State-of-the-Art Lectures
Cutting Edge Symposia
General Sessions
Interactive Luncheon Workshops
e-Poster Viewing Tours
Industry Exhibition
Networking Breaks and Reception

The international multidisciplinary forum for liver cancer experts around the latest innovations in research and care

Abstract submissions open in January 2017

www.ilca2017.org
HCC is associated with numerous etiologies such as HBV, HCV, alcohol, obesity, or chemical carcinogens. Consequently, different etiologies may elicit different molecular mechanisms on normal cells to induce HCC. As such, HCC is genomically heterogeneous and is highly resistant to therapy. Genomic analyses of HCC by whole genome sequencing reveal a complex mutational landscape with a vast inter-tumour heterogeneity and a different combination of cancer drivers in each tumour. Moreover, transcriptomic analyses also reveal that HCC consists of multiple molecular subtypes that differ in biology and microenvironment. The presence of considerable genomic alterations in tumour cells along with altered unique microenvironments constitutes a bottleneck to effectively rank and evaluate candidate drivers as druggable targets. It is well known that rodent models such as mice are powerful tools to study cancer biology since they are extremely sensitive to hepatocarcinogenesis. However, a previous seminal study suggested that some murine HCC may not mimic biology of human HCC (Lee JS et al, Nat Genet 36: 1306-11, 2004). A key question remains as to which models are most relevant to human HCC useful to facilitate bench-to-bedside research. It seems that precision models that incorporate both genomic changes in tumour cells and appropriate hepatic microenvironmental milieu are needed. These models will provide a rapid avenue for functional cancer genomics and pave the way for precision cancer medicine. This pre-conference workshop is a timely step for our liver cancer scientific community to gather together towards the development of a consensus view on this challenging question.

Hepatocellular carcinoma (HCC) is one of the leading causes of death by cancer worldwide. It is mainly developed on cirrhosis due to chronic hepatitis B and C, metabolic and alcoholic liver diseases in Western countries. Recent advances in molecular classification and dissection of genetic and epigenetic drivers have increased our knowledge of the molecular diversity of benign and malignant liver tumours. Using genomic approaches, we identified several new oncogenes and tumour suppressor genes. Recently, using sequencing, we identified TERT promoter mutations activating telomerase as the most important mechanism of malignant transformation of both adenoma in carcinoma and of cirrhotic nodules in carcinoma. We also found new etiological factors predisposing to liver tumour development with the finding of recurrent AAV2 insertions in cancer driver genes but also mutational signatures as the result of exposure to specific genotoxic agents. Finally, next generation sequencing was particularly fruitful to identify new drug targets in hepatocellular carcinoma and these finding open new avenues to develop genome based clinical trials.

The most prevalent risk factor for HCC development is chronic liver inflammation (hepatitis) mainly caused by viral infection, alcohol consumption and non-alcoholic fatty liver disease (NAFLD) and subsequent non-alcoholic steatohepatitis (NASH). Many labs, including our own, utilise and develop models of inflammation driven HCC to unravel the mechanisms linking hepatitis and HCC. Using such mouse models we deciphered several mechanisms through which inflammation mediates HCC aggressiveness including 1. Upregulation of antiapoptotic cytokines throughout the liver parenchyma depending on NF-κB; 2. Generation of an immunosuppressive tumour permissive microenvironment; 3. Identified genomic aberrations which mediate sensitivity to sorafenib in a subgroup of HCCs; and 4. Formation of Ectopic lymphoid-like structures (ELSs), a unique form of local adaptive immunity which paradoxically form microniches that support the growth of HCC progenitors. Focusing on the latter mechanism, we developed a new mouse model of ELS-induced
Identification of Novel Targets to Treat NASH and its Transition to HCC
Mathias Heikenwälder, MD, PhD (Germany)

Due to the consumption of high caloric food combined with an increased sedentary lifestyle, the incidence of overweight and obesity has grown rapidly in Western cultures, like the USA and Europe but notably also in developing countries (e.g. India, China). Although chronic viral infections with Hepatitis B or C are still the leading etiology causing hepatocellular carcinoma (HCC), it has become more and more clear that non-alcoholic fatty liver disease (NAFLD) and subsequent non-alcoholic steatohepatitis (NASH) are increasingly important etiologies for HCC development. Dietary etiology greatly contributes to the fact that HCC currently is the fastest rising cancer in the USA, with a similar trend in Europe. In the recent past, we and others have generated several pre-clinical mouse models that enabled to study the cellular and molecular mechanisms of NASH development and NASH to HCC transition in the context of a chronic metabolic syndrome. Remarkably, these models recapitulated several pathophysiological hallmarks of NASH on the basis of a metabolic syndrome in humans and develop HCC. Here, I will report on the characterisation and identification of novel targets that could be used to treat NASH and subsequent liver cancer development.

WNT/Beta-Catenin Activation in Mice Models
Sabine Colnot, PhD (France)

An aberrant activation of beta-catenin pathway has emerged in the past two decades as a key oncogenic signalling in the liver. Its modeling in transgenic mice has been widely done, targeting many partners of the signaling cascade, such as beta-catenin itself through activating or inactivating mutations, the Apc and Axin1 tumour suppressors, studied alone or associated with other mutational events.

I will report here what has been the contribution of these models to our knowledge about beta-catenin-dependent hepatocarcinogenesis. I will also present the technological tools we currently have to study this inescapable pathway in liver physiopathology.

Bridging the Gap between Emerging Biology and Drug Discovery to Enable Precision Medicine in HCC
Klaus Hoeflich, PhD (USA)

There are currently no molecularly defined diagnostics or therapeutics for hepatocellular carcinoma (HCC). However, recent genomic analyses have identified driver genes, and in parallel, we have extensively investigated the genomic underpinnings of key growth factor and lineage pathways that represent immediately actionable targets for therapeutic intervention (Cancer Discov 2015, Nature Commun 2014). Following from this work, novel targeted therapies with patient selection strategies are in development. For example, BLU-554 is a potent, selective and irreversible, small molecule inhibitor that selectively targets FGFR4 while sparing FGFR1-3 in FGF19-amplified HCC. BLU-554 induces tumour regression in preclinical models of HCC with activated FGF19/FGFR4 signaling.

In our FIH clinical trial, tumour / liquid biopsies and diagnostic assays to detect pathway activation have also
been implemented to translate our biomarker hypotheses into patient selection strategies. Another example of an immediately actionable target is DNAJB1-PRKACA kinase fusions that are very prevalent in fibrolamellar HCC, a rare and distinct form of liver cancer. Using potent tool compounds that have been generated from our proprietary kinase inhibitor library, PRKACA biology in patient-derived xenograft and ex vivo cell culture models of fibrolamellar HCC is being characterised. Lastly, we are investigating the role that these oncogenic signaling pathways may play in modulating the immune component of the tumour microenvironment. Novel immune-modulatory mechanisms for both FGFR4 and PRKACA are being explored and we have initiated collaborations to develop a novel platform to identify immunokinase targets and enable design of combination treatments with immune checkpoint inhibitors in HCC. Taken together, we believe that these targeted approaches will enable higher response rates, more durable responses for patients, and contribute to the changing landscape of liver cancer treatment opportunities.

15:30 – 16:00  
Coffee & Networking Break

16:00 – 18:50  
Paradoxical Differences in Animal Models of Hepatocarcinogenesis  
Gen-Sheng Feng, PhD (USA)

Both clinical and experimental data indicate that liver carcinogenesis is triggered by over-activation of proto-oncogenes and/or inactivation of tumour suppressors. Therefore, great efforts have been devoted to development of pharmaceutical compounds that disrupt the classical oncogenic pathways for HCC treatment, with Sorafenib, a multi-kinase inhibitor, as the most widely used drug for advanced HCC patients. Unfortunately, Sorafenib and other similar oncoprotein inhibitors have achieved very little therapeutic benefit in the clinic. We believe that the systematic failure in the “mechanism-based” approach is evidently due to poor understanding of the complexity in hepatocarcinogenesis. One interesting finding made by several groups recently is the unanticipated anti-oncogenic effect for classical oncoproteins. Deletion of Met, Egfr, ctnnb1, Ikkβ or Ikkγ in hepatocytes surprisingly enhanced HCC development induced by a chemical carcinogen diethylnitrosamine, DEN. These new “paradoxical” data may explain why inhibiting the classical oncogenic pathways achieved little therapeutic effect for HCC patients, and also unlock previously unrecognised complexity of liver tumourigenesis, which urgently needs elucidation. Shp2/Ptpn11 is the first identified proto-oncogene that encodes a tyrosine phosphatase, with dominantly activating mutations detected in leukemia patients. Shp2 positively regulates cell survival and proliferation by promoting Ras-Erk signaling. However, our recent data showed that ablating Shp2 in hepatocytes enhanced DEN-induced HCC, similar to the effect of Met, EGFR, IKKβ, β-catenin and Jnk deletion. Nevertheless, the concept that these oncoproteins act as tumour suppressors in the liver is at odds with the conventional view on oncogenesis, and has not been well accepted because of concerns on the relevance of the DEN-induced animal models to liver cancer patients. To elucidate the “paradoxical” anti-oncogenic role of pro-oncogenic molecules, we have focused on the functional interaction of Shp2 with a classical tumour suppressor Pten. Interestingly, dual deletion of Shp2 and Pten promotes liver tumorigenesis in mice, by accelerating the progression from NAFLD to NASH and by inducing earlier genesis of liver tumour-initiating cells (TICs). Poor prognosis was observed for liver cancer patients with deficient expression of SHP2 and PTEN. Thus, Shp2/Ptpn11 is a bona fide tumour suppressor that cooperates with Pten in guarding hepatic homeostasis and functions. This concerted action of Shp2 and Pten in hepatocytes stands in sharp contrast to the opposing effects between the two molecules in myeloid cells, in which additional removal of Shp2 abrogates myeloproliferative neoplasm induced by Pten loss.
Functional Target Discovery and Academic Drug Discovery in Hepatocellular Carcinoma
Lars Zender, MD, PhD (Germany)

Hepatocellular Carcinoma shows intrinsic resistance to cytotoxics, and although the multikinase inhibitor sorafenib is approved as the first systemic treatment for patients with advanced HCC, the survival advantage conferred to these patients from sorafenib therapy averages only 2.8 months. In my talk I will give examples how innovative mosaic mouse models can be combined with stable in vivo RNAi or Crispr/Cas technology to identify new therapeutic targets for the treatment of liver cancer. I will discuss the pivotal role of academic drug discovery infrastructures for rapidly translating validated therapeutic target structures into clinical applications and will give an example of a novel and promising drug for the treatment of liver cancer which entered the phase of clinical testing only 13 months after completion of preclinical evaluation of the drug.

Xenografted Tumours: Mice as Human Avatar?
Supriya Saha, MD (USA)

Model systems including genetically-engineered mouse models (GEMMs), cell lines, and patient-derived xenografts (PDXs) each have their own strengths and weaknesses for studying pathogenic mechanisms as well as novel therapeutic approaches in cancer. We recently used a combination of these model systems to evaluate the use of Src-family kinase inhibitors in a genetic subset of intrahepatic cholangiocarcinoma (ICC), all of which demonstrated a remarkable consistency in their response. Technical approaches for generating, expanding, and cryopreserving PDXs will be reviewed. Finally, controversies in the use of xenografted tumours to guide personalised medicine will be discussed.

Which Model for Immune Therapy?
Tim Greten, MD (USA)

With the recent approval of different checkpoint inhibitors for the treatment of cancer, the interest in this type of treatment approaches has caught significant interest. Immunotherapy require the use of animal models with an intact immune system, tumours occurring in the correct environment and cancers mimicking the human disease. A number of novel animal models have recently been described, which address at least some of the factors. I will describe and discuss the best animal models, which can be used for preclinical immunotherapy studies and will discuss what type of novel immune based approaches will be tested in the near future.

In Cellulo Approaches to Test Drug Sensitivity
Richard Finn, MD (USA)

“Pre-clinical models do not predict” is a common mantra in the field of drug development. One of the main challenges in modern cancer drug development is the ability to identify predictive markers of response with novel therapeutics. The reality is that when used in a robust manner, pre-clinical models can help guide clinical development. This means not relying on one single cell line or a model that is engineered to be dependent on a target/pathway of interest. While these approaches are useful for understanding fundamental biology, they may not recapitulate the true molecular heterogeneity of the clinical disease. We will review our platform that uses a large panel of human cancer cell lines, including HCC and how after building a database with molecular data including DNA copy number changes, point-mutations, gene expression data, and protein expression/ activation with reverse-phase proteomics we can show that we recapitulate the molecular diversity of human cancers in vitro. We can then use this platform for not only targeted drug discovery and validation but also the identification of novel predictive markers for patient selection. We will review examples of how this platform has been used to bring a diverse range of drugs into clinical development. While this approach has limitations as an ex-vivo system, this platform can be used to generate hypothesis for clinical testing, as compared to traditional clinical development that is more empiric and has often lead to disappointing results.
Round Table Discussion

Josep M. Llovet, MD (Spain/USA) and Valérie Paradis, MD, PhD (France)

What is an Ideal Pre-Clinical Model for Drug Development for HCC?
Josep M. Llovet, MD (Spain/USA)

Hepatocellular carcinoma (HCC) represents 90% of all cases of primary liver cancer, with an incidence of approximately 800,000 new cases per year. Few treatments have been accepted for the management of this disease. Thus, discovery of new treatments is an urgent unmet medical need, particularly at advanced stages. Modelling of HCC development in mice is a useful approach for identifying new and non-toxic therapies. For drug screening, aside of HCC cell lines, three types of animal models are commonly used for testing drug response: xenograft models (primary tumours xenografted in immunodeficient mice), genetically engineered mouse models (GEMM) and specific models for testing immune therapies.

Xenograft models are the most popular approach to test drugs in HCC by implanting either human HCC cell lines or patient tumour cells in immune-compromised mice, either ectopically or orthotopically. Athymic (nude) or severe combined immune deficient (SCID) mice are often used as hosts. When using human HCC cell lines for xenograft, multiple cell lines must be used for drug screening since different outcomes often occur due to the heterogeneity of cell lines. Patient derived xenografts (PDX) retain morphological and molecular characteristics of the primary human tumour. These models have been used to test systemic therapies, molecular targeted therapies and immunotherapies. PDX also made possible the generation of metastatic models, by orthotopically implanting primary tumour tissue in nude mice.

Although xenograft models offer a fast solution for drug screening, serve as a part of all standard drug development pipelines and are a pre-requisite to clinical trials, most of them fail to accurately predict the clinical efficacy of novel anticancer agents in human patients, largely due to their inability to recapitulate the complexity and heterogeneity of human tumours.

GEMM could be another approach to test drugs in HCC by deletion of tumour suppressor genes or overexpression of oncogenes. More recently, siRNA and CRISPR–Cas9 techniques have emerged as powerful methods to generate tumours in mice and to subsequently test for (biomarker based) drug responses and to design combination therapies. For instance, siRNA screening strategies have identified Mapk14 inhibitor as a promising approach to overcome sorafenib resistance. Additionally, AURKA inhibitors have been proposed as therapeutic strategies to treat TP53-altered HCC. Furthermore, combinations of GEMM and DEN-based toxic approaches have also been proposed.

For preclinical testing of immune therapies in cancer, several pre-clinical models have been used to demonstrate the efficacy of anti-CTLA-4 or anti-PD-1/PD-L1 antibodies in different models, such as 1) murine xenograft models with adoptive T cell transfer; 2) genetically engineered mouse model, and 3) humanised mouse model with human tumour xenografts.
Preclinical Model of Hepatocellular Carcinoma – The pathologist Point of View
Valérie Paradis, MD, PhD (France)

Hepatocellular carcinoma (HCC) is one of the main complications of chronic liver disease, arising in a background of cirrhosis, resulting from accumulation of genetic and molecular changes. Thus, HCC develops, in most of cases, from the malignant transformation of preneoplastic cirrhotic nodules, usually recognised as macronodules, ranging from regenerative to low grade and high grade dysplastic nodules. Although a great number of preclinical models of HCC have been developed, mostly chemically induced and transgenic models in mice, almost none of them does not recapitulate the full spectrum of malignant transformation observed in human. An ideal preclinical model of HCC should be triggered by similar causes of chronic liver diseases as in human and may reflect the morphological stepwise of liver carcinogenesis, with for instance, occurrence of dysplastic nodules. Recent advances have been made in the context of Non Alcoholic Fatty Liver diseases. Indeed, a diet-induced mouse model of NASH has been described mimicking metabolic, transcriptomic and morphological features of human disease. Interestingly, development of HCC was reported in 89% of mice between weeks 32 and 52 (Asharpour A, J Hepatol 2016).

Overall, the lack of appropriate preclinical models of chronic liver diseases and HCC significantly hampers the development and screening of therapeutic targets. The ex vivo culture model of tumour slices may help to fill the gap by allowing drug screening directly on human HCC slices.
Friday, 9 September 2016

08:00 – 09:30 ILCA Symposium 1: New Targets in Hepatocellular Carcinoma
Pacific Ballroom
Conference Floor

Chairs: Richard Finn, MD (USA) and Peter R. Galle, MD, PhD (Germany)

SIRT6 – An Epigenetic Player in Liver Differentiation and Cancer
Peter R. Galle, MD, PhD (Germany)

Sirtuin 6 (SIRT6) is a member of the sirtuin family of NAD+-dependent deacetylases involved in epigenetic gene silencing. Its ablation in mice results in a severe aging-like phenotype with impaired liver function and premature death. We investigated SIRT6 expression in primary human liver cancers, normal and cirrhotic livers using microarray data and further analysed gene expression signatures, we generated from isolated hepatocytes of SIRT6-deficient mice. We could show that the SIRT6-deficient hepatocyte signature is prognostically relevant for the patients in relation to survival and tumour recurrence rates. Among the genes we found are the HCC biomarkers alpha-fetoprotein (AFP), insulin-like growth factor 2 (IGF2), H19 and glypican-3 (GPC3), indicating an important role of SIRT6 in silencing of cancer-related genes.

Further, analysis of epigenetic alterations caused by SIRT6 deficiency in hepatocytes revealed genome-wide DNA hypomethylation and an enhanced acetylation pattern of histones that marks activated gene loci. Site-specific histone modifications are a major epigenetic mechanism for controlling stable transcriptional activity, but the consequences of histone modification changes in HCC development are not well understood. Using the IGF2/H19 gene locus as a model we could show by ChIP and chromatin conformation capture (3C) that SIRT6 suppresses permissive chromatin remodeling and binding of pioneer transcription factors.

Beta-Catenin Mutations in HCC: Biological and Therapeutic Implications
Satdarshan (Paul) S. Monga, MD (USA)

Stabilizing somatic point mutations in exon-3 of β-catenin gene or CTNNB1 are evident in a large subset of HCC patients. However, several transgenic mice models that express the stable mutants of the gene don’t exhibit spontaneous tumorigenesis. To investigate cooperation with any additional pathways, we have queried HCC databases to identify possible coexistence of CTNNB1 mutations with other signaling aberrations. One relevant observation has been the identification of simultaneous HMET overexpression or hMet activation and CTNNB1 mutations in around 9-12% of all HCC patients in two independent HCC datasets. Based on this observation, we have co-expressed HMET and serine 45/33-mutant-β-catenin in mouse liver using sleeping beauty (SB) transposon-transposase plasmids and hydrodynamic tail vein injection. This combination led to robust tumorigenesis in mice in the form of well differentiated HCC which shows activation of β-catenin and Met signaling. In fact β-catenin activation leads to enhanced expression of glutamine synthetase and cyclin-D1 in the tumours, whereas Met activation induces PI3K/Kras/Erk and Akt/MTOR signaling. Introduction of dominant negative TCF4 prevents HCC in this mouse model by blocking both β-catenin and Met signaling. Since Kras activation was observed in this model, we also examined its cooperation with mutant β-catenin. Indeed, coexpression of active Kras and serine 45/33-β-catenin (Kras-β-catenin) also led to robust HCC that were histologically similar to Met-β-catenin tumours. Intriguingly, the gene expression of the tumours in both models was highly congruent. To address any correlation with human HCC, we used the limma differential expression pipeline to contrast the expression of HMET-high and CTNNB1 mutant human samples relative to the other HCC samples. Next, to assess the degree of similarity between the human differential expression analysis of this subset of HCC cases and hMet-β-catenin mouse model, we mapped mouse genes to their human orthologs according to the MGI mouse-human orthology database and assessed the fold-change correlation for genes that were significant at q-value FDR of 0.2 and had a minimum log2 fold-change of 1.7 in both datasets. This analysis revealed a significantly high correlation between the sets of changes in the two groups with a Pearson correlation of 0.6 and a p-value of 2.3466e−05. Lastly, we wanted to investigate any therapeutic efficacy of β-catenin suppression in any of the current animal models based on our previous studies in DEN/PB model. We used Kras-β-catenin model and after establishing tumours, we delivered lipid nanoparticle (LNP) with siRNA against β-catenin or placebo at a specific dosing schedule. A pronounced and
significant decrease in tumour burden was visible as reflected by lower liver weight body weight ratio as well as by
gross and microscopic analysis. This coincided with a notable suppression of \(\beta\)-catenin and its downstream signaling.
In summary, \(\beta\)-catenin mutations often coexist with aberrations in other signaling pathways and elucidation, validation
and characterisation of such combinations in mouse models will be crucial for personalised medicine. Mutant
\(\beta\)-catenin-Met or mutant \(\beta\)-catenin-Kras coexpression in liver leads to HCC that significantly resembles human HCC
at a molecular level. \(\beta\)-Catenin suppression by LNP in mutant \(\beta\)-catenin-Kras model led to a notable therapeutic
response.

**Hepatocellular Carcinoma – Liver Cancer Stem Cells**  
Irene Ng, MD, PhD (Hong Kong)

Hepatocarcinogenesis is a multistep process evolving from chronic hepatitis and cirrhosis to hepatocellular
carcinoma. Recent advances in molecular methods have led to a growing understanding of the underlying
mechanisms of hepatocarcinogenesis. Many lines of evidence have demonstrated that cancer stem cells (CSCs,
or more appropriately, cancer propagating cells) residing within the bulk tumour are capable of self-renewal and
maintaining tumour propagation. They are also capable of metastasis and chemo-resistance. CSCs are considered
a pivotal target for the eradication of cancers. Hence besides killing the bulk tumour, there is a need to also
target this specific CSC subpopulation for novel. Using in vitro and in vivo models, we have identified CD24 and
CD47, among others, as novel liver cancer stem cell markers. They are functional liver CSC markers that drive
hepatocarcinogenesis through specific signaling pathways. Genomic analysis of these liver CSCs will also be
discussed. Some of our recent translational work targeting these markers has shown promising data in animal
models and will be presented and discussed. This presentation attempts to highlight the importance of liver CSCs
implicated in the pathogenesis of hepatocellular carcinoma as well as potential targets for therapy. Detailed
understanding of the molecular pathogenesis is crucial for the development of new therapeutic approaches against
hepatocellular carcinoma.

**Therapeutic Targeting of IGF2 in Liver Cancer**  
Daniela Sia, PhD (Italy)

Hepatocarcinogenesis is a complex, multistep process involving alteration of several signaling pathways. Among
them, the insulin-like growth factor (IGF) leads to a multitude of effects that modulate fetal development, cell
growth, proliferation, and apoptosis. Aberrant activation of IGF pathway has been observed in up to 20% of hepatocellular carcinoma (HCC) through several mechanisms, including epigenetic alterations leading to over-expression of IGF2 and deregulation of the IGF binding proteins, IGFBP2 and IGFBP3. Evidences gathered in transgenic mouse models strongly support the oncogenic role of IGF2 and have driven the enthusiastic development of several monoclonal antibodies and small molecules blocking IGF1 receptor (IGF1R). Nonetheless, initial phase III clinical trials using anti-IGF1R therapies in unselected patients have been disappointing due to their toxicity or lack of efficacy. Future trials may benefit from the recent development of novel therapeutic strategies targeting the IGF ligands rather than the receptors or from the use of predictive biomarkers able to identify patients likely to respond to these treatments. BI836845, the anti-IGF2 monoclonal antibody, is currently under investigation in Phase I clinical trial. Preclinical studies show that BI836845 reduces cell proliferation in vitro and significantly delays tumour growth in HCC xenograft models. This data suggests that targeting of the IGF ligand may represent an attractive therapeutic strategy in IGF2-dependent tumours.
State-of-the-Art Lecture 1: Immunology and Immunotherapy of Hepatocellular Carcinoma

Chair: Andrew X. Zhu, MD, PhD (USA)
Speaker: Tim Greten, MD (USA)

HCC represents a typical inflammation associated cancer. Chronic viral hepatitis and non-alcoholic steatohepatitis represent important risk factors for the development of HCC. Hepatitis B vaccination has been shown to reduce HCC incidence. Thus there is a good scientific rationale to study how chronic immune responses promote hepatocarcinogenesis, but also immune-based approaches can be utilised to treat patients with HCC. Very early results from clinical trials indeed suggest a possible role for immunotherapy in the treatment of cancer. I will summarize recent data about how from our laboratory how tumours and/or the tumour microenvironment promotes tumour growth by suppressing anti-tumour immunity and provide an overview of currently ongoing experimental approaches to treat patients with HCC using immune-based approaches. Finally, I will try to provide a perspective where the field of immunotherapy of HCC may move in the near future.

Coffee & Networking Break

Welcome Address

Richard Finn, MD (USA), Jessica Zucman-Rossi, MD, PhD (France), Morris Sherman, MD, PhD (Canada) and Peter R. Galle, MD, PhD (Germany)

General Session 1: Molecular Pathogenesis

Chairs: Irene Ng, MD, PhD (Hong Kong) and Augusto Villanueva, MD, PhD (USA)

O-001 The Thailand Initiative in Genomics and Expression Research for Liver Cancer (TIGER-LC): Race/Ethnicity-Related Common Molecular Subtypes among Asian Hepatocellular Carcinoma and Cholangiocarcinoma Identified by Integrated Genomics

A Budhu1, J Chaisaingmongkol2, H Dang1, S Rabibhadana1, B Pupacdi2, S Kwon1, M Forgues1, V Bhudhisawasdi1, N Lertrprasertsuke1, A Chotirosniramit3, C Pairojkul1, C Auewarakul1, T Sricharunrat1, K Phromphutkul1, S Sangrajrang1, M Cam1, P He4, S Hewitt1, X Wu1, S Thorgeirsson1, P Meltzer1, C Loffredo4, R Wiltout1, C Harris1, C Mahidol1, M Ruchirawat1, X Wang1

1National Institutes Of Health, Bethesda, United States, 2Chulabhorn Research Institute, Bangkok, 3Khon Kaen University, Khon Kaen, 4Chiang Mai University, Chiang Mai, 5Chulabhorn Hospital, Bangkok, 6Rajavej hospital and Lampang Cancer Center, Chiang Mai, 7National Cancer Institute, Bangkok, Thailand, 8FDA, Bethesda, 9Georgetown University Medical Center, Washington, DC, United States

O-002 Cancer Stem Cells Promote Liver Cancer Metastasis Independent of PROM1

L Zhu1, L Li1, M Qian2, D Finkelstein2, A Bahrami3, D López-Terrada3

1St. Jude Children’s Research Hospital, Memphis, United States, 2St. Jude Children’s Research Hospital, Memphis, 3Baylor College of Medicine, Houston, United States

O-003 Oncogenic Activation of the RNA Binding Protein RDBP and c-Myc Signaling in Hepatocellular Carcinoma

H Dang1, A Takai1, M Forgues1, X Wang1

1NIH/NCI, Bethesda, United States

O-004 The SWI/SNF Chromatin-Remodeling Component ARID1A Regulates Regenerative Capacity and Carcinogenesis in a Dose-Dependent Fashion

X Sun1, S Wang2, P Gopal3, A Singal4, A Yopp2, H Zhu1

1UT Southwestern, Dallas, United States, 2UT Southwestern, Dallas, United States, 3UT Southwestern, Dallas, United States, 4UT Southwestern, Dallas, United States
0-005 Genetic Deletion of Insulin-Like Growth Factor Binding Protein-7 (IGFBP7) Promotes Hepatocellular Carcinoma (HCC): A Novel Role of IGFBP7 in Regulating Anti-Tumor Immune Surveillance

M Akiel1, C Guo1, X Li1, D Rajasekaran1, R Mendoza1, C Robertson1, N Jariwala1, M Subler1, J Windle1, D Garcia2, Z Lai3, H Chen4, Y Chen4, S Giashuddin6, P Fisher1, XY Wang1, D Sarkar1

1Virginia Commonwealth University, Richmond, 2University of Texas Health Science Center at San Antonio, San Antonio, United States, 3University of Texas Health Science Center at San Antonio, San Antonio, United States, 4University of Texas Health Science Center at San Antonio, San Antonio, United States, 5New York Presbyterian Health System at Weill Cornell Medical College, New York, United States

0-006 Germline and Somatic DICER1 Mutations are Associated with CTNNB1 Mutation and a Specific Microrna Expression Profile in Hepatocellular Carcinoma

S Caruso1,2,3,4,5, J Calderaro1,6,7, E Letouzé1,2,3,4, JC Nault1,2,3,4, JC Nault1,2,3,4, GCouchy1,2,3,4, A Boulais1,2,3,4, A Luciani9, ES Zafrani6, P Bioulac-Sage10,11,12, O Seror13, S Imbeaud1,2,3,4, J Zucman-Rossi1,2,3,4,5

1UMR-1162, Génomique fonctionnelle des Tumeurs solides, IJH, INSERM, 2Labex Immuno-Oncology, Sorbonne Paris Cité, Faculté de Médecine, Université Paris Descartes, 3Université Paris Diderot, Paris, 4Université Paris 13, Sorbonne Paris Cité, Bobigny, 5AP-HP, Hôpital Européen Georges Pompidou, Paris, 6AP-HP, CHU Henri Mondor, 7Université Paris-Est Créteil, Créteil, 8AP-HP, Hôpitaux Universitaires Paris–Seine Saint-Denis, Site Jean Verdier, Bondy, 9AP-HP, CHU Henri Mondor, Créteil, 10INSERM, UMR 1053, 11Université de Bordeaux, 12CHU Bordeaux, Pellegrin Hospital, Bordeaux, 13AP-HP, Hôpitaux Universitaires Paris–Seine Saint-Denis, Site Jean Verdier, Bondy, France

12:45 – 13:00 Session Break

British Columbia Ballroom
Conference Floor

13:00 – 14:30 Bayer Lunch Symposium: HCC Management Today and Tomorrow: Using Clinical Evidence to Guide Therapeutic Approaches to Optimise Patient Survival

Opening Remarks
Morris Sherman, MD, PhD (Canada)

Optimising Systemic Therapy in HCC
Richard Finn, MD (USA)

(Over)utilisation of TACE/LRTs
Riccardo Lencioni, MD, PhD (Italy)

Defining the Systemic Sequence in HCC
Jordi Bruix, MD, PhD (Spain)

Closing Remarks
Morris Sherman, MD, PhD (Canada)

14:30 – 14:45 Session Break

British Columbia Ballroom
Conference Floor
ILCA ANNUAL CONFERENCE, 2016
Friday, 9 September 2016

General Session 2: Molecular Pathology

**O-007 Characterization of the Immune Class of Hepatocellular Carcinoma**

D Sia1,2, Y Jiao1, I Martinez-Quetglas1,2, O Kuchuk1,2, C Villacorta Martin1, G Camprecios1, S Thung1, V Mazzaferr10, A Villanueva1, J Llovet1,2,4

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**O-008 Identification of a New Subgroup of Hepatocellular Adenomas Characterized by Dysregulation of Sonic Hedgehog and Prostaglandin Pathways**

J Nault1, G Coughy1, P Bioulac-Sage2, Y Bacq1, J Calderaro3, V Gremm14, N Sturm1, C Guettier1, M Fabre2, E Savier1, L Chiche1, P Labrune1, J Selves1, D Wendum15, G Morcrette1, E Gelabale1, C Pilati1, A Laurent1, A De Muret1, J Blanc1, S Imbeaud1, C Balabaud1, S Rebouissou1, J Zucman-Rossi1

1INSERM UMR1162, Paris, 2Pathology department, Bordeaux, 3Liver unit, Tours, 4Pathology department, Creteil, 5Pathology department, Beaujon Hospital, Clichy, 6Pathology department, Montpellier, 7Pathology department, Institut Gustave Roussy, Villejuif, 8Pathology department, Lille, 9Pathology department, Grenoble, 10Pathology department, Bicetre hospital, Bicetre, 11Hepatobiliary surgery, pitie salpetriere hospital, Paris, 12Hepatobiliary surgery, Bordeaux, 13Pediatric department, Clamart, 14Pathology department, Toulouse, 15Pathology department, Saint Antoine hospital, Paris, 16Hepatobiliary surgery, Henri Mondor Hospital, Creteil, 17Pathology department, Tours, 18Liver unit, Bordeaux, France

**O-009 Distinct Spatial Distribution of Gene Expression and Mutations within Single-Nodule Hepatocellular Carcinoma Captures Intra-Tumoural Heterogeneity**

A Craig1, M Ahsen1,2, C Villacorta-Martin1, X Chen1, I Labgaa1, A Stueck1, D D’avola1, S Ward4, M Fiel1, G Gunasekaran3, J Llovet1,2, S Thung1, M Schwartz5, B Losic3, G Stolovitzky1,2, A Villanueva1,7

1Icahn School of Medicine at Mount Sinai, New York, 2IBM, Yorktown Heights, 3Icahn School of Medicine at Mount Sinai, New York, United States, 4Icahn School of Medicine at Mount Sinai, New York, United States, 5Icahn School of Medicine at Mount Sinai, New York, United States, 6CIBERehd, Hospital Clinic, Barcelona, Catalonia, Spain, 7Icahn School of Medicine at Mount Sinai, New York, United States

**O-010 Blocking Several Co-Inhibitory Pathways Can Revitalize the Functionality of Tumour-Infiltrating T Cells in Hepatocellular Carcinoma**

G Zhou1, D Sprengers1, P Boor1, M Doukas1, W Polak3, J de Jonge1, K Thielemans1, J IJzermans1, M Bruno1, J Kwékkeboom1

1Erasmus Medical Center, Rotterdam, Netherlands, 2Erasmus Medical Center, Rotterdam, Netherlands, 3Erasmus Medical Center, Brussels, Belgium

**O-011 Role of the Tumour-Initiating Cells in the Development of Chemoresistance during Anti-Angiogenic Therapies in Hepatocellular Carcinoma**

D Castven1, C Czauderna1, D Becker1, D Wilhelmi1, M Wörns1, S Thorgeirsson1, P Grimminger1, H Lang1, P Galle1, J Marquardt1

1Johannes Gutenberg University Mainz, Mainz, Germany, 2CCR/NCI/NH, Bethesda, United States, 3Johannes Gutenberg University Mainz, Mainz, Germany

Coffee & Networking Break
ILCA Symposium 2: Controversies in Liver Cancer (Pros and Cons Session)

Chairs: Masatoshi Kudo, MD, PhD (Japan) and Kwang-Hyub Han, MD (Republic of Korea)

Y90 vs. TACE
Bruno Sangro, MD, PhD (Spain) vs. Valérie Vilgrain, PhD (France)

Y90
Bruno Sangro, MD, PhD (Spain)

Transarterial chemoembolization (TACE) and Y90-radioembolization (Y90) are at the core of the treatment of patients with hepatocellular carcinoma who cannot receive potentially curative therapies such as transplantation, resection or percutaneous ablation. They differ in the mechanism of action (ischemia and increase cytotoxic drug exposure for TACE, internal irradiation for Y90), the need for superselective injection (mandatory for TACE), the range of biological effects, and the complexity of the procedure (higher for Y90). Cytoreduction is achieved in most patients after TACE and Y90 but complete tumour ablation may be achieved and lead to extended survival. TACE with cytotoxic drug-eluting beads is a more standardised although not necessarily more effective way of performing chemoembolization. For these and other reasons including strategic development decisions, TACE and Y90 have so far targeted different patient populations. However, patient outcomes in three small randomised controlled trials have been basically similar. Grade 1 level of evidence support the use of TACE for the treatment of patients in the early and intermediate stages while grade 2 evidence supports the use of Y90 for the treatment of patients in intermediate to advanced stages. Selecting the best candidates for both techniques is still a work in progress that ongoing clinical trials are trying to address. Overall, TACE and Y90 are useful tools in the locoregional armamentarium against hepatocellular carcinoma.

TACE
Valérie Vilgrain, PhD (France)

Transarterial chemoembolization (TACE) and Y90 selective intra-arterial radiation therapy (SIRT) also named radioembolization are both intra-arterial treatments of liver cancer requiring selective catheterisation of intrahepatic arterial branches. The aim of these treatments is to get complete tumour necrosis by focusing administration of chemotherapy or radiation therapy at the tumour site. However there are many differences. First, TACE is an all-in one procedure whereas SIRT requires different steps (coiling of extrahepatic arteries in some cases, Technetium-99m macroaggregated albumin (99mTc-MAA) scan performed to assess the lung shunt fraction and splanchnic shunting, and the treatment, which is usually done several days after. Second, the tolerance of TACE and SIRT is very different, as most patients treated with TACE experience post embolization syndrome requiring short hospitalisation and analgesia. On the contrary, SIRT is much better tolerated and can be performed in patients with complete obstruction of the portal vein. Third, indications of TACE and SIRT are still different in patients with hepatocellular carcinoma (HCC). While TACE is the classical treatment in intermediate patients according to BCLC, TACE is not recommended in more advanced patients. The role of SIRT is currently being evaluated in locally advanced patients where the reference treatment is sorafenib. Besides these main indications, there are many more including patients with HCC on the waiting list of liver transplantation, or as a bridge to major liver resection. Last, there have been many improvements in the TACE technique while SIRT is still emerging and will certainly change over time. In particular, single-session radioembolization (pre-treatment angiography/99mTc-MAA scan/radioembolization on same day) have been reported recently and could become standard of care in the future, thus minimising the costs.
What to Expect after Sorafenib?
Ann-Lii Cheng, MD, PhD (Taiwan) vs. Jordi Bruix, MD, PhD (Spain)

Making the Most out of Immune and Targeted Therapies
Ann-Lii Cheng, MD, PhD (Taiwan)

Similar to many other cancer types, HCC has modest, yet definite response to immune checkpoint inhibitors. This finding is particularly significant in HCC which, for 8 years, has been faltering in drug development. However, further exploitation of the whole field of immunotherapy would take a better understanding of the immune microenvironmen of HCC. Some of the discoveries have started to shed light. For examples, a relative abundance of MDSC and M2-polarized macrophage in HCC microenvironment may suggest CSFIR inhibitors and anti-TIM3 reasonable drugs to be tested in this cancer type; and high expression of galectin-9 on the kupffer cells of HBV-related HCC further addresses this point.

It is well known that classical molecular targeted agents may direct or indirectly affect immune microenvironment, and therefore be potentially beneficial partners of cancer immunotherapy. For example, sorafenib down-regulates Treg and PD-1 expressing T cells, and act synergistically with anti-PD-1 and anti-CTLA-4 in murine HCC models. Further, activated Wnt/β-catenin, the most frequently altered pathway in HCC, is closely linked to T cell depletion in tumour microenvironmen of malignant melanoma. Its role in HCC and the potential application of Wnt/β-catenin inhibitors and other targeted therapies to enhance the efficacy of immune checkpoint inhibitors are now under enthusiastic investigation.

The whole field of immune therapy, on top of the already protean targeted therapy, promises a quick breakthrough in drug discovery for HCC.

What to Expect after Sorafenib
Jordi Bruix, MD, PhD (Spain)

Systemic treatment of hepatocellular carcinoma has been a very disappointing field until very recently. The success of sorafenib was a landmark result that showed that years of research in methodology and molecular targets pay off. Sorafenib improved the survival of the patients but at the same time challenged several established concepts in Oncology. The improvement in survival was achieved without a significant number of objective responses and the benefit came through a delay in tumour progression.

The success of sorafenib raised major optimism about the potential of several agents that were in early clinical evaluation both for 1st and 2nd line. Unfortunately, all agents tested offered negative results in phase 3. Thus, for several years sorafenib remained as the sole effective systemic agent for patients with liver cancer.

This negative setting primed the willingness to develop trials with enrichment of patients based in the targets to be affected by the new drugs and also to develop new methods to identify promising signals in early phase 1-2 trials. While no robust methods have been identified for signal identification, it is now obvious that tumour heterogeneity poses major threats to reliable molecular enrichment. Trial design has been slightly refined with new prognostic parameters (AFP) that will be probably complemented by stratification according to progression pattern.

Major hope has been placed in the benefits of immune treatment but data are still preliminary and the optimistic feelings raised by the impact in other cancer types has to be validated in liver cancer. In the meanwhile, the new agent regorafenib has been proven to be effective after progression under sorafenib. Thus, all the developments in the field will now have to take into account this agent and have it as a comparator in the trials in second line. Placebo controlled trials will just be justified in 3rd line.
Transplant beyond Milan
Gonzalo Sapisochin, MD (Canada) vs. Francis Yao, MD (USA)

Transplant beyond Milan – Aggressive
Gonzalo Sapisochin, MD (Canada)

Liver transplantation (LT) is the best treatment option for patients with selected hepatocellular carcinoma (HCC). The Milan criteria\(^1\) moved the field forward and set the bar for LT for HCC. The main criticism to this criteria is that it is very stringent denying the chance of cure to patients that would otherwise do well after LT. It still remains an answered question what is the acceptable survival for patients transplanted with HCC\(^2\). Markers of tumour biology beyond size and number are helpful to expand the Milan criteria and to include patients with extended criteria tumours in the waiting list that can achieve good results after LT. Biomarkers that can be obtained before the transplant such as alpha-fetoprotein (AFP)\(^3\), inflammatory markers or tumour differentiation\(^4\) can help to aggressively expand the Milan criteria. Some institutions have reported good outcomes expanding the size and number of the tumours and combining this with biomarkers. Patients with HCC within a total tumour volume (TTV) <115 cm\(^3\) and AFP <400 ng/mL can achieve a 4-year survival of 75\(^%\)\(^5\). Furthermore, patients with no cancer-related symptoms, with no limitation on size and number of HCC that are not poorly differentiated can achieve 5-survival rates ~70\(^%\)\(^4\). Tumour recurrence after LT may constitute a concern as expanding the transplant criteria for HCC increases the risk of recurrence in some instances. Aggressive management of tumour recurrence can increase patient survival after this event occurs\(^6\). The criteria to include patients with HCC in the waiting list for LT can be aggressively expanded beyond Milan. LT represents the best “oncological” treatment for intra-abdominal malignancies.

Transplant beyond Milan – Conservative
Francis Yao, MD (USA)

The Milan criteria have been the benchmark for the selection of candidates with hepatocellular carcinoma (HCC) for liver transplant (LT) for the past 2 decades. A 5-year survival of 75-80\(^%\) can be achieved after LT for HCC within Milan criteria. Modest expansion of tumour size limits beyond Milan criteria may achieve 5-year post-LT survival in the 60-70\(^%\) range, but a higher bar is set for outcome after LT for HCC to be the same as that for non-tumour indications. Improved candidate selection may be achieved by considering not only tumour size and number (or volume), but also other prognostic markers including alpha-fetoprotein (AFP) and response to local regional therapy (LRT). These markers have been shown to predict prognosis after LT not only for HCC beyond Milan criteria, but also for tumours initially within Milan criteria. Applying LRT to all patients and observing response to these treatments and the change in AFP over time (ablate and wait) represent a paradigm shift in recent years. This dynamic, adoptive approach would exclude those with tumours within Milan criteria but progressing rapidly despite LRT, and include patients with HCC outside of Milan criteria but responding well to LRT over a period of observation. Adhering to this principle, a conservative approach to LT beyond Milan criteria is down-staging to within Milan criteria, and this could achieve similar 5-year survival and recurrence probabilities as that for patients with HCC meeting Milan criteria without requiring down-staging.
Assessment of Tumour Response after Treatment
Richard Kinh Gian Do, MD, PhD (USA) vs. Haesun Choi, MD (USA)

Assessment of Tumour Response: why RECIST Still Matters
Richard Kinh Gian Do, MD, PhD (USA)

Response evaluation in clinical trials for patients with solid tumours is based on one-dimensional measurements of tumour size over the course of treatment. This simple concept forms the basis of Response Evaluation Criteria for Solid Tumours (RECIST), which has been the gold standard for clinical trials, defining treatment effectiveness for new therapies under investigation.

There is increasing concerns over the limitations of RECIST, especially for targeted therapies in a subset of malignancies where tumour shrinkage is minimal. Alternative response criteria to RECIST have been proposed, such as the Choi Criteria for gastrointestinal stromal tumours, and immune related RECIST for patients on immunotherapy. For therapies directed at hepatocellular carcinoma (HCC), decreases in tumour enhancement can occur without significant changes in tumour sizes. To address this limitation, new HCC response criteria have been devised to improve the assessment of treatment response. For HCC, the European Association for the Study of Liver Disease (EASL) criteria was first proposed in 2000, followed by modified RECIST (mRECIST) in 2009, both based on the measurement of enhancing tumours on the arterial phase of contrast enhancement.

Validation of alternative treatment response criteria to RECIST remains a challenge. The goal of response assessment is not only to quantify the response, but to provide an alternative end-point to patient survival for clinical trials. The evidence needed to validate a new imaging biomarker can be considerable. We will discuss the evidence for mRECIST and why traditional RECIST is still necessary in HCC clinical trials setting.

Tumour Response Evaluation: mRECIST
Haesun Choi, MD (USA)

Traditionally, response evaluation of solid tumour has been based on the changes in tumour size over time. The Response Evaluation Criteria for Solid Tumours (RECIST) has been the standard practice in clinical trials and the only criteria that has been accepted by regulatory in the US as of today.

Historically, RECIST is a modification of WHO criteria, which was created based on the clinical experience with cytotoxic agents and from the pre-era of cross sectional imaging (e.g. CT). Measuring the tumour size has become more accurate with evolution of computerised imaging with the capability of thinner section acquisition (e.g. 5mm or less) and availability of an electronic caliber.

Over the last decade, however, we have been increasingly experiencing that the response based on RECIST does not predict the survival in several different types of tumours, particularly in those that are treated with the new molecularly-targeted agents. These include, but not limited to, colorectal cancer liver metastasis, gastrointestinal stromal tumours, neuroendocrine tumours, renal cell carcinomas and hepatocellular carcinomas.

Based on the typically arterially-enhancing nature of hepatocellular carcinomas (HCC) on contrast enhanced CT images, in 2000, the European Association for the Study of Liver Disease (EASL) suggested the use of tumour tissue with arterial enhancement, “viable tumour,” in response evaluation for HCC that are treated with targeted agents, such as sunitinib. This concept was adopted by the American Association for the Study of Liver Disease (AASLD) and first formally included in the AASLD–JNCI (Journal of National Cancer Institute) guideline for response evaluation of HCC in 2008, named, modified RECIST (mRECIST). Pros and cons of mRECIST in HCC will be discussed in this presentation.
Saturday, 10 September 2016

07:30 – 08:30
Sirtex Symposium: SIR-Spheres Y-90 Resin Microspheres – An Alternative Approach for Primary Liver Cancer

Chair: Jordi Bruix, MD, PhD (Spain)

Welcome and Introduction

Current Evidence for SIR-Spheres Microspheres in HCC
Bruno Sangro, MD, PhD (Spain)

The SIR-Spheres Y-90 Resin Microspheres HCC Phase 3 Study Programme
Valérie Vilgrain, PhD (France)

Developing Future Evidence in Intrahepatic Cholangiocarcinoma – the New SIRCCA Study
Jordi Bruix, MD, PhD (Spain)

Panel Discussion

All

08:30 – 10:00
General Session 3: Epidemiology and Diagnosis

Chairs: Morris Sherman, MD, PhD (Canada) and Sheng-Long Ye, MD, PhD (P.R. China)

O-012 Incidence of Cholangiocarcinoma and Extrahepatic Cancer Taking into Account Virological Control in Patients with Compensated Viral Cirrhosis (ANRS C012 CirVir Prospective Cohort)


1CHU Côte de Nacre, CAEN, 2AP-HP Hôpital Jean Verdier, BONDI, 3AP-HP, Hôpital Henri Mondor, CRETEIL, 4ANRS, PARIS, 5AP-HP, Hôpital Beaujon, CLICHY, 6CHU Pontchaillou, RENNES, 7Hôpital Saint Eloi, MONTPELLIER, 8Hôpital Haut-Lévêque, BORDEAUX, 9Institut Arnaud Tzanck, SAINT LAURENT DU VAR, 10Hôpital Avicenne, BOBIGNY, 11CHU , NICE, 12CHU de NANCY, VANDOEUVRE-LES-NANCY, 13Hôpital Michallon, GRENOBLE, 14Hôpital Charles Nicolle, ROUEN, 15CHU, ANGERS, 16CHU Purpan, TOULOUSE, France, 17CHU Purpan, TOULOUSE, 18Hôpital Saint Joseph, MARSEILLE, 19Hôpital Claude Huriez, LILLE, France


K Ueshima1, M Kudo1, N Izumi1, M Kadoya2, S Kaneko3, Y Ku4, N Kokudo5, T Takayama6, M Sakamoto6, O Nakashima6, Y Matsuyama10

1Kindai University Faculty of Medicine, Osaka-Sayama, 2Musashino Red Cross Hospital, Tokyo, 3Shinshu University School of Medicine, Matsumoto, 4Kanazawa University Hospital, Kanazawa, 5Kobe University Graduate School of Medicine, Kobe, 6The Tokyo University Hospital, 7Nihon University School of Medicine, 8Keio University School of Medicine, Tokyo, 9Kurume University Hospital, Kurume, 10The University of Tokyo, Tokyo, Japan
O-014 Compliance to Hepatocellular Carcinoma Screening Guidelines in Patients with Compensated Viral Cirrhosis Increases the Probability of Curative Treatment and Survival Taking into Account Lead-Time Bias (ANRS CO12 CirVir Cohort)

C Costentin1, R layese2, V Boursier3, L Corvi3, V Petro-Sanchez4, P Marcellin5, D Guyader6, S Polo7, D Larrey8, V de Ledinghen9, A Tran10, P Mathurin11, L Alric12, J Peron13, A sutton14, J zucman-rossi14, J bronowicki16, J zarski17, F Zoulim18, G Riachi19, D Ouzan20, P Cales21, M Bourlière22, F Roudot-thoraval23, P Nahon1

1Hopital Henri Mondor, 2Henri Mondor Hospital, Creteil, 3Jean Verdier Hospital, Bondy, 4ANRS, Paris, 5Beaujon Hospital, Clichy, 6Hôpital de Rennes, Rennes, 7Cochin Hospital, Paris, 8CHU de Montpellier, Montpellier, 9CHU Bordeaux, Bordeaux, 10CHU Nice, Nice, 11CHU de Lille, Lille, 12CHU Toulouse, Toulouse, France, 13CHU Toulouse, Toulouse, 14INSERM U874/1162, Paris, 15CHU Avicennes, Avicennes, 16CHU Nancy, Nancy, 17CHU Grenoble, Grenoble, 18CHU Lyon, Lyon, 19CHU de Rouen, Rouen, 20Institut Arnault Tranck, St Laurent du Var, 21CHU Angers, Angers, 22Hôpital Saint Joseph, Marseille, 23Hopital Henri Mondor, Creteil, France

O-015 Hospital Volume and Survival after Hepatocellular Carcinoma Diagnosis

A Mokdad1, H Zhu1, J Marrero1, J Mansour1, A Singal1, A Yopp1

1University of Texas Southwestern, Dallas, United States

O-016 Randomized Controlled Trial of Outreach Strategies to Improve Hepatocellular Carcinoma Screening Rates

A Singal1, J Tiro1, J Marrero2, K McCallister3, J Sanders3, W Bishop3, N Santini3, E Halm3

1UT Southwestern Medical Center, Dallas, United States

O-017 Comparison of Clinical Feature of Nonalcoholic Fatty Liver Disease (NAFLD) Associated Hepatocellular Carcinoma with Versus without Liver Cirrhosis


1MAYO CLINIC, Rochester, United States, 2MAYO CLINIC, Rochester, United States, 3University of Vienna, Vienna, 4University of Graz, Graz, Austria, 5Hôpital Beaufort, Beaufort, 6Hôpital Saint-André, Saint-André, 7Clinic Universitaire d’Hépato-Gastroentérologie, 8Hôpital Jean Verdier, 9Hôpital Henri Mondor, France, 10Hôpital St-Eloi, Montpellier, France, 11University of Wuerzburg, Wuerzburg, 12Charité Berlin, Berlin, Germany, 13Ospedale Maggiore di Milano, Milano, Italy, 14 Dipartimento Esophago-Gastro-Bileopancreatico, Naples, Italy, 15Hospital Santa Maria, Lisbon, Portugal, 16Hospital General U. de Alicante, Alicante, 17Hospital del Mar de Barcelona, Barcelona, 18Hospital G.U. Gregorio Maranon (Madrid), Madrid, Spain, 19Gastroenterum Medicin, Karolinska Universitetssjukhuset Huddinge, Karolinska Universitetssjukhuset Huddinge, 20Kliniska klinikan, Akademiska, Akademiska, Sweden, 21University of Birmingham, Birmingham, 22Beatos West of Scotland Cancer Centre, Glasgow, 23Royal Free Hospital, 24Kings College, London, 25University Hospital Aintree, Liverpool, United Kingdom, 26CHUM St-Luc, Montréal, Canada, 27Mount Sinai, New York, United States

10:00 – 11:00

British Columbia Ballroom

Conference Floor

e-Poster Viewing Tour & Networking Break

Opened by Richard Finn, MD (USA)
O-018 Unexpected High Rate of Tumour Recurrence in Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma Undergoing Interferon-Free Therapy
M Reig1, Z Mariño2, C Perelló3, M Iñarrairaegui4, R Andrea1, S Lens2, A Diaz2, R Vilana6, A Darnell5, M Varela7, B Sangro1, J Calleja1, X Forés2, J Bruix1

1Hospital Clinic de Barcelona, Barcelona, Spain, 2Hospital Clinic de Barcelona, Barcelona, 3Hospital Universitario Puerta de Hierro, Madrid, 4Clínica Universidad de Navarra, Pamplona, 5Hospital Clinic de Barcelona, Barcelona, Spain, 6Hospital Universitario Central de Asturias, Oviedo, Spain

O-033 Lack of Evidence of an Effect of Direct Acting Antivirals on the Recurrence of Hepatocellular Carcinoma: Data from three Prospective French Cohorts (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT)
Nathalie Ganne-Carrié for The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts)

O-019 Safety and AntiTumour Activity of Nivolumab (Nivo) in Patients with Advanced Hepatocellular Carcinoma (HCC): Interim Analysis of Dose-Expansion Cohorts from the Phase 1/2 Checkmate-040 Study
B Sangro1, I Melero1, T Yau2, C Hsu3, M Kudo4, T Crocenzi5, TY Kim6, SP Choo7, J Trojan8, T Meyer9, YK Kang10, J Anderson11, C dela Cruz11, L Lang11, J Neely11, A El-Khoueiry12

1Clinica Universidad de Navarra and CIBERehd, Pamplona, Spain, 2University of Hong Kong, Hong Kong, China, 3National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan, Republic of China, 4Kinki University School of Medicine, Osaka, Japan, 5Providence Cancer Center, Portland, OR, United States, 6Seoul National University Hospital, Seoul, Korea, Republic Of, 7National Cancer Center Singapore, Singapore, Singapore, 8Goethe University, Frankfurt, Germany, 9Royal Free Hospital, London, United Kingdom, 10University of Ulsan College of Medicine, Seoul, Korea, Republic Of, 11Bristol-Myers Squibb, Princeton, NJ, 12University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, United States

O-020 Classical and Novel Histological Subtypes of Hepatocellular Carcinoma are Related to Gene Mutations and Transcriptomic Classification
J Calderaro1,2,3, JC Nault3,4, G Couchy2,3, S Imbeaud2,3, JF Blanc2,3, Y Hajji2, A Laurent5, P Bioulac-Sage6, J Zucman-Rossi2,3

1Henri Mondor University Hospital, Créteil, 2Inserm UMR1162, Génomique fonctionnelle des tumeurs solides, 3Université Paris Descartes, Labex Immuno-Oncology, Paris, 4Hopital Jean Verdier, Bondy, 5CHU Bordeaux, Bordeaux, 6Inserm UMR1162, Paris, 7Henri Mondor University Hospital, Créteil, 8CHU Bordeaux, Bordeaux, France
ILCA Special Interest Groups (SIGs) Luncheon Workshops

ILCA 2016 Programme
Saturday, 10 September 2016

**12:45 – 14:00**
**SIG 1: Molecular Classification and Signalling Pathways**
*Single Cell Genome in Liver Cancer*

Chairs: Xin Wei Wang, PhD (USA) and Keji Zhao, PhD (USA)

Liver cancer is clinically, molecularly and biologically heterogeneous, and highly resistant to treatment. A major barrier to improving patient outcome is the incomplete understanding of cancer heterogeneity and our inability to define key cancer vulnerabilities for effective therapeutic intervention. Genomic analyses of HCC and ICC by whole genome or exome sequencing reveal a complex mutational landscape with a vast inter-tumour heterogeneity. These studies also reveal that each primary tumour lesion may consist of cells that differ genetically and epigenetically, referred as intra-tumour heterogeneity, which may result in a phenotypic heterogeneity. Currently, it is unclear how these heterogeneous tumour cells cooperate each other and whether collective behavior and collective regulation of these tumour cells exist as an efficient community unique to each tumour subtype. Thus, understanding molecular features of tumour cells at a single cell level would provide a better understanding of tumour cell communities and help define key drivers responsible for tumour metastasis. The recent development of single-cell genome sequencing technologies has generated many new insights into complex biological systems including human cancer. Single tumour cell analysis may provide the level of sensitivity and specificity to understand tumour biology with regard to collective behavior and collective regulation of a given tumour cell community. It is anticipated that molecular characterisations of tumour cells and immune cells at the single cell levels will provide a detailed molecular portrait of tumour cell communities specific to a particular tumour type with a unique clinical feature and a therapeutic response.

**12:45 – 14:00**
**SIG 2 : Surveillance, Biomarkers and Molecular Pathology**
*Biomarkers: A Review of the Present and a Glimpse of the Future*

Chair: Neehar Parikh, MD (USA)

Early detection of hepatocellular carcinoma (HCC) is associated with improved patient outcomes, however we lack adequate biomarkers to reliably identify patients with early stage disease. In addition, once HCC is diagnosed, we lack adequate prognostic biomarkers that aid in predicting disease course or response to HCC treatment. Thus, there have been concerted efforts on multiple fronts in order to discover potential biomarkers for HCC. In this session we will discuss the currently available biomarkers for HCC, such as alpha fetoprotein (AFP), alpha fetoprotein-L3 (AFP-L3), and Des-gamma carboxyprothrombin (DCP). We will review the 5 phases of biomarker discovery: 1) Preclinical exploratory studies; 2) Clinical assay development for clinical disease; 3) Retrospective Longitudinal repository studies; 4) Prospective screening studies; and 5) Cancer control studies. We will discuss investigational biomarkers that are currently under development and the phase of discovery each potential biomarker is in. We will also discuss recent technological advances in genomic profiling in order to identify patients with HCC, including recent data regarding the use of miRNAs. Finally we will discuss the several multcenter ongoing efforts in HCC biomarker discovery, including the National Cancer Institute Early Detection Research Network and the Cancer Prevention and Research Institute of Texas. Attendees of this session will have a greater understanding of the current landscape of diagnostic and prognostic biomarkers for HCC.

**12:45 – 14:00**
**SIG 3: Imaging and Loco-Regional Therapies**
*Methods of Response Assessment: Comparing Systemic and Locoregional Therapies*

Chairs: Riad Salem, MD (USA) and Bruno Sangro, MD, PhD (Spain)

Although the mainstay of hepatocellular carcinoma (HCC) treatment has been locoregional, new systemic agents have demonstrated significant improvement in time-to-progression (TTP) and survival, leading some to postulate TTP as a surrogate of survival. While there is some rationale supporting this concept in advanced disease, complexities in HCC imaging should temper expanding this enthusiasm to early/intermediate disease until more robust evidence is available. Several examples of this lack of correlation exist in the radiofrequency ablation
(RFA), chemoembolization (TACE)/radioembolization, and systemic therapy literature. Although we agree with EASL-EORTC guidelines that mRECIST helps move the field forward, several imaging complexities remain unaddressed. The first imaging complexity relates to arterial embolic therapies. Since these are performed at staged intervals, imaging follow-up involves the simultaneous radiologic interpretation of treated/untreated disease. This creates difficulty in assessing response; should response only be measured in the treated lesion(a)? How should untreated targets be considered if they have sufficiently enlarged to meet progressive disease criteria? Should imaging only be assessed when all tumours have been treated and if so, how should patients never completing all treatments (toxicities/decompensation) be reported? These methodological nuances are under-reported in locoregional therapy studies. Accurately assessing response/progression (or lack thereof) in the liver is critical since HCC progression is predominantly local.

The second issue relates to “confirmatory progression”. Evaluating cirrhotic livers for new lesions can be quite challenging. Hypervascularity/washout is not a perfect criterion. It is not uncommon for equivocal lesions to become suspicious of HCC, yet at follow-up, become less conspicuous. Hence, confirmatory progression (particularly of new nodules) in HCC should be considered. This approach will minimize premature discontinuation of treatment. We have observed this artifact where a “new nodule” in a patient on sorafenib is declared as progressive disease (PD) with treatment discontinuation. At follow-up, despite no treatment, the lesion has disappeared, suggesting sorafenib was prematurely discontinued (PD overcall).

The third issue relates to retrospective adjudication. Guidelines suggest that an equivocal lesion, ultimately determined to represent an HCC, should be retrospectively adjudicated to the time it was first observed. It is therefore possible to exhibit a TTP of 0 if a baseline equivocal lesion was only later confirmed to be HCC. Although unlikely, observing this phenomenon weakens any TTP/survival correlation.

The fourth issue relates to the need to capture HCC-related portal vein thrombosis in response guidelines. Despite no change in index lesion size, HCC treatment may result in the retraction/disappearance of portal vein thrombosis (PVT). We acknowledge that mRECIST appropriately labels PVT as non-target with subjective response/progression assessment. Imaging tools that objectively/consistently quantify this relevant finding are needed.

The fifth point involves the interobserver reproducibility of measuring the longest uni/bidimensional diameter of enhancing tissue. While RFA may result in clear zones of necrosis and viable tissue, this is not the case with embolotherapies. There are challenges when multiple readers attempt to reliably define the same (or comparable) areas of enhancing tissue following embolotherapy. This is a critical issue needing further investigation, with solutions that may potentially require automated imaging tools.

Finally, and potentially most importantly, the mechanism of action and the time-dependence of response are often ignored. Embolic therapies lead to reduced tumour enhancement because of vascular occlusion. Since this finding may be observed on a contrast scan immediately after embolization, this cannot simply be labeled as necrosis. Alternatively, non-embolic therapies (Yttrium-90/radiotherapy/systemic) require time for response to manifest and in fact, may not lead to pronounced “necrotic” features. The lack of reduction in enhancement does not necessarily suggest treatment failure. Rather, it may represent tissue in the process of undergoing cell death, with lack of enhancement observed at a later date. Furthermore, although systemic agents may lead to reduced enhancement, this finding of “necrosis” may not necessarily represent cell death. In fact, tumoural enhancement may quickly return once the systemic agent is discontinued, suggesting hypoenhancement may not necessarily represent “necrosis” as we understand it pathologically.

The enthusiasm for new imaging methodologies should be tempered until more controlled studies are completed, including radiology–pathology correlation. The above mentioned methodological complexities/nuances, among others, need to be incorporated in future versions of guidelines as we believe this granularity of detail is essential when reporting response in HCC studies.

When it comes to HCC and response assessment, there is still a lot of work to do including standardisation, interobserver reproducibility, volume analysis, radiology–pathology correlation and imaging surrogates of survival. While automated software appears to be an attractive tool for response assessment, further research and validation are needed before being able to implement these in routine clinical care.
Emerging Systemic Therapies on Advanced Hepatocellular Carcinoma

Chairs: Joong-Won Park, MD, PhD (Republic of Korea) and Tim Meyer, MD, PhD (United Kingdom)

Although a significant survival advantage was achieved with sorafenib, prolongation of survival was modest, even in the cases of Child-Pugh class A. Unfortunately, subsequent RCTs in the first-line or the second-line setting with potent molecular targeted agents (MTAs) (sunitinib, brivanib, linifanib, erlotinib, everolimus, ramucirumab, ADI-PEG) resulted in failure suggesting that tumour heterogeneity and a lack of predictive response biomarkers remain a challenge. A recently reported first line trial of doxorubicin combined with sorafenib was also negative but, in the second line, the oral multi-kinase inhibitor regorafenib has been shown to improve survival compared with placebo, and this represents the first positive randomised trial systemic therapy since the approval of sorafenib.

There are a number of ongoing or unreported phase III studies including a second line trial of Cabozantinib (XL184), a RTK inhibitor of c-MET/VEGFR2, and a first line trial of Lenvatinib, an oral TKI against VEGFR, FGFR, RET, KIT and PDGFR. Additionally, a number of stratified trials are in progress including Tivantinib, a selective, non-ATP-competitive inhibitor of c-MET, which is being evaluated in patients with MET-high tumours, Ramucirumab for patients with AFP >400, Refametinib in RAS mutated tumours and BLU9931, a highly specific FGFR4, for which FGF19 expression is a selection criteria.

There is also increasing interest in immunotherapy approaches with very promising data reported for Nivolumab in a large phase II trial. Overall, the response rate was 16% and Nivolumab is now being evaluated in first and second line randomised trials.

Liver Transplantation vs. Resection for Hepatocellular Carcinoma

Chair: Katsuhiko Yanaga, MD, PhD (Japan)

Hepatocellular carcinoma (HCC) complicates patients with concomitant liver diseases. In Western countries, liver cirrhosis is generally regarded as a contraindication to hepatic resection, while in Eastern countries where cadaveric organ donation is scarce, liver transplantation is often reserved for advanced liver cirrhosis with non-advanced HCC. However, recent studies are showing good results in extended criteria such as resection in patients with portal hypertension, and liver transplantation with extended criteria or after down-staging. During this luncheon, these new data are presented and discussed with the audience.

An Update on Risk Factors for Cholangiocarcinoma

Chairs: Shahid A. Khan, MD, PhD (United Kingdom) and Lewis R. Roberts, PhD (USA)

There are well established risk factors for cholangiocarcinoma but these vary geographically around the world. Over the last few years, although increasing knowledge has accumulated regarding these risk factors, including for different types of cholangiocarcinoma, their individual contributions as risk factors remain unclear. The aim of this session is to analyse established and emerging potential risk factors by a systematic examination of the literature, including case-control series from geographically diverse regions. I will also provide a summary of changing patterns of incidence and mortality rates of cholangiocarcinoma from the international literature.
**General Session 4: Staging and Curative Treatments**

Chairs: Bruno Sangro, MD, PhD (Spain) and Myron Schwartz, MD (USA)

**O-021 The Detection of Circulating Tumour-Initiating Cells for Diagnosis, Prognosis and Therapeutic Response Evaluation in Hepatocellular Carcinoma: A Large-Scale, Multicentre Study**

XR Yang, W Guo, YF Sun, J Zhou, J Fan

1) Zhongshan hospital, Fudan University, Shanghai, China

**O-022 Recurrence Patterns and Disease Free Survival after Resection of Intrahepatic Cholangiocarcinoma: Preoperative and Postoperative Prognostic Models**

A Doussot, M Gönen, J Wiggers, B Groot Koerkamp, R DeMatteo, D Fuks, P Allen, O Farges, T Kingham, J Regimbeau, M D’Angelica, D Azoulay, W Jarnagin

1) CHU Henri Mondor, PARIS, France, 2) Memorial Sloan Kettering Cancer Center, New York, United States, 3) Memorial Sloan Kettering Cancer Center, New York, United States, 4) Erasmus Medical Center, Rotterdam, Netherlands, 5) Institut Mutualiste Montsouris, 6) Hospital Beaujon, PARIS, 7) CHU Amiens, Amiens, France

**O-023 Early Detection and Curative Treatment of Hepatocellular Carcinoma: A Cost Effectiveness Analysis Based on Prospective French Cohorts (ANRS CO12 CirVir and Changh)**

I Durand-Zaleski, B Cadier, J Bulsei, P Nahon, O Seror, A Laurent, I Rosa, R Layese, C Cagnot, K Chevreuil


**O-024 A Propensity Score Analysis on Survival Benefit of Liver Resection for Hepatocellular Carcinoma Associated with Portal Vein Invasion Using Nationwide Survey Data in Japan**


1) The University of Tokyo, 2) School of Public Health University of Tokyo, 3) Nihon University School of Medicine, Tokyo, 4) Shinshu University School of Medicine, Matsumoto, 5) Kinki University School of Medicine, Osaka, 6) Kobe University Graduate School of Medicine, Kobe, 7) Keio University School of Medicine, Tokyo, 8) Kurume University Hospital, Kurume, 9) Kanazawa University Hospital, Ishikawa, 10) Musashino Red Cross Hospital, Tokyo, Japan

**O-025 Ten-Year Outcomes of Radiofrequency Ablation for Hepatocellular Carcinoma: A Nomogram Study of the Albumin-Bilirubin Grade**

PC Chen, CW Su, YY Chien, WY Kao, KC Fang, TI Huo, YH Huang, MC Hou, HC Lin, JC Wu

1) Taipei Veterans General Hospital, 2) National Yang-Ming University, 3) Taipei Veterans General Hospital, 4) Taipei Medical University Hospital, 5) Taipei Medical University, Taipei, Taiwan, Republic of China, 6) National Yang-Ming University, Taipei, Taiwan, Republic of China, 7) National Yang-Ming University, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China, 8) Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China

**O-026 Substaging of Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma by Tumour Factors and Liver Function**

D Lee, H Yim, S Na, S Kim, S Suh, J Hyun, S Jung, Y Jung, J Koo, J Kim, Y Seo, J Yeon, S Lee, K Byun, S Um

1) Korea University Ansan Hospital, 2) Korea University Guro Hospital, 3) Korea University Anam hospital, Seoul, Korea, Republic Of
Molecular Classification of Hepatocellular Adenomas in Clinical Practice
Jean-Charles Nault, MD (France)

Hepatocellular adenomas (HCA) are rare benign liver tumours developed in young women using oral contraception. Symptomatic bleeding is the most frequent complication with a frequency between 10 and 20% whereas malignant transformation in HCC is observed in 4 to 5% of HCA in surgical series. A genotype/phenotype classification linked with risk factors, clinical, pathological and radiological features and based on molecular analysis has revealed that HCA are divided into several subtypes: HNF1A mutated HCA, inflammatory HCA, HCA with mutations in exon 3 of CTNNB1 (coding for β-catenin), HCA with mutations in exon 7 and 8 of CTNNB1, HCA with both CTNNB1 mutation and inflammatory phenotype and unclassified HCA. This molecular classification could be used in pathological routine practice using a panel of antibodies and has been validated by several groups worldwide. The description of the molecular heterogeneity of HCA has led to the identification of new risk factors (HNF1A germline mutation and liver adenomatosis, obesity and inflammatory HCA) and improved invasive and noninvasive diagnostic techniques (using MRI and immunohistochemical analysis), evaluation of prognosis, and treatment (association of CTNNB1 exon 3 mutations with the risk of malignant transformation). Recent studies have deciphered the multistep process of malignant transformation with CTNNB1 exon3 mutations as an early genetic event and TERT promoter mutations and telomerase reactivation at the last step of the process. The translation of genomic studies in the clinical care of patients with HCA is an example of the role of genotype/phenotype analyses in modern translational studies.

What is New in Hepatocellular Adenoma Morphological Types?
Valérie Paradis, MD, PhD (France)

Hepatocellular adenomas (HCA) encompass various types of clonal benign hepatocellular proliferations characterised by molecular and morphological features defining three main subtypes (1). The pathomolecular classification of HCA recognises (1) HCA inactivated for HNF1A (H-HCA), (2) Inflammatory HCA (I-HCA), and (3) β-catenin activated HCA (β-HCA). In less than 5% of cases, no specific morphological features, nor gene mutations are present (Unclassified HCA). Importantly, risks of complications, mostly haemorrhage and malignant transformation into hepatocellular carcinoma (HCC), are closely associated with specific subtypes and tumour size as well. Most striking morphological features of the different subtypes are steatosis, sinusoidal dilatations and inflammatory infiltrates, and cellular atypias, respectively. Importantly, immunophenotypical hallmarks are also characteristic for the different subtypes, loss of LFABP hepatocellular expression for H-HCA, hepatocellular positivity for SAA and CRP for I-HCA, and nuclear β-catenin expression for β-HCA.

The recent advances obtained in the field of HCA include:
1. The identification of new β-catenin mutations involving exons 7 and 8, that can be combined with mutations defining the I-HCA (gp130 and GNAS), without any association with increased risk of malignant transformation,
2. The identification of additional mutations resulting in the activation of the JAK/STAT pathway in the group of I-HCA,
3. The performance of imaging and biopsy for HCA subtyping
4. The characterisation of HCA developed in specific context, including vascular liver disorders
5. The clinical impact of the pathomolecular classification on the management of patients with HCA which may take into account gender, HCA subtype and tumour size.
Surgery, Resection or Ablation for Small Adenoma
Thomas van Gulik, MD, PhD (Netherlands)

Hepatocellular adenoma (HCA) larger than 5cm is an indication for resection because of the risk of bleeding or malignant degeneration. The other indication is abdominal complaints ascribed to tumours even smaller than 5cm although correlation with symptoms is difficult. Since HCA is a benign tumour, limited resections usually suffice to remove all tumour tissue. Most of these tumours are amenable to parenchyma sparing techniques in which local excision or enucleation of the lesion suffices. Depending on location and size, the lesions are preferably treated by laparoscopic excision. Larger lesions however, are excised using the open approach. In specialised centers, HCA is resected without mortality and only minor complications. Resection of HCA proves beneficial in case of abdominal complaints as 88% in our series showed symptom relief. Especially patients with lesions in the left-lateral segments that give rise to gastric complaints benefit from surgery. However, size was not correlated with symptoms in our study. Percutaneous radio frequency ablation (RFA) has been performed for HCA with good results and cost-efficiency. However, the procedure is limited by the location and size of the tumour. In conclusion, most patients with HCA require limited surgery and excision can be carried out with low morbidity and without mortality. When feasible, a laparoscopic resection is preferred over an open procedure. Finally, patients with symptoms may benefit from surgery with a high chance of symptom relief (88%).

Radiologic-Pathologic Correlation of Hepatocellular Adenomas
Alexander Kagen, MD (USA)

Hepatocellular adenoma (HCA) detection and characterisation has evolved over the years as technology has progressed. In particular, and with respect to imaging, detection and characterisation of liver disease has improved as imaging equipment (both in terms of hardware and software) has advanced. More recently, the introduction of hepatocyte-specific contrast agents (such as gadoxetic acid) in Magnetic Resonance Imaging (MRI), has helped advance the field even further and has shown to play a role in HCA subtype analysis. However, perhaps the most significant advances in HCA characterisation have resulted from the bridging of radiologic and pathologic disciplines. By using a multidisciplinary approach of expert opinion on subtype analysis, care pathways may be proposed based on what is seen macroscopically by in vivo imaging, and more importantly, what cannot be reliably diagnosed without pathology.
## Sunday, 11 September 2016

<table>
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| 07:30 – 08:30 | **Bristol-Myers Squibb Symposium: Evolving Landscape of Immuno-Oncology Research in HCC**  
Pacific Ballroom  
Conference Floor  
Chair: Anthony El-Khoueiry, MD (USA)  
Welcome and Introductions  
Anthony El-Khoueiry, MD (USA)  
Harnessing the Immune System in Cancer Research  
Anthony El-Khoueiry, MD (USA)  
Shifting Landscape in HCC – US/EU Perspective  
Shifting Landscape in HCC – Asian Perspective  
Joong-Won Park, MD, PhD (Republic of Korea)  
Biomarker Research in HCC  
Jörg Trojan, MD (Germany)  
Q&A and Meeting Close |
| 08:30 – 09:15 | **ILCA General Assembly**  
Pacific Ballroom  
Conference Floor  
| 09:15 – 09:45 | **Coffee & Networking Break**  
British Columbia Ballroom  
Conference Floor  
| 09:45 – 10:45 | **State-of-the-Art Lecture 2: Assessing Hepatocellular Carcinoma Risk**  
Pacific Ballroom  
Conference Floor  
Chairs: Josep M. Llovet, MD (Spain/USA)  
Speaker: Morris Sherman, MD, PhD (Canada)  
Global risk factors for hepatocellular carcinoma (HCC) are well known, hepatitis B and cirrhosis of any cause. However, within those broad categories only a minority of individuals will ever develop HCC. Thus a large proportion of these groups will undergo HCC screening that is not really necessary. The challenge is to identify those who are at highest risk of developing HCC. To this end several risk assessment scores have been developed, each in specific populations. For hepatitis B there is the REACH-B score or the GAG-HCC score, for cirrhosis there is the ADDRES score, the Toronto score and there is even a score for the general public developed in Taiwan, where HCC occurs with sufficient frequency in the general population to make this score worthwhile. None of these score are yet in general use or are included in guidelines, and their applicability in populations different that those in which they were originally developed is uncertain. The effect of treatment on risk is not captured by any of these scores. Although these scores have the potential to narrow the size of the at-risk population and reduce the number of candidates for screening a still further problem remains. Identifying who is at risk is not sufficient. It is also necessary to identify when they are at risk. In addition, there is a need to simplify screening by identifying methods that use blood tests only, reserving ultrasound for those at the highest risk. At present it is not possible to do this, but there is active research into these issues. |
General Session 5: From New Targets to Clinical Trials

Pacific Ballroom
Conference Floor

Chairs: Sandrine Faivre, MD, PhD (France) and Thomas Yau, MD (USA)

O-027 Prospective Randomized Controlled Phase III Trial Comparing the Efficacy of Sorafenib versus Sorafenib in Combination with Low-Dose Cisplatin/Fluorouracil Hepatic Arterial Infusion Chemotherapy in Patients with Advanced Hepatocellular Carcinoma

M Kudo1, K Ueshima1, O Yokosuka1, S Obi1, N Izumi2, H Aikata1, H Nagano2, E Hatano2, Y Sasaki2, K Hino2, T Kumaida2, K Yamamoto1, Y Imai1, Y Iwadou1, C Ogawa1, T Okusaka2, Y Arai2, F Kanai2, K Akazawa2

1Kindai University Faculty of Medicine, Osaka-Sayama, 2Chiba University Graduate School of Medicine, Chiba, 3Kyoyoundo Hospital, Tokyo, 4Japanese Red Cross Musashino Hospital, Musashino, 5Hiroshima University Hospital, Hiroshima, 6Osaka University Graduate School of Medicine, Osaka, 7Kyoto University, Graduate School of Medicine, Kyoto, 8Kumamoto University Graduate School of Medical Sciences, Kumamoto, 9Kawasaki Medical School, Kurashiki, 10Ogaki Municipal Hospital, Ogaki, 11Okayama University Medical School, Okayama, 12Ikeda Municipal Hospital, Ikeda, 13Hiroshima City Hospital, Hiroshima, 14Takamatsu Red Cross Hospital, Takamatsu, 15National Cancer Center Hospital, Tokyo, 16Nagata University, Niigata, Japan

O-028 Proliferation Markers are Associated with Met Expression in Hepatocellular Carcinoma and Predict Tivantinib Sensitivity in Vitro

S Rebouissou1,2,3,4, T La Bella1,2,3,4, S Rekik1,2,3,4, AL Calatayud1,2,3,4, N Rohr-Udilova5, P Bioulac-Sage6,7, G Couchy1,2,3,4, B Grasl-Kraupp4, J Zucman-Rossi1,2,3,4,9

1UMR-1162, Génomique fonctionnelle des Tumeurs solides, IUH, INSERM, 2Labex Immuno-Oncology, Sorbonne Paris Cité, Faculté de Médecine, Université Paris Descartes, 3Université Paris Diderot, Paris, 4Sorbonne Paris Cité, UFR SMBH, F-93000, Université Paris 13, Bobigny, France, 5Department of Medicine III, Medical University of Vienna, Vienna, Austria, 6UMR- 1053, INSERM, 7CHU de Bordeaux, Department of Hepatology, Hôpital Saint-André, Bordeaux, France, 8Department of Medicine I, Division: Institute of Cancer Research, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, 9Hôpital European Georges Pompidou, F-75015, Assistance Publique-Hôpitaux de Paris, Paris, France

O-029 Radiation Improves Antitumor Effect of Immune Checkpoint Inhibitor, Anti-PD-L1 in Murine Hepatocarcinoma Model

J Seong1, KJ Kim1, JH Kim1, EJ Lee1

1YONSEI UNIVERSITY, seoul, Korea, Republic Of

O-030 Cost-Effectiveness of Sorafenib Therapy for Advanced Hepatocellular Carcinoma: An Analysis of the Seer-Medicare Database

N Parikh1, V Marshall2, A Singal3

1University of Michigan, Ann Arbor, United States, 2University of Michigan, Ann Arbor, 3UT Southwestern Medical Center, Dallas, United States

O-031 Transcriptional Deregulation in Hepatoblastoma Patients Points to a New Oncogenic Mechanism and Treatment

AA Raymond1, K Hooks2, J Audoux3, H Fazili2, S Lesjean1, L Brugière3, M Fabre3, A Rullier3, MA Buendia1, T Commes3, C Grosset2

1INSERM 1035, 2Université de Bordeaux, Bordeaux, 3Université de Montpellier, Montpellier, 4Gustave Roussy Institute, Villejuif, 5Hôpital Necker-Enfants Malades, Paris, 6Centre Hospitalier Universitaire, Bordeaux, 7Centre Hospitalier Universitaire –Hôpital universitaire Paul Brousse, Villejuif, France

O-032 MTOR Inhibitor for the Treatment of AKT/YAP[S127A] Driven Cholangiocarcinoma in Mice

X Chen1, S Zhang1, D Calvisi2

1UCSF, San Francisco, United States, 2University Medicine Greifswald, Greifswald, Germany
Practicalities
Practicalities

About Vancouver

Majestic mountains, a sparkling ocean, rainforests and beautiful foliage. All four seasons make Vancouver one of the most beautiful cities in the world. Canada is known for its people’s friendly nature, and Vancouver’s citizens take great pride in their welcoming, clean and safe streets – day or night, all year round.

One of Vancouver’s greatest strengths is its diversity and whether you are visiting for a day or a month, there is plenty to explore. Pack a picnic and enjoy one of the city’s many botanical gardens, hop onto a boat and go whale watching just minutes from the city, or explore the many landmark sights of the city – there is so much to see.

Currency and Banking

The official currency is the Canadian Dollar (CAD). Most foreign currencies can be changed in banks and hotels or exchange offices. ATMs are open 24 hours and are widely available. Credit cards are accepted in nearly all shops, restaurants, and hotels.

Electricity

The standard plug in Vancouver uses 120 Volts, using the two plug socket. For European electrical appliances, you may need a voltage transformer, as well as an adaptor for the plug. If your appliances are dual voltage you do not need a transformer.

Emergency Phone Number

For Police, Fire service or Medical service, call 911. It can be dialled free of charge from any telephone.

Health and Safety

Vancouver is a very safe place to be. However, as with any large city, normal precautions should be taken. Secure your purse or wallet, stay in well-lit areas and do not walk around in less-travelled areas late at night. The best protection against pickpockets: hang on tightly to your bag in the throng of public transit, avoid dark parks and corners at night and stow valuable items like cameras in your bag rather than having them hang from your neck for all to see. If you need to contact the emergency services, ring 911.

Insurance and Liability

ILCA is insured only to meet claims arising from incidents caused by the organisers and their equipment. Participants, exhibitors and visitors are strongly recommended to be properly insured against accidents they may suffer when travelling and during the conference.

Public Transport

The easiest and cheapest way to get around Vancouver is by using the extensive public transport available. This includes Tram, Bus and Skytrain. Rapid transit (automated trains that run above and below ground) consists of two lines, the Expo Line and the Millennium Line. A third system, called Canada Line, provides the travel from the airport to Downtown Vancouver.

There is also bus service provided throughout the day. In addition to traditional buses there are express lines that make fewer stops.

The SeaBus crosses the Burrard Inlet to provide travel between Waterfront Station in Downtown Vancouver and Lonsdale Quay in North Vancouver.

Taxis

Usually taxi ranks can be found in front of hotels or important landmarks. However, hailing a taxi from the curb is quite common as well. Otherwise you can always call a cab or book online.

- Vancouver Taxi: 604-871-1111
- MacLure’s Cabs: 604-831-1111
- Yellow Cab: 604-681-1111

Restaurants

The cuisine of Vancouver is very diverse and Asian cooking of all kinds is incredibly popular. Izakayas, or Japanese-style tapas, have taken the city’s habitats by storm in recent years for their atmosphere and unique dishes, and hot-dogs are being served with seaweed and okonomiyaki sauce.

Due to its location, fresh fruits and vegetables can be found everywhere as well as just-caught seafood. Also locally made cheese is something that should not be missed.

One thing can be guaranteed when you visit Vancouver though: diversity. For years Vancouver has been known for its multiculturalism and the great variety of expression that has emerged as a result, whether through music, art, or cuisine.

Taxes and Tipping

In Canada, price labels do not include tax and service and the tax is usually added when paying for goods (the latter is around 12% of the total price). Tipping around 15 to 20 percent of the total bill is standard practice.

Time Difference

Vancouver is 8 hours behind of GMT (GMT -8).
About ILCA

The International Liver Cancer Association (ILCA) is the only international organisation devoted exclusively to liver cancer research for experts from all related disciplines.

ILCA aims at creating an international multidisciplinary forum to address the increasing incidence of liver cancer through the enhancement of the knowledge of clinical, translational and basic research, ultimately creating novel preventive, diagnostic and therapeutic strategies.

The purpose for which ILCA was established is the advancement of medical education, research and clinical care in the field of liver cancer.

Please come and visit us at the ILCA stand where the ILCA Team will be delighted to provide any information you may wish to have on ILCA activities, membership and future conferences. Information is also available at www.ilca-online.org.

Badges

For security purposes, all participants will be issued with a conference badge onsite, which must be worn at all times during the conference and at any other officially related functions.

Certificate of Attendance

A certificate of attendance will be sent by email after the conference.

Conference Capture

The main sessions of the conference will be recorded and made available to ILCA members and conference participants at www.ilca-online.org shortly after the event. You will be notified by email when the capture is available.

ILCA thanks its Diamond Partner, Bayer Healthcare, for making the Conference Capture possible through an unrestricted educational grant.

Disclaimer

ILCA and/or the conference organisers will not be liable for personal injury or safety of any participant, nor for any loss or damage of private property of registered participants during the conference.

e-Poster Viewing Tours

e-Poster Viewing Tours will be held on Saturday, 10 September 2016 from 10:00 – 11:00 and from 15:45 – 16:45.

Both of the e-Poster Viewing Tours will be opened by ILCA’s prominent scientists. Prof. Richard Finn, ILCA President, and Prof. Jessica Zucman-Rossi, ILCA Executive Secretary, will open the morning tour (from 10:00 – 11:00). Prof. Morris Sherman, ILCA Treasurer, and Prof. Xin-Wei Wang, ILCA Governing Board Member, will open the afternoon tour (from 15:45 – 16:45). The e-Poster Viewing Tours will be partly dedicated to the 40 top scored abstracts displayed as paper board posters.

e-Posters

e-Posters will be displayed in the British Columbia Ballroom, Conference Floor, throughout the conference and e-Poster presenters will have opportunity to introduce their research findings described in their e-Poster to the Conference participants during the specific e-Poster Viewing Tours.

Paper board posters

Paper board poster presentations will take place at the beginning of each e-Poster Viewing Tour in the Poster of Excellence Area (British Columbia Ballroom, Conference Floor). Presenters will be invited to give a brief summary of their major findings described in the poster. During the e-Poster Viewing Tours, all abstract authors must ensure that at least one author per poster is in attendance to present the research and answer any questions from visitors in attendance. Please refer to the Book of Abstracts for details on poster locations during the e-Poster Viewing Tours.

General Sessions – Oral Communications

Presenters are allowed 10 minutes for each presentation, followed by 5 minutes for questions and answers. They must be present in the corresponding room at least 15 minutes before the session starts.

ILCA Pre-Conference Workshop on Immunopathogenesis and Immunotherapy in HCC

The main objectives of this workshop will be to understand the need for precision liver cancer models due to liver tumour molecular heterogeneity and complex tumour microenvironment, to grasp pros and cons of the current models and to develop consensus criteria to define most clinically relevant pre-clinical models.

The members of the Workshop Organising Committee, Eli Pikarsky, Xin-Wei Wang and ILCA Executive Secretary Jessica Zucman-Rossi, will drive the content of the workshop and will subsequently work on producing the manuscript based on the contribution from the speakers and participants.
As a result of this workshop, another edition of ILCA Consensus Guidelines will be produced.

**Industry Exhibition**
The Industry Exhibition will take place in the British Columbia Ballroom, Conference Floor. Opening hours are as follows:

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| Friday, 9 September | 10:30 – 11:00 Coffee break in exhibition area  
12:45 – 14:45 Session breaks in the exhibition area and lunch in the plenary room  
16:15 – 16:45 Coffee break in exhibition area  
18:15 – 19:00 Welcome Reception in exhibition area |
| Saturday, 10 September | 10:00 – 11:00 Coffee, Networking Break and e-Poster Viewing Tour  
12:30 – 14:15 Session break and lunch  
15:45 – 16:45 Coffee, networking break and e-Poster Viewing Tour |
| Sunday, 11 September | 09:15 – 09:45 Coffee break in the exhibition area |

**Junior Investigator Awards**
ILCA will recognise extraordinary achievements in liver cancer research across disciplines and support the professional development of four junior investigators in training. The awards will be given for novel and significant liver cancer research across the fields of basic cancer research; translational cancer research; cancer diagnosis; the prevention of cancer; or cancer patients treatment.

The investigators who submit the best clinical oral and poster presentations and the best basic-translational oral and poster presentations will be honoured on Saturday, 10 September 2016 during the Plenary Session of the 10th ILCA Annual Conference.

**Nelson Fausto Recognition Award**
ILCA will grant the Nelson Fausto Recognition Award at the 10th ILCA Annual Conference to recognise a senior professional for outstanding contributions to liver cancer science.

**Official Language**
The official language of the conference is English. Simultaneous translation will not be provided.
PLEASE JOIN US AT ILCA FOR A SYMPOSIUM PRESENTED BY BRISTOL-MYERS SQUIBB

EVOLVING LANDSCAPE OF IMMUNO-ONCOLOGY RESEARCH IN HCC

Sunday, September 11, 2016 | 7:30–8:30 AM
Pacific Ballroom
Fairmont Hotel
Vancouver, Canada

EXPERT PANELISTS:

Anthony El-Khoueiry, MD
Associate Professor of Clinical Medicine
Norris Comprehensive Cancer Center,
Keck School of Medicine of USC

Jörg Trojan, MD
Professor
University Hospital Frankfurt,
Goethe University

Joong-Won Park, MD, PhD
Professor, Principal Scientist
National Cancer Center Korea

TOPICS INCLUDE:

Harnessing the Immune System in Cancer Research
I-O Research in HCC
Regional Variations in the HCC Landscape
Conference Area Floor Plan

Conference Floor
Level 1

Discovery Floor
Level 2
Exhibition Area

- REGISTRATION DESK
- ENTRANCE
- CATERING
- E-POSTERS
- BAYER
- CELSION
- BTG
- SIRTEX

Practicalities
About the Conference
ENROLLING NOW: HEPATOCELLULAR CARCINOMA TRIAL

NCT02435433 (REACH-2)

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-line Therapy With Sorafenib*

Key Inclusion Criteria
- Hepatocellular carcinoma (HCC)
- Barcelona Clinic Liver Cancer stage C or B that is refractory or not amenable to locoregional therapy
- At least one target lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Child-Pugh class A
- Baseline serum AFP ≥403 ng/mL
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Received prior sorafenib as the only systemic therapeutic intervention and experienced radiographically confirmed disease progression during or after discontinuation or discontinued sorafenib because of intolerance
- Adequate hematologic and biochemical parameters

Key Exclusion Criteria
- Uncontrolled hypertension
- Ecchymosis or gastrointestinal varices requiring treatment
- Received prior anti-VEGF pathway therapy other than sorafenib
- Hepatic or locoregional treatment after sorafenib
- Ongoing or recent hepatorenal syndrome
- Prior liver transplant
- Major surgery within 28 days
- Arterial thrombotic event within 6 months
- Received prior therapeutic anticoagulation or chronic antiplatelet agents, including nonsteroidal anti-inflammatory drugs
- History of or current hepatic encephalopathy [any grade] or ascites grade ≥2

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02435433].

* This clinical trial is being conducted globally. REACH-2 eligibility criteria, including baseline serum AFP criteria, are based on the efficacy and safety results of REACH.

For more information, please contact the Lilly Clinical Trials Support Center at 1-877-CTLILLY.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
Exhibitors, Sponsors, Media and other Partners
ILCA warmly thanks all its partners and sponsors for their involvement in ILCA 2016.

Diamond Partner

Bayer is committed to delivering SCIENCE FOR A BETTER LIFE by advancing a portfolio of innovative treatments. Bayer’s oncology franchise now includes three oncology products and several other compounds in various stages of clinical development. Together, these products reflect the company’s approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated. More information is available at www.bayer.com

Gold Partners

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit www.bms.com or follow us on Twitter.

Sirtex Medical is actively engaged in the field of liver-directed therapies for cancer patients. Our innovative technology, SIR-Spheres® microspheres (Yttrium-90 resin beads), was approved in 2002 for use in the treatment of a variety of unresectable liver tumours as well as in hepatocellular carcinoma within the European Union under a CE Mark. SIR-Spheres® microspheres are presently used at more than 250 institutions in Europe. ™SIR-Spheres is a Registered Trademark of Sirtex SIR-Spheres Pty Ltd

Sponsors & Exhibitors

BTG is an international specialist healthcare company. Our growing portfolio of Interventional Medicine therapies is designed to advance the treatment of liver tumours, advanced emphysema, severe blood clots, and varicose veins. No company does more to help doctors in their quest to see more, reach further and treat smarter. www.btg-im.com

Celsion is a fully-integrated oncology company focused on developing a portfolio of innovative cancer treatments, including directed chemotherapies, immunotherapies and RNA- or DNA-based therapies. The Company’s lead program is ThermoDox®, a proprietary heat-activated liposomal encapsulation of doxorubicin, currently in a phase III clinical trial (OPTIMA Study) for primary liver cancer.

For more than 50 years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly’s commitment to people with cancer, please visit www.LillyOncology.com.
Exhibitors, Sponsors, Media and other Partners

Media Partners
ILCA thanks the following scientific publications for their support:

- AMOR: Advances in Modern Oncology Research
- APS: American Physiological Society
- EJSO: European Journal of Surgical Oncology
- EMJ: European Medical Journal
- Hepatic Oncology
- Hepatoma Research
- THE LANCET Oncology

Partner Societies
ILCA has established partnerships with several professional scientific societies and institutions that share the goal of advancing multidisciplinary research in liver cancer.

Related entities that have welcomed and/or supported ILCA since its foundation are:

- American Association for Cancer Research (ACCR)
- American Association for the Study of Liver Diseases (AASLD)
- American Hepato-Pancreato-Biliary Association (AHPBA)
- Asian Pacific Association for the Study of the Liver (APASL)
- Cardiovascular and Interventional Radiology European Society (CIRSE)
- European Association for the Study of the Liver (EASL)
- European Liver and Intestine Transplant Association (ELITA)
- International Agency for Research on Cancer (IARC)
- Japanese Society of Hepatology (JSH)
- National Cancer Institute (NCI)
- World Gastroenterology Organisation (WGO)
CONCISE, PEER-REVIEWED, OPEN ACCESS OPINION based ARTICLES & VIDEOS from KEY OPINION LEADERS ACCESS and DOWNLOAD FREE

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Speakers’ Portfolio
Speakers’ Portfolio

► Jordi Bruix, MD, PhD (Spain)

Jordi Bruix, MD, PhD, is Professor of Medicine at the University of Barcelona and Director of the Barcelona Clinic Liver Cancer (BCLC) Group within the Liver Unit at the Hospital Clinic of Barcelona, Spain.

Prof. Bruix is a Member of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). He founded the International Liver Cancer Association (ILCA) and was its president from 2006 to 2009. He has been Associate Editor of *Journal of Hepatology*, *Liver Transplantation* and *Hepatology*, and has been appointed to Editor in *Chief of Seminars in Liver Disease*.

Prof. Bruix has been the principal investigator of studies and clinical trials that have changed practice in the field of hepatocellular carcinoma (HCC), including development of diagnostic criteria and prognostic models and establishment of chemoembolization and sorafenib and regorafenib as conventional therapy. He developed the BCLC staging and treatment strategy that has been endorsed by several international scientific associations to guide management of patients with HCC. He has also authored more than 200 original investigations and led the development of Evidence-Based Practice Guidelines for Hepatocellular Carcinoma at EASL, AASLD, and the World Gastroenterology Organisation (WGO). He has been nominated Scientific Director of the Spanish Network for Research in Hepatic and Digestive Diseases within the Spanish National Institute of Health.

► Ann-Lii Cheng, MD, PhD (Taiwan)

Ann-Lii Cheng is distinguished Professor and Director of the NTU Cancer Center of National Taiwan University. He received his MD degree, PhD degree, and his specialty training in internal medicine and medical oncology at the Medical School of the National Taiwan University. In 1990, he was a Research Fellow at the Comprehensive Cancer Center of the University of Wisconsin, Madison, USA.

Dr. Cheng has been actively involved in basic and translational research in hepatocellular carcinoma and has published more than 300 peer-reviewed articles. He was elected as Fellow of American Association for the Advancement of Science (AAAS) in 2007. He received the national award of “outstanding contributions for science and technology” in 2008, and a most prestigious national award for academic excellence in 2010. He served as president of the Taiwan Oncology Society during 2009-2011. He was elected as National Chair Professorship in 2013, and became the founding director of NTU Cancer Center since 2013.

► Haesun Choi, MD (USA)

Haesun Choi is a Radiologist and Professor at the University of Texas MD Anderson Cancer Center. She is specialised in body MRI and CT. Her clinical experience is focused on liver imaging, male and female pelvic MRI, including the prostate, uterus, cervix and rectum, functional MRI, including dynamic contrast enhanced (DCE) - MRI, DWI and spectroscopy (MRS). She has extensive clinical experience on prostate MRI parallels with building up a highly successful prostate imaging programme at MD Anderson Cancer Center.

Over the last 10 years, Dr. Choi has been involved in the development and application of the non-invasive methods for liver fat and iron quantitation and evaluation of the underlying liver fibrosis and hepatocellular carcinoma. One of the most important Dr. Choi’s contributions in research as well as clinical patient care, as an oncologic radiologist, is provision of accurate and reliable measures of tumour response, which has led to develop the so called “Choi Criteria”. She has been involved in multiple clinical drug development trials as a site reader, a central reader and a consultant for the pharmaceutical companies.

She currently serves as a member of the imaging committee of SWOG and a member of NET task force of GI steering committee of NCI.
Sabine Colnot, PhD (France)

Sabine Colnot, PhD, is a Research Director at the French National Institute for Health and Medical Research (INSERM) in Paris, at Cochin Institute. Her lab focuses on characterising in vivo key steps of liver carcinogenesis, at the molecular and cellular levels. The team generates and uses genetically-engineered modified mice to reproduce mutations occurring in hepatocellular cancer, with a focus on the beta-catenin/Apc signaling. In particular, they showed that beta-catenin when aberrantly activated, plays a major role in liver carcinogenesis. They also demonstrated that conversely, a physiological Wnt/beta-catenin signaling controls embryonic hepatogenesis and liver adult metabolic zonation.

Richard Kinh Gian Do, MD, PhD (USA)

Richard K. Do joined the Department of Radiology, Body Imaging Service, at Memorial Sloan Kettering (MSK) in 2009. Dr. Do received his MD PhD from Weill Cornell Medicine. His residency training in Radiology and MR imaging fellowship were completed at NYU Langone Medical Center. This was followed by his appointment at MSK as an Assistant Attending.

Dr. Do serves as the Radiology Co-Chair of the Hepatopancreatobiliary Disease Management Team at MSK. He is the reference radiologists on over a dozen clinical trials using REGIST 1.1 for tumour response assessment. He is a current member of the American College of Radiology Steering Committee for LI-RADS: Liver Imaging Reporting and Data Systems, and is the Chair of its Tumor Response Working Group. Dr. Do has participated as a speaker on hepatopancreatobiliary disease at educational programmes at multiple universities, the Radiological Society of North America and International Society of Magnetic Resonance in Medicine.

Gen-Sheng Feng, PhD (USA)

Gen-Sheng Feng is a Professor of Pathology and Molecular Biology at the University of California San Diego (UCSD). He is a Co-Director of the Primary Liver Cancer Task Force of the Moores UCSD Cancer Center. Dr. Feng’s research aims at understanding the intertwining of signaling pathways in health and diseases, by focusing on tyrosine phosphatase Shp2 that he discovered during postdoc studies. His most recent work has uncovered pro- and anti-tumorigenic roles of Shp2 in hepatic and blood malignancies, and the current interests are in delineating molecular and cellular mechanisms that drive liver tumour initiation, in isolating and characterising liver tumour-initiating cells, and in dissecting the dynamic interplay between tumours and the hepatic microenvironment. The goal is to elucidate the anti-oncogenic effects of the classical oncoproteins in liver cancer, which will lead to development of better diagnostic and therapeutic recipes.
Richard Finn, MD (USA)

Richard Finn is an Associate Professor of Medicine in the Division of Hematology/Oncology at the UCLA David Geffen School of Medicine and co-director of the Signal Transduction Program in the Jonsson Comprehensive Cancer Center at UCLA.

He currently splits his time between patient care and laboratory and clinical research. His research interests lie in the development of molecular targeted agents and biomarkers in liver cancer and breast cancer. Dr. Finn has served as principal and sub-investigator in trials exploring the use of targeted therapies in breast and hepatocellular cancers. He has a particular interest in identifying predictive markers of response to novel therapeutics. His work has been published in journals such as *Lancet Oncology*, *Journal of Clinical Oncology*, *Cancer Research*, *Clinical Cancer Research*, *Hepatology*, *Cancer Cell* and elsewhere. Dr. Finn has also given oral presentations at major meetings including American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO), and International Liver Cancer Association (ILCA) annual meetings.

Dr. Finn is a member of ASCO, American Association of Cancer Research (AACR). He is a Senior Editor for *Hepatic Oncology* and is on the editorial board of *Clinical Cancer Research*. He is the current President of the International Liver Cancer Association (ILCA).

Peter R. Galle, MD, PhD (Germany)

Peter Galle majored in internal medicine at the Universities of Berlin and Marburg/Germany, Hammersmith Hospital, London/UK and University of Texas/USA and received his MD degree from Marburg University and PhD degree from Heidelberg University.

Initially he held a position as postdoctoral fellow in Molecular Biology at the Centre for Molecular Biology Heidelberg working on the replication of hepatitis B viruses. Afterwards he completed his residency in Internal Medicine and Gastroenterology at the University Hospital of Heidelberg. In 1998 he became Director of the I. Medical Department in Mainz and from 2005 – 2008 he held the CEO position of Mainz University Hospital.

He is member of several national and international societies such as the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), served as Co-editor for the *Journal of Hepatology* and is on the Editorial Boards of several other journals. He served as Congress President of the German Society for Digestive Diseases (DGVS) in 2014. He is member of the Executive Board and Past President of the International Liver Cancer Association (ILCA).

His research has focused on elucidating important aspects of apoptotic cell death in the liver, immune escape of tumour cells and on clinical and molecular aspects of hepatocellular carcinoma. He was awarded several prizes, amongst others the prestigious Tannhauser award, the highest prize of the German Society for Digestive Diseases. He has published more than 500 peer-reviewed papers.
Tim Greten, MD (USA)

Tim Greten received his medical training in Gastroenterology, Hepatology and Medical Oncology, which provides an ideal clinical background to treat patients with GI malignancies and to develop and test innovative approaches for the treatment of patients with primary liver tumours or liver metastasis. His research interest has been and continues to be to understand how tumours evade anti-tumour immunity in patients with primary and secondary liver cancer. A better understand of the liver-cancer-immunology complex will ultimately guide to novel immune based treatment approaches. In particular, he has been very interested in understanding the biology of myeloid derived suppressor cells, which we described in 2008 as one of the first groups as CD14+HLA-DRlo cells. Based on these initial studies in patients with liver cancer he studied these cells in multiple tumour models, both in mice and men. Very recently he started to explore how metabolic factors found in the context of fatty liver disease control anti-tumour immunity. These findings were published in Nature. As a Physician Scientist his major interest has always been to connect the basic research interest with the clinical experience. As a result, he has conducted a number of immunotherapy studies in HCC.

Mathias Heikenwälder, MD, PhD (Germany)

Mathias Heikenwälder is Professor at the German Cancer Research Center (DKFZ) and heads the department of “Chronic Inflammation and Cancer”. In the past his group has contributed to the understanding how hepatitis B and C virus induced chronic hepatitis causes liver cancer (e.g. Haybaek et al., Cancer Cell 2009). Moreover, his group has identified that activation of the Lymphotoxin beta receptor signaling pathway eliminates Hepatitis B virus by degradation of cccDNA in a non-hepatotoxic manner (Lucifora et al., Science 2014). Recently, his group has established a NASH mouse model in the context of a chronic metabolic syndrome in which an unepxected cross talk between CD8, NKT cells and hepatocytes was identified to trigger NASH development and NASH to HCC transition (Wolf et al., Cancer Cell 2014).

Klaus Hoeflich, PhD (USA)

Klaus Hoeflich has directed the FGFR4 and PRKACA programmes at Blueprint, and is a scientific leader with in-depth experience in small molecule drug development and 20 years of experience in studying kinases. Blueprint Medicines is focused on crafting highly selective kinase inhibitors for patients with genomically-defined diseases. Blueprint has advanced novel oncology therapeutics to the clinic, including BLU-554 for FGF19/FGFR4-dependent hepatocellular carcinoma and BLU-285 for KIT (exon 17 mutant) and PDGFRα (D842V) gastrointestinal stromal tumours, and has entered into strategic collaborations with Roche and Alexion for undisclosed targets. Prior to joining Blueprint Medicines, Prof. Klaus spent 11 years at Genentech in various roles and led biology efforts for MAPK pathway inhibitors, including CotellicTM (Cobimetinib).
Alexander Kagen, MD (USA)

Alexander Kagen, MD, is the Site Chair of Radiology at Mount Sinai West and Mount Sinai St. Luke’s in New York City. He has lectured nationally and internationally on imaging of the liver, prostate, and gastrointestinal systems. He has multiple peer-reviewed publications and research interests in MRI of the liver and vascular systems.

A regional authority in the field of Body MRI, he serves on local, national and international committees. He serves as Co-Chairman of the Radiology-Pathology working group of the American College of Radiology (ACR) Liver Imaging and Reporting Database System (LI-RADS), and is a member of the MR Prostate Imaging and Reporting Database System (MR-PI-RADS) Committee.

Dr. Kagen received his medical degree from the College of Medicine at SUNY Downstate Medical Center where he also completed his residency, after a medicine internship at Lenox Hill Hospital. He completed a fellowship in Body MRI at Johns Hopkins Hospital.

Shahid A. Khan, MD, PhD (United Kingdom)

Shahid A. Khan is a Consultant Physician and Hepatologist at St Mary’s Hospital, Imperial College Healthcare NHS Trust and Adjunct Reader at Imperial College London. He qualified from Guy’s Hospital Medical School in 1994 and underwent specialist training in the Northwest London. He was awarded a PhD for studies on liver cancer from the University of London in 2003. Dr. Khan is the lead author on the British guidelines for cholangiocarcinoma and co-author for the ILCA guidelines. He has published extensively in the international literature, including original research articles, reviews and book chapters. Dr. Khan is also Clinical Lead for Liver Cancer in the Dept of Hepatology, Director of the Gastroenterology/Hepatology BSc degree course and Admissions Tutor for Imperial College London Medical School.

Josep M. Llovet, MD (Spain/USA)

Josep M. Llovet is Professor of Research-ICREA in the BCLC Group, Liver Unit, IDIBAPS-Hospital Clinic of Barcelona (Spain), Director of the Liver Cancer Program and Full Professor of Medicine at the Mount Sinai School of Medicine, New York University (USA), and Professor at Faculty of Medicine, University of Barcelona. Professor Llovet obtained his degree in Medicine and Surgery from the University of Barcelona in 1986 and his PhD from the Autonomous University of Barcelona in 1995.

Prof. Llovet has been President of the International Liver Cancer Association (ILCA) and Chairman of the European Clinical Practice Guidelines of management of liver cancer (EASL-EORTC). He has published more than 230 articles in peer-reviewed journals such as New England Journal of Medicine, Nature, Nature Genetics, Lancet, Lancet Oncology, Cancer Cell, Nature Biotech, Nature Com, Nature Rev Clin Oncol, J Clin Oncol, J Clin Invest, JNCI and Gastroenterology (total citations 41,962, total impact factor 2541; h index 81), more than 40 chapters of books, and has delivered more than 500 lectures. He is Senior Editor of Clinical Cancer Research. He is Director of the Official Master in Translational Medicine at the University of Barcelona.

During the last 20 years, Prof. Llovet received the AACR-Landon International Award (2009), the International Hans Popper award (2012), Premi Josep Trueta (2013) and was nominated as Fellow of the American Association for the Study of Liver Diseases (2015). He has received competitive funding from the European Comission (FP7-HEALTH, HEPROMIC, 2010; HEP-CAR, Horizon 2020) and the US National Institute of Health (R01, 2008; NCI designation 2015).
Tim Meyer, MD, PhD (United Kingdom)

Tim Meyer is Professor of Experimental Cancer Medicine at UCL and Honorary Consultant in Medical Oncology at the Royal Free and UCLH Hospitals. He is Cancer Director of the NIHR/Wellcome UCH Clinical Research Facility and also Director of the UCL Experimental Cancer Medicine Centre.

He was awarded his BSc in Physiology and his Medical Degree at UCL and practised general medicine before specialising in Medical Oncology. He won a Clinical Research Training Fellowship from the Imperial Cancer Research Fund and was awarded his PhD in 1999. In 2002 he was appointed to his current post in which he specialises in the management of hepatocellular and neuroendocrine cancer. He leads a large portfolio of clinical trials and runs a translational research program in the UCL Cancer Institute.

Satdarshan (Paul) S. Monga, MD (USA)

Satdarshan (Paul) Singh Monga is a Professor of Pathology and Medicine at the University of Pittsburgh, School of Medicine. He is also the Endowed Chair for Experimental Pathology, Vice Chair and Chief of the Division of Experimental Pathology and Assistant Dean for the Medical Scientists Training Program. His research is focused on elucidating the cellular and molecular basis of liver pathophysiology including that of hepatic tumours such as hepatoblastoma and hepatocellular cancer. Using patient tissues, animal models and cell lines, his group has identified an important role of aberrant $\beta$-catenin signaling as well as its cooperation with other signaling pathways such as Hippo, HGF/Met and others in various hepatic tumours. His research is funded by the National Institutes of Health, private pharmaceutical companies, and foundations such as St. Baldrick’s.

Jean-Charles Nault, MD (France)

Jean-Charles Nault received is MD and PhD from Paris Descartes University in France. He is currently working in the liver unit of the Jean Verdier Hospital in Bondy, France, with a high priority on early detection of primary liver tumours and on therapeutic innovation. He is also an active member of the laboratory of “functional genomics of solid tumours” at the INSERM UMR 1162 headed by the Pr Jessica-Zucman Rossi. His research is dedicated to translational research in particular the identification of new driver genes in hepatocellular adenoma and hepatocellular carcinoma, of new therapeutic targets and of the molecular determinants of hepatocellular carcinoma’s prognosis.

Irene Ng, MD, PhD (Hong Kong)

Irene Ng Oi-lin is Chair Professor and Head of Department of Pathology at The University of Hong Kong and Loke Yew Professor in Pathology. She is also the Director of the State Key Laboratory for Liver Research.

Prof. Ng’s research work focuses on the molecular pathogenesis of liver cancer, including liver cancer stem cells and identification and characterisation of important genes and signaling pathways. She has established useful pathological and biological parameters with prognostic significance for patient management. Her research studies have provided insight in the understanding of liver cancer development and may help identify potential targets in novel cancer therapy.

She has published more than 300 peer-reviewed journal articles. She is among the top 1% of most cited scientists in ‘Clinical Medicine’ and ‘All Fields’ of ISI Essential Science Indicators. She has received a number of awards including The World Academy of Science (Medical Science) 2014, Croucher Senior Medical Fellowship (2013 and 2005), and University of Hong Kong Outstanding Researcher Award. Prof. Ng is the Chief Pathologist responsible for liver transplantation pathology service at Queen Mary Hospital.
Valérie Paradis, MD, PhD (France)

Valérie Paradis, Professor in Pathology, is involved in clinical practice (in charge of pathological activity from Liver surgery and liver transplantation) and basic research as the team leader (“From inflammation to cancer in digestive diseases”) in Research Center on Inflammation / INSERM U1149. Fields of interest and research include pathological and molecular aspects of liver fibrosis and tumours (benign and malignant) with a specific interest of hepatocellular carcinomas arising in the context of metabolic syndrome. To address these issues, her team has developed original in situ proteomic approach (MALDI imaging mass spectrometry) allowing the identification of new tissue biomarkers. In addition, the culture of precision-cut human tumoral slices as a dedicated tool for research and evaluation of novel anticancer drugs has been set up in the lab.

Prof. Paradis is involved in educational activities, tutoring students in Medicine and research, and chairing the specialty “Epithelium: interface structure” in the Master BCPP/M2 Mention “Cellular biology-Physiology-Pathology”. She is co-coordinator of the DHU UNITY “Unmet Needs for Innovation in HepatoLogy and GastroenterologY” (Coordinantor Pr DC Valla).

Neehar Parikh, MD (USA)

Neehar Parikh is a Transplant Hepatologist and clinical/health services researcher who is primarily focused on hepatocellular carcinoma detection and treatment effectiveness and cost effectiveness. He is currently the medical director of the Liver Tumor Clinic at the University of Michigan and at the Ann Arbor VA Healthcare System. He is a co-investigator in the multicenter National Cancer Institute Hepatocellular carcinoma Early Detection Strategy study designed to discover biomarkers for patients with hepatocellular carcinoma.

Joong-Won Park, MD, PhD (Republic of Korea)

Joong-Won Park is a Principal Scientist of the National Cancer Center, Korea and a Professor of Graduate School of Cancer Science and Policy, NCC Korea. He was the Head of the Center for Liver Cancer, NCC, Korea from 2002 to 2010, and was the Head of Translational and Clinical Research at the National Cancer Center Research Institute from 2008 to 2011. Dr. Park completed his Medical degree at Seoul National University in 1984 followed by a residency in Internal Medicine and a Clinical Fellowship in Hepatology at Seoul National University Hospital. He completed a PhD in Medicine at Seoul National University in 1996. He was an Assistant and Associate Professor of Chung-Ang University Medical College from 1993 to 2002 and was a Visiting Scientist at the Center for Basic Research in Digestive Diseases, Mayo Clinic, Rochester, USA, from 1997 to 1999. Prof. Park has published over 160 papers extensively in both International and Korean journals and given many invited lectures on hepatitis and liver cancer.

He is a Chair of the Scientific Committee of Asian-Pacific Primary Liver Cancer Experts Group and served as Chair of the Committee for the Hepatocellular Carcinoma Management Guidelines of the Korea Liver Cancer Study Group (KLCSGy–NCC Korea and also as Chair of the Committee for the HBV Chronic Hepatitis Management Guidelines of the Korean Association for the Study of the Liver (KASL).

His research interests are the management of hepatocellular carcinoma, molecularly targeted therapy, and hepatocarcinogenesis.
Eli Pikarsky, MD, PhD (Israel)

Eli Pikarsky is the Chairman of Pathology at the Hadassah-Hebrew University Medical Center and is a Member of the Lautenberg Center for Immunology and Cancer Research at the Hebrew University. He divides his time between research, teaching and clinical activity. He is the chairman of the research committee of the Israel Cancer Association and a member of the executive board of the EACR.

Among his major achievements were giving proof of concept that inflammatory cytokines can modulate epithelial cell fate, rendering them more susceptible to malignant transformation; describing a new mode for liver regeneration based on hepatocyte hypertrophy; identifying an invasion suppression function of p53 in the gut and showing that tumour amplicons, which were thought solely to affect signaling processes in the malignant cells themselves, could also govern heterotypic intercellular communication; revealing unexpected protumorigenic roles for tertiary lymphoid organs, a unique form of local adaptive immunity, in HCC.

Lewis R. Roberts, PhD (USA)

Lewis R. Roberts is the Peter and Frances Georgeson Professor in Gastroenterology Cancer Research and a Consultant in the Division of Gastroenterology and Hepatology at the Mayo Clinic, where he is Director of the Hepatobiliary Neoplasia Clinic, Associate Director of Pre-Doctoral Programs in the Center for Clinical and Translational Sciences, and Director for Research at Mayo Medical School. Dr. Roberts earned his medical degree from the University of Ghana Medical School and a PhD in Physiology and Biophysics from The University of Iowa. Subsequently, Dr. Roberts completed postgraduate training in Internal Medicine, Gastroenterology and Hepatology, and Cancer Genetics at Mayo Clinic.

Dr. Roberts maintains a clinical practice focused on liver and bile duct cancers and gastrointestinal endoscopy. His research interests include studies of the molecular mechanisms of liver and biliary carcinogenesis; development of biomarkers and clinical tests to improve the diagnosis and treatment of liver, bile duct and pancreas cancers; and improvements in prevention, diagnosis and treatment of hepatitis and liver cancer in Africa as well as in immigrant African communities in the USA. His research has been funded by the National Institutes of Health, The Robert Wood Johnson Foundation, and the AGA Foundation for Digestive Health and Nutrition. He has authored over 200 articles, book chapters, abstracts and letters.

Dr. Roberts has served as Associate Editor of Clinical Gastroenterology and Hepatology and currently serves on the Editorial Boards of Hepatology, Liver Cancer and Hepatic Oncology. He also serves as President of Africa Partners Medical, a non-profit organisation focused on improving healthcare delivery in Africa through medical education, practical skills training, and provision of medical equipment and supplies.

Supriya Saha, MD (USA)

In caring for patients with biliary tract malignancies as a medical oncology fellow at the Dana-Farber Cancer Institute, Supriya Saha quickly recognised the urgent need for more translational research in this area. As a post-doctoral research fellow in the laboratory of Dr. Nabeel Bardeesy, he helped to elucidate the pathogenesis of isocitrate dehydrogenase (IDH) mutant intrahepatic cholangiocarcinoma (ICC) using a novel genetically engineered mouse model (GEMM) (Saha, et al, Nature 2014). His current work involves a collaboration between basic scientists and clinicians across the United States to generate a comprehensive panel of ICC model systems including GEMMs, patient-derived xenografts (PDXs) and human cell lines, which he is using to develop novel targeted therapies for genetically-defined subsets of liver cancer. This work has already led to the first investigator initiated clinical trial for IDH mutant ICC hoping it will be the first of many.
**Riad Salem, MD (USA)**

Riad Salem, MD, MBA, is a Vice-Chair, Image-Guided Therapy and Chief, Interventional Radiology and Oncology in the Department of Radiology at Northwestern University (Chicago). His areas of interest include the use of image-guided techniques for the treatment of malignancies. These include chemoembolisation, bland embolisation, radioembolisation, radiofrequency and cryo/alcohol ablation. He is a graduate of McGill University in Montreal, Canada. He completed his radiology residency in Washington, DC. He has also completed a fellowship in interventional radiology (University of Pennsylvania), as well as a Master’s in Business Administration (Finance). He is a member of Alpha Omega Alpha medical honor society and a Fellow of the Society of Interventional Radiology. He has lectured internationally and published extensively on the subject of image-guided interventions and interventional oncology. Recently, he completed his term on the NCCN guidelines panel for hepatocellular carcinoma (2007-2010). His current research focus on hepatocellular carcinoma includes advances in minimally invasive therapies as well as imaging methodologies following locoregional treatment. He serves as co-PI of 2 international, randomised phase III trials involving locoregional therapy (radioembolisation) and sorafenib (STOP-HCC, YES-p).

**Bruno Sangro, MD, PhD (Spain)**

Bruno Sangro is Director of the Liver Unit and Co-Director of the HPB Oncology Area at Clínica Universidad de Navarra in Pamplona, Spain. Over the years his interest in medical research has focused on therapeutic innovation in the field of liver diseases and most specifically primary and secondary liver cancer. He has worked in the Group of Translational Hepatology in the Spanish Network for Biomedical Research on Hepatic and Digestive Diseases, where he is now the Principal Investigator, and he is currently the Director of the Area of Digestive and Metabolic Diseases in the Navarra Institute of Health Research. Under his collaboration or direction, the Liver Unit and the HPB Oncology Area at Clínica Universidad de Navarra have pioneered several approaches to the treatment of liver tumours including the use of expanded criteria to indicate liver transplantation in patients with hepatocellular carcinoma, the improvement in platforms and techniques for the intra-arterial treatment of primary and secondary liver tumours, the early clinical development of locoregional gene therapy for liver cancer and more recently advances in the field of immunotherapy of liver cancer, from peptide and cell vaccination to immune checkpoint inhibition.

**Gonzalo Sapisochin, MD (Canada)**

Gonzalo Sapisochin received his Medical Degree from the University Compluense of Madrid in Spain in 2005. He trained in General Surgery in Spain at Vall d’Hebron Hospital in Barcelona, and presented his doctoral thesis in 2011. He then was appointed as a “junior” staff in Hepato-pancreato-biliary (HPB) Surgical Oncology and Transplantation at the same institution. Dr. Sapisochin then completed a 2 year HPB Surgical Oncology & Abdominal Transplant Fellowship at the University of Toronto.

Dr. Sapisochin has been recently appointed as an Abdominal Transplant surgeon as well as an HPB Surgical Oncologist at the University Health Network. He is also appointed as an Assistant Professor in the Department of Surgery, University of Toronto. He has special expertise and research interest studying the interface between solid organ transplantation and malignant diseases of the hepatobiliary system. His research has been mainly focused on liver cancer (both hepatocellular carcinoma and intrahepatic cholangiocarcinoma) and liver transplantation and he has authored and co-authored several international publications. Dr. Sapisochin future research direction will continue focusing in the management of these malignancies and he is planning to develop a programme for liver transplantation for patients with cancer.
Morris Sherman, MD, PhD (Canada)

Morris Sherman earned his medical degree from University of Witwatersrand, Johannesburg, South Africa and his PhD degree from University of Cape Town, South Africa. He carried out his post graduate work at Albert Einstein College of Medicine in New York.

He serves at Toronto General Hospital since 1984 and now acts as Professor of Medicine at University of Toronto. He was previously President of Canadian Association for Study of the Liver and currently Chair of the Canadian Liver Foundation. His clinical and research interests include viral hepatitis and hepatocellular carcinoma. Dr. Sherman is the current Treasurer of the International Liver Cancer Association (ILCA) and also one of the founding members of ILCA.

Daniela Sia, PhD (Italy)

Daniela Sia studied medical biotechnology and molecular medicine at the University of Milan where she received her master and PhD in 2005 and 2008, respectively. Since finishing her PhD, she has completed two post-doctoral fellowships both under the mentorship of Prof. Josep M. Llovet. Her first fellowship, at the HCC Translation Research Laboratory in Barcelona focused on the development of a molecular classification of intrahepatic cholangiocarcinoma and the identification of novel oncogenic drivers amenable for therapeutic intervention. She continued this work during her second fellowship with the HCC Liver Cancer Program at Icahn School of Medicine at Mount Sinai where she is has been recently appointed as Assistant Professor. Her current work focuses on a functional understanding of the molecular pathogenesis of Liver Cancers including hepatocellular carcinoma and cholangiocarcinoma.

Thomas van Gulik, MD, PhD (Netherlands)

Thomas M. van Gulik completed his surgical training at the University of Amsterdam in the Netherlands. He received his PhD degree in Experimental surgery in Amsterdam. From 1988-1989, he was a fellow at the Transplantation laboratory of the University of Wisconsin Hospital. In 1990 he became a member of the surgical staff at the Academic Medical Center in Amsterdam and specialised in surgery of the liver, biliary tract and the pancreas (HPB surgery). He was appointed as professor of surgery in 1997 at the Academic Medical Center, University of Amsterdam. As the director of the Surgical laboratory in that institution, his main interests in surgical research have focussed on ischemia/reperfusion injury in relation with organ preservation and liver resection, liver regeneration and liver function. His main clinical interest currently is in liver tumours and bile duct cancer. He has a wide experience in the surgical management of perihilar cholangiocarcinoma.
Valérie Vilgrain, PhD (France)

Valérie Vilgrain is Chair of the Department of Radiology at the University Beaujon Hospital and Full Professor of Radiology at the Paris Diderot University, Sorbonne Paris Cité, France. Her major research interests are diagnostic and interventional imaging of the liver, pancreas and bile ducts with a special interest in multidetector CT and MR imaging and contrast-enhanced ultrasound, functional imaging (CT perfusion, dynamic contrast-enhanced MR imaging, diffusion-weighted MR imaging, MR elastography).

Dr. Vilgrain received her MD from the Rene Descartes University of Paris, Medical School, in 1985. She was resident in Radiology at Paris University and she completed a Fellowship in Radiology at the University Beaujon Hospital, Clichy, France (1987-1988).

She is member of several international and national societies, such as RSNA (Radiological Society of North America), ESR (European Society of Radiology), ESGAR (European Society of Gastro and Abdominal Radiology), EASL (European Association for the Study of Liver) and SFR (French Radiological Society). She was chairman of the Education Program Committee of the French annual meeting from 2000-2008 and Vice-Chairman of the French Radiological Society (2010-2014). She is member of several ECR committees (EIBALL, and EIBIR) and has been appointed as chair of the RSNA Regional Committee for Europe in 2015.

Dr. Vilgrain has published numerous peer-reviewed papers (more than 330 hits on Pub Med) (H-INDEX: Hirsch Number: 54). Dr. Vilgrain has been PI of large multicentric institutional trials.

Xin-Wei Wang, PhD (USA)

Xin-Wei Wang is a Senior Investigator, Chief of the Liver Carcinogenesis Section, Deputy Chief of the Laboratory of Human Carcinogenesis, NCI, NIH. He received his PhD training from New York University School of Medicine. Dr. Wang is a world renowned cancer researcher with a special focus on functional genomics of liver cancer using genome-scale technologies paired with several international collaborative initiatives and clinical studies. He oversees a basic/translational research program emphasizing new molecular approaches to define tumour subtypes and cancer drivers. Currently, he serves on the editorial board of Hepatology, Molecular Carcinogenesis, Journal of International Biological Sciences, etc. He also serves on the International Liver Cancer Association (ILCA) Governing Board and as Chair of the ILCA SIG on Molecular Classification and Signaling Pathways. He is recipients of the NIH Director’s Award, NCI Director’s Award and the NCI Mentor of Merit Award. He has co-authored over 180 scientific articles.
Katsuhiko Yanaga, MD, PhD (Japan)

Katsuhiko Yanaga, MD, PhD, FACS, is a Professor of Surgery and Chief of the Division of Digestive Surgery at The Jikei University School of Medicine, the oldest private medical school in Japan. He has a medical license in Japan as well as in the United States, and underwent surgical training in both countries. Prof. Yanaga is board-certified in General Surgery, Gastroenterological Surgery, Hepatology, and Gastroenterology in Japan, and is a Certified Instructor in Hepatobiliary and Pancreatic (HBP) Surgery in Japan. Prof. Yanaga has expertise in HBP surgery and liver transplantation.

Prof. Yanaga is the President of the Japan Chapter of the American College of Surgeons, Governor-at-Large representing Japan, and a Vice President of the Japanese College of Surgeons. He is a Board Member of the Japanese Society of Gastroenterological Surgery and Japan Human Cell Society, and is an Executive Board Member of the Japanese Society of Clinical Surgeons, while serving as an Auditor for the Japanese Society for Transplantation, Japanese Society of HBP Surgery and Japanese Society for Treatment of Obesity. He is also a Councilor of the Japan Surgical Society, Association of Japanese Surgeons for Vascular Surgery, Japan Society of Gastroenterology, Japan Society of Hepatology, Japan Society of Clinical Oncology, Japan Surgical Society, Japan Gastric Cancer Association, Japan Esophageal Society, Japanese Society of Adult Diseases, Japanese Society for Surgical Metabolism and Nutrition and Japanese Society for Parenteral and Enteral Nutrition.

Francis Yao, MD (USA)

Francis Yao, MD, is Professor of Clinical Medicine and Surgery, and Medical Director of Liver Transplant at the University of California, San Francisco. Much of Dr. Yao’s research has been dedicated to hepatocellular carcinoma, with a special focus on liver transplant as a potentially curative treatment for hepatocellular carcinoma. He has authored close to 200 original articles, reviews, book chapters, and abstracts. Some highlights of his work include the development of UCSF criteria and down-staging of hepatocellular carcinoma for liver transplant. Dr. Yao served on several committees of the American Association for the Study of Liver Diseases (AASLD), including the Awards Review Committee and the Education Committee, and has been a member of the AASLD Hepatobiliary Neoplasia Special Interest Group. He was an Associate Editor for the journal *Liver Transplantation* from 2010 to 2015, and has served as an ad hoc reviewer for more than 30 peer-reviewed journals.

Lars Zender, MD, PhD (Germany)

Lars Zender, MD, is Professor and Head of the Division of Gastrointestinal Oncology at University Hospital Tübingen, Germany. Lars Zender’s work especially focuses on the identification of new cancer genes involved in liver cancer development. He developed novel mosaic (chimaeric) liver cancer mouse models, which allow for high throughput functional genomic analyses. Together with a limited number of other laboratories worldwide, Lars Zender’s group has the expertise to conduct stable RNA interference screens for the identification and validation of new cancer genes directly in vivo. Another key aspect in the scientific work of Lars Zender is his work on cellular senescence. In particular the Zender laboratory is studying the senescence associated secretory phenotype and how senescent tumour cells and pre-cancerous cells are recognised and cleared by the immune system. Recent work from Lars Zender’s laboratory showed that a continuous antigen specific immune clearance of premalignant senescent hepatocytes is crucial for tumour suppression in the liver.
Keji Zhao, PhD (USA)

Keji Zhao, PhD, is director of the Systems Biology Center at the NHLBI, as well as a senior investigator in the Laboratory of Epigenome Biology. Dr. Zhao joined the NHLBI in 1999 and has been a senior investigator since 2007.

Dr. Zhao received his undergraduate degree from Changwei Normal College in Weifang, China in 1980 and his Doctor of Philosophy from the University of Geneva, Switzerland in 1996. Prior to joining the NHLBI, Dr. Zhao was a Damon Runyon-Walter Winchel Cancer Research Postdoctoral Fellow at Stanford University, Calif.

Dr. Zhao’s research focuses on the epigenetic regulation of chromatin. Understanding how epigenetic patterns are established during development and how improper epigenetic signals contribute to disease is the long-term goal for his lab. His lab developed the ChIP-SAGE, ChIP-Seq, MNase-Seq, and scDNase-seq techniques and also developed corresponding algorithms to analyze these data. Using these approaches, Dr. Zhao’s lab has been pioneering whole-genome analyses of chromatin modifications in higher eukaryotic systems. By identifying these genome-wide epigenetic patterns, Dr. Zhao’s research has revealed numerous insights into the relationship between the epigenome, chromatin-modifying enzymes, and gene expression.

Jessica Zucman-Rossi, MD, PhD (France)

Jessica Zucman-Rossi is Professor of Medicine at University Paris Descartes, within the department of Oncology at the European Hospital Geaorges Pompidou (AP-HP). She leads an INSERM laboratory in “Functional Genomics of Solid Tumours”, with a focus on liver, mesothelial and renal tumours. Her team aims to develop basic genomic approaches based on human tumours analyses to identify new mechanisms of tumorigenesis and to transfer this knowledge into biomarkers that could be introduced in clinical care. In particular, the group was pioneer in the elucidation of the molecular classification of benign and malignant liver tumours. Prof Zucman-Rossi leads the French liver tumour project in the International Cancer Genome Consortium (ICGC). Currently, she is Chairman of the scientific committee “Genetic, Epigenetic and Cancer” at INSERM, Executive Secretary of ILCA (International Liver Cancer Association) and she acts as co-Editor for *Journal of Hepatology*. 

The International Liver Cancer Association
Priming Knowledge in Liver Cancer across Disciplines

► Share ILCA Mission
• Advancing research in the pathogenesis, prevention and treatment of liver cancer
• Promoting novel pathogenic, diagnostic and therapeutic interventions for liver cancer
• Bringing together scientists, physicians and allied professionals from all interrelated fields

► Enjoy ILCA Membership
• Exciting professional networking and educational opportunities
• Significant registration discounts to attend ILCA Annual Conferences and other educational events
• Access to the latest information on liver cancer related news and initiatives
• Active involvement in association affairs
• Opportunity to be involved in Special Interest Groups
• Opportunity to apply for the ILCA fellowship programme or to support one of your team members as a mentor through the fellowship application process

Visit the ILCA stand and know more about ILCA activities

ILCA is the only international and multi-disciplinary association devoted exclusively to liver cancer research, treatment and care

Join ILCA today!
and participate in advancing liver cancer science worldwide

To learn more about ILCA, visit www.ilca-online.org
Genesis
Liver cancer is rapidly increasing worldwide, triggering widespread interest and strong focus surrounding all aspects of this disease. Given the naturally multidisciplinary nature of liver cancer, however, no single association has before the International Liver Cancer Association (ILCA) adopted a transversal approach to liver cancer by connecting expertise from interrelated fields, research and treatment levels. In response to this shortfall, ILCA was established in 2006 and is currently the only international organisation devoted exclusively to liver cancer across disciplines.

Our Mission
ILCA strives to advance research in the pathogenesis, prevention, and treatment of liver cancer, by promoting novel pathogenic, diagnostic and therapeutic interventions for liver cancer, and taking a transversal approach to research. Indeed, ILCA brings together scientists, physicians and allied professionals from all interrelated fields and countries, and strives to welcome and incorporate individuals involved in all the scientific disciplines devoted to basic, translational and clinical research in liver cancer as individual members. ILCA actively partners with other professional associations involved in any aspect related to liver cancer research, with the objective to join efforts for the benefit of science.

Joining Our Community
We invite you to discover more about ILCA on www.ilca-online.org, as well as to connect with our expanding group of interested physicians, scientists, and allied health professionals from various fields and from around the world.

Membership to ILCA not only provides you with exclusive benefits such as reduced registration rates to our Annual Conferences, exciting networking and educational opportunities and active involvement in association affairs; it also helps us to develop our activities and our reach to advance liver cancer research and care.

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* Liaison in an advisory capacity
All abstracts listed in ILCA’s 10th Annual Conference Book of Abstracts have been assigned a prefix for the type of presentation, and a sequential abstract number. The authors’ whose names are in bold and followed by an asterisk are the presenting authors.

Oral Communication = O  Poster = P

Oral Communications are listed by day and time of presentation.

Posters and Top Scored Posters
In the Book of Abstracts’ section, you will first find the Top Scored Posters, then the Posters (e-Posters) listed by topics:

1. Molecular pathogenesis, molecular pathology, cell biology and translational research
2. Epidemiology, staging and prognosis
3. Diagnosis, imaging and biomarkers
4. Clinical trials and treatment research & Miscellaneous

e-Poster Viewing Tours
40 Top Scored Posters will be presented in the form of paper board poster at the beginning of each e-Poster Viewing Tour (20 paper poster presentations within each e-Poster Viewing Tour) in the Poster of Excellence area (British Columbia Ballroom).

Viewing of all e-Posters takes place in the British Columbia Ballroom at the same time.

TOP SCORED POSTERS (paper posters):
• In the morning (as of 10:00)
P-001, P-002, P-003, P-004, P-005, P-006, P-007, P-008, P-009, P-031, P-032, P-033, P-034, P-035, P-036, P-037, P-038, P-039
• In the afternoon (as of 15:45)
P-010, P-011, P-012, P-013, P-014, P-015, P-016, P-017, P-018, P-019, P-020, P-021, P-022, P-023, P-024, P-025, P-026, P-027, P-028, P-029, P-030

Hanging and removal of paper board posters
Poster boards will be marked with the final abstract numbers. Posters mounting time: Thursday, 8 September 2016, as of 14:00. Posters need to be mounted prior to Thursday, 8 September 2016, 19:00. Posters removal time: Sunday, 11 September 2016, as of 10:00. Posters that have not been removed by 13:00 will be disposed of by the organiser.

Top Scored Posters will be available also in a form of e-Poster on all e-Poster screens throughout the Conference.

ALL POSTERS (e-Posters):
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General Session 1: Molecular Pathogenesis

0-001 THE THAILAND INITIATIVE IN GENOMICS AND EXPRESSION RESEARCH FOR LIVER CANCER (TIGER-LC): RACE/EThNICITY-IDENTIFIED COMMON Molecular SUBTYPES AMONG ASIAN HEPATOCELLULAR CARCINOMA AND CHOLANGIOCARCINOMA IDENTIFIED BY INTEGRATED GENOMICS

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Introduction: Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (CCA) represent two distinct histological cancer subtypes confined within the liver. They are clinically and biologically heterogeneous and are highly resistant to treatment, making liver cancer the second most lethal malignancy in the world. In Thailand, liver cancer represents the primary cause of cancer-related death and is a major health problem. While HBV and HCV are major etiological factors for HCC globally, liver fluke infection (O. viverrini) is a major etiological factor for CCA in Thailand, especially in north-eastern Thailand where O. viverrini is endemic and approximately 70% of liver cancers are CCA. These unique risk factor patterns provide an opportunity to study cancer heterogeneity and unique liver tumor biology. The Thailand Initiative in Genomics and Expression Research for Liver Cancer (TIGER-LC) consortium was established to identify genomic and expression factors that may modify HCC and CCA susceptibility and progression. In a Phase I study, we determined molecular subtypes and features of HCC and CCA through systems integration of genomic, transcriptomic and metabolic profiles.

Methods: We performed genome-wide profiling of 386 surgical specimens derived from 199 Thai liver cancer patients. We employed the Affymetrix Human Transcriptome Array 2.0 to examine transcriptome profiles, the Affymetrix Genome-Wide Human SNP Array 6.0 to determine somatic copy number alterations (SCNA), Metabolon’s Discovery HD4 platform to identify cancer metabolic profiles and Whole Exome Sequencing to identify mutations. Unsupervised Consensus Clustering (cCluster), Subclass Mapping (SM), Gene Set Enrichment Analysis (GSEA), class comparison, loss of heterozygosity and minimum segmentation, Pearson and rank correlation algorithms were used to analyze omics data. The results were validated in 852 independent Asian or Caucasian HCC or CCA cases.

Results: Transcriptomic analyses revealed that Thai HCC mainly consisted of 3 stable subgroups (C1-C3), while Thai CCA contained 4 stable subgroups (C1-C4). Interestingly, HCC-C1 and CCA-C1 subtypes shared a similar gene expression matrix, as did HCC-C2 and CCA-C2 representing a separate pattern, which correlated with patient survival. These prognostic subtypes were validated in independent Asian HCC and CCA cohorts, but not in Caucasian patients, and were associated with tumor biology rather than etiology. GSEA revealed that C1 subtype is enriched for mitotic checkpoint and DNA replication, while C2 subtype is linked to an increased body mass index, inflammatory responses and unique tumor metabolic activities.

Conclusion: Our study, for the first time, demonstrated that CSCs promote liver cancer metastasis in mice. Our data also revealed the differential molecular property between the primary liver tumors and the metastases despite their histological resemblance, strongly suggesting the need to develop specific therapy towards primary and metastatic diseases. PROM1, while widely used as a CSC marker, is not essential for liver CSC function.

Disclosure of Interest: None Declared

0-002 CANCER STEM CELLS PROMOTE LIVER CANCER METASTASIS INDEPENDENT OF PROM1

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Introduction: Liver cancer is the second leading cause of cancer death worldwide largely due to its profound drug resistance and frequent metastasis. Only 3% of the liver cancer patients develop metastasis survive over five years. However, little effort has been devoted to establishing animal models of the metastatic, late-stage liver cancer, which is undoubtedly the key to understanding its biology and test new therapy. Cancer stem cells (CSCs), a subpopulation of cancer cells with stem-like properties, have been hypothesized to drive metastasis. However, a clear, functional connection between liver CSCs and metastatic disease remains largely elusive. Prominin1 (PROM1, also called CD133 in humans) is a bona fide marker of stemness in multiple normal and malignant tissue types including the liver. We previously made a knock-in mouse with an inducible CreERT2-LacZ allele inserted into the Prom1 locus (Prom1−/− (Zhu et al., 2009). We demonstrated that Prom1−/− cells in the neonatal liver are bipolet liver progenitors and targeting neonatal Prom1−/− cells with conditional loss of tumor suppressor genes Pten and Tp53 reliably developed liver cancers. 67.9% of Prom1−/−; Pten−/−; Tp53−/− Rosa26 GFP mice (referred as PPTg mice hereinafter) developed liver cancers and 13.9% had metastases Zhu et al., under review in Cell. We reasoned that this model would allow us to characterize liver CSCs and their role in metastasis.

Methods: We enriched CSCs from the primary PPTg liver tumors to characterize their role in liver cancer metastasis. Due to the controversies over the ability of stem cell (SC) markers to define functionally distinct CSCs, we did not rely on the expression of any SC markers to select CSCs. Instead, we chose a functional approach to enrich liver cancer cells that were able to survive and propagate under a serum-free, matrigel-coated liver SC culture condition (Huch et al., 2013). We then established an orthotopic liver cancer allograft models by engrafting liver CSCs using a novel ultrason-guided intrahepatic implantation.

Results: The enriched CSC population showed high expression of a wide range of liver SC markers including PROM1, EpCAM, Hnf19, Sca1, CD24 and CD44. The implanted liver CSCs rapidly developed into aggressive liver tumors with extensive intrahepatic, abdominal and pulmonary metastasis (animal median survival = 91 days). Intriguingly, a large RNA-seq analysis revealed a striking molecular resemblance of the CSC-driven allograft tumors to the spontaneous metastases in the parental PPTg model, both of which shared a transcriptome profile distinct from the primary liver tumors. Gene Set Enrichment Analysis identified significant enrichment of the recurrent and metastatic human liver cancer gene signatures in the CSC-driven allograft tumors compared to the parental PPTg tumors. Finally, we showed that Prom1−/− deficient CSCs displayed no defects in their abilities to grow in vitro or to drive metastatic tumors in vivo.

Image:

Conclusion: Our study, for the first time, demonstrated that CSCs promote liver cancer metastasis in mice. Our data also revealed the differential molecular property between the primary liver tumors and the metastases despite their histological resemblance, strongly suggesting the need to develop specific therapy towards primary and metastatic diseases. PROM1, while widely used as a CSC marker, is not essential for liver CSC function.


Disclosure of Interest: None Declared

0-003 ONCOCgenic Activation of the RNA Binding PROtein RDBP AND c-NYC SIGNaling in Hepatocellular Carcinoma

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Introduction: Global transcriptomic alterations of both coding and non-coding RNA species are a ubiquitous feature associated with human cancers including hepatocellular carcinoma (HCC). One such trait may be due to dysregulation of RNA-binding proteins (RBP), the key regulators of RNA processing by modulating the maturation, stability, transport, editing and translation of RNA transcripts. In this study, we investigated the oncogenic role of mRNP factors (mRBP) in HCC.
GENETIC DELETION OF INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-7 (IGFBP7) PROMOTES HEPATOCELLULAR CARCINOMA (HCC): A NOVEL ROLE OF IGFBP7 IN REGULATING ANTI-TUMOR IMMUNE SURVEILLANCE

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Introduction: In the US, the incidence and mortality rates of hepatocellular carcinoma (HCC) are alarmingly increasing since no effective therapy is available for the advanced disease. Activation of IGF signaling is a major oncogenic event in diverse cancers, including HCC. Insulin-like growth factor binding protein-7 (IGFBP7) inhibits IGF signaling by binding to IGF-1 receptor (IGF-1R) and functions as a potential tumor suppressor for HCC. IGFBP7 abrogates tumors by inducing cancer-specific senescence and apoptosis and inhibiting angiogenesis. The present studies focused on in-depth analysis of the tumor suppressor functions of IGFBP7 using a knockout (IGfbp7−/−) mouse model.

Methods: Igpfb7−/− mice were generated using Cre-loxP technology. HCC was induced by i.p. injection of N-nitrosodimethylamine (NDMA) into 2 wks old male mice. Differential gene expression was analyzed by RNA-sequencing. Cell proliferation, cell cycle and senescence were analyzed by standard assays. Activation of IGF-1 and its downstream signaling and NF-kappaB was studied by Western blotting. Antigen presentation was checked by co-culturing gp100-loaded bone marrow derived dendritic cells with pmel-17 T lymphocytes. Role of CD8+ and CD4+ cells in mediating IGFBP7-induced inhibition of tumor growth was analyzed by antibody-mediated depletion assay in syngeneic mice containing xenografts of IGFBP7-overexpressing mouse hepatoma cells.

Results: Igfbp7−/− mice shows constitutive activation of IGF signaling, presents with pro-inflammatory and immunosuppressive microenvironment, and develops spontaneous tumors in livers and liver and markedly accelerated carcinogen-induced HCC. Loss of Igfbp7 resulted in increased proliferation, accelerated cell cycle progression and decreased senescence in hepatocytes and mouse embryonic fibroblasts that could be blocked by an IGF-1 receptor inhibitor. A significant inhibition of genes regulating immune surveillance was observed in Igfbp7−/− livers which was associated with marked inhibition in antigen cross-presentation by Igfbp7−/− dendritic cells. IGFBP7 overexpression inhibited growth of HCC cells in syngeneic immunocompetent mice which could be abolished by depletion of CD4+ or CD8+ T lymphocytes.

Conclusion: Our studies unravel immunomodulatory role of IGF signaling, presents with pro-inflammatory and immunosuppressive microenvironment, and develops spontaneous tumors in livers and liver and markedly accelerated carcinogen-induced HCC. Loss of Igfbp7 resulted in increased proliferation, accelerated cell cycle progression and decreased senescence in hepatocytes and mouse embryonic fibroblasts that could be blocked by an IGF-1 receptor inhibitor. A significant inhibition of genes regulating immune surveillance was observed in Igfbp7−/− livers which was associated with marked inhibition in antigen cross-presentation by Igfbp7−/− dendritic cells. IGFBP7 overexpression inhibited growth of HCC cells in syngeneic immunocompetent mice which could be abolished by depletion of CD4+ or CD8+ T lymphocytes.

Disclosure of Interest: None Declared

0-006 GERMLINE AND SOMATIC DICER1 MUTATIONS ARE ASSOCIATED WITH CTNNB1 MUTATION AND A SPECIFIC MICRONA EXPRESSION PROFILE IN HEPATOCELLULAR CARCINOMA

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Conclusion: Our models show that full deletion of Arid1a can enhance mammalian regeneration and suppress cancer, but heterozygous loss promotes cancer initiation and metastasis in multiple HCC mouse models. Future work will attempt to clarify the exact molecular changes responsible for differences between full, half, and null Arid1a dosage states, information that may lead to unexpected therapeutic strategies.

Disclosure of Interest: None Declared

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**Introduction:** A growing number of evidence suggests that family history of liver cancer significantly increases the risk of hepatocellular carcinoma (HCC), independently from the presence of other risk factors. However, further studies to elucidate the contribution of genetic predisposition in the HCC occurrence are needed. Here, we report a novel germine DICER1 mutation associated with familial recurrent liver tumors. Next, we studied the impact of constitutional and somatic DICER1 mutations on the microRNA (miRNA) expression profile in HCC.

**Methods:** We investigated two individuals, a father and his son, with no notable past medical history, which developed recurrent well-differentiated hepatocellular tumors over the years. Whole-exome sequencing was performed on constitutional DNA extracted from circulating lymphocytes in both patients. The presence of candidate gene mutations was analyzed in exome sequencing data from 243 liver tumors. miRNA sequencing was performed in 50 liver tumors, including 2 tumors from the son. Consensus clustering analysis was performed and differentially expressed miRNAs (DEmiRs) identified.

**Results:** In both individuals of the family, exome sequencing revealed a common germline mutation in DICER1, leading to a deleterious amino acid substitution Y181H. Moreover, both patients showed an alteration of the liver zonation similar to that observed in DICR knock-out mice. Screening for DICER1 mutations in 243 sporadic liver tumors identified 6 samples with different somatic mutations. Interestingly, DICER1 somatic mutations were frequently associated with CTNNB1 activating mutation in HCCs (4 out of 5, p-value: 0.03). Unsupervised analysis of the miRNA sequencing data in 50 liver tumors identified 5 major clusters of which C1 included only DICER1-mutated samples and was significantly associated with the mutation. A total of 20 DEMIs in C1 compared to the remaining clusters were identified and all of them were down-regulated. Notably, among the down-regulated DEMIs, let-7a and miR-365 are processed by Dicer also in mice. In contrast to mature miRNAs, there was no difference in the expression of mRNA precursors between C1 and the remaining clusters.

**Conclusion:** DICER1 germline mutations are usually associated with development of pleuropulmonary blastoma and ovarian Sertoli-Leydig cell tumors. Here, we described familial HCC associated with DICER1 germline mutation and altered zonation. Familial and sporadic HCCs carrying DICER1 mutations are associated with CTNNB1 mutation and characterized by a decreased expression of specific mature miRNAs.

**Disclosure of Interest:** None Declared

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### General Session 2: Molecular Pathology

#### 0-007 CHARACTERIZATION OF THE IMMUNE CLASS OF HEPATOCELLULAR CARCINOMA


**Introduction:** Oral Communications

**Disclosure of Interest:** None Declared

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**0-008 IDENTIFICATION OF A NEW SUBGROUP OF HEPATOCELLULAR ADENOMAS CHARACTERIZED BY DYSREGULATION OF SONIC HEDGEHOG AND PROSTAGLANDIN PATHWAYS**


**Disclosure of Interest:** None Declared

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**0-007 CHARACTERIZATION OF THE IMMUNE CLASS OF HEPATOCELLULAR CARCINOMA**


**Introduction:** Encouraging survival results have been obtained in different solid tumors (i.e. melanoma and lung) with immunotherapy inhibitors directed to enhance T cell response. Hepatocellular carcinoma (HCC) is an inflammation-related cancer for which immune-based therapies are actively tested. However, little is known about the immune-component of HCC or the presence of potential biomarkers that could predict response to these therapies. Aims: a) To perform comprehensive characterization of the immunological profile of HCC and b) to identify biomarkers able to select candidates to receive immunotherapies.

**Methods:** Genes expression data of 228 HCC resected tumors and their matched surrounding non-tumoral tissue was virtually microdissected by non-negative matrix factorization and clustered with random forest. Characterization of the transcriptional immune landscape was conducted using gene set enrichment and > 1,000 gene signatures representing different states of inflammation or distinct immune cells. The higher cumulative consumption of oral contraceptives was observed in patients with IHCA and highest BMI with a median value of 32 and have frequent steatosis in their non-tumor liver tissues. We further classified the 533 HCA in 8 different molecular subgroups: HHCA (n=179, 33.5%), IHCA (n=183, 33.4%), bHCAex3 (n=33, 7%), bIHCA ex3 (n=34, 6%), bHCA ex7/8 (n=17, 3%), bIHCA ex7/8 (n=21, 4%), PHCA (n=22, 4%) and UHCA (n=40, 7.5%). Patients with PHCA demonstrated the highest BMI with a median value of 32 and have frequent steatosis in their non-tumor liver tissues. The higher cumulative consumption of oral contraceptives was observed in patients with HCA and PHCA. However, PHCA showed frequent histological hematomas (81% in PHCA versus 51% in others HCA P=0.006). Patients with PHCA were also significantly associated with symptomatic bleeding (71% of bleeding in PHCA versus 14% in other molecular subgroups, P<0.0001).

**Conclusion:** Prostategnalin C is a new subgroup of adenomas defined by specific dysregulation of prostat glandin and sonic hedgehog pathways, associated with metabolic syndrome and a high risk of bleeding.

**Disclosure of Interest:** None Declared
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New York, United States, 6HCC Translational Research Laboratory, BCLC Group, IDIBAPS, CIBEREHD, in 3/10 HCCs included in our study, as defined by transcriptomic outliers. These outliers show unique concordant results in the measurement of molecular heterogeneity. There is substantial heterogeneity of PTEN, BRAF, and JAK1.

Results: were identified using Varscan2 and functional impact predicted with SIFT and Polyphen. Combining PD-L1, TIM-3 and LAG-3 with neutralizing monoclonal antibodies increased ex vivo proliferation of CD8+ and CD4+ TIL to polyclonal stimuli and to BTLA or MAGE-C2 presented by INRAA-transfected autologous antigen-presenting cells, and also enhanced IFN-γ and TNF-α production of CD8+ TIL in polyclonal and HCC TAA-specific peptide stimulation assays. Combining PD-L1 blockade with TIM-3 or LAG-3 blockade further enhanced these effects.

Conclusion: Blocking these co-inhibitory pathways revitalizes the functionality of tumor-infiltrating CD8+ and CD4+ T cells, while combined blocking shows additive effects. Therefore, these three co-inhibitory pathways may be promising immunotherapeutic targets for the most prevalent type of primary liver cancer.

Disclosure of Interest: None Declared

Methods: To determine whether co-inhibitory pathways contribute to intra-tumoral suppression of T cell responses in HCC, we used paired samples of leukocytes freshly isolated from resected liver tumors, tumor-free liver tissues (TFL), and peripheral blood of patients with HCC. Expression of co-inhibitory receptors on T cells was then measured by flow cytometry.

Results: We found that expression of PD-L1, TIM-3 and LAG-3 on CD8+ cytotoxic T cells, and expression of PD-1, TIM-3 and CTLA-4 on CD4+ and CD8+ T helper cells were significantly higher in the tumor than in TFL or in the blood. In contrast, no up-regulation of BTLA on T cells in the tumor was observed. Using MHC class I tetramers loaded with immunogenic peptides derived from Gp36-3 or MAGE-C2, which are both tumor-associated antigens (TAA) that are expressed in HCC tumors, we found that the majority of TAA-specific CD8+ tumor-infiltrating lymphocytes (TIL) expressed PD-1, TIM-3 and LAG-3. In addition, co-inhibitory ligands PD-L1, Galectin-9, MHC-I, CD80 and CD86 were expressed on dendritic cells, monocyties and B cells in the tumor. Compared to the cells without expression, CD8+ and CD4+ expressing TIL expressing these co-inhibitory receptors displayed a more activated status (HLA-DR+, CD69+). However, they did not show increased expression of granzyme B, and neither displayed enhanced effector cytokine production upon polyclonal stimulation, suggesting restricted functionality. Moreover, blocking PD-L1, TIM-3 and LAG-3 with neutralizing monoclonal antibodies increased ex vivo proliferation of CD8+ and CD4+ TIL to polyclonal stimuli and to Gp36-3 or MAGE-C2 presented by INRAA-transfected autologous antigen-presenting cells, and also enhanced IFN-γ and TNF-α production of CD8+ TIL in polyclonal and HCC TAA-specific peptide stimulation assays. Combining PD-L1 blockade with TIM-3 or LAG-3 blockade further enhanced these effects.

Conclusion: PD-1, TIM-3 and LAG-3 are up-regulated on tumor-infiltrating TAA-specific T cells in HCC patients. Blocking these co-inhibitory pathways revitalizes the functionality of tumor-infiltrating CD8+ and CD4+ T cells, while combined blocking shows additive effects. Therefore, these three co-inhibitory pathways may be promising immunotherapeutic targets for the most prevalent type of primary liver cancer.

Disclosure of Interest: None Declared

Methods: Multi-region sampling was performed on single-nodule HCCs from 10 patients treated with surgical resection; all samples were at least 1 cm apart. Hepatopathologists assessed H&E sections from each region and evaluated 11 histological parameters, including differentiation and inflammation. Each region was subjected to FNA-seq (Poly-A enriched, HSq5) and targeted DNA sequencing of the most prevalent recurrent mutations in HCC (Agilent SureSelect®, 58 genes). To identify heterogeneity, defined as tumors with at least one non-clustering region, multi-dimensional scaling (MDS) clustering was performed. Data analysis included consensus clustering, differential gene expression, gene set enrichment analysis, and identification of fusion transcripts. Somatic mutations were identified using Varscan2 and functional impact predicted with SIFT and Polyphen.

Results: Patients enrolled were mostly males (7/10) with an average age of 59. Median tumor size was 5.3 cm and hepatoma B (HBV) was the most common etiology (5/10). The study included 38 HCC samples and 16 adjacent non-tumoral tissues, resulting in an average of 5.4 regions per patient. Histologically, 4/10 patients had intra-tumoral variability in tumor grade and inflammatory infiltrate. The most prevalent recurrent mutations in 3/10 patients. Whole genome sequencing to histology, the non-clustering outlier regions were poorly differentiated. Regions of the same tumor showed high concordance of gene expression when compared to each other, with the exception of the outlier regions that had a weaker correlation (Spearman’s r=0.96 vs 0.15). Candidate HCC drivers such as LNR28B1 were significantly up-regulated (5–50 fold, FDR=0.001) in outlier regions compared to the other regions of the same patient. Hierarchical clustering using enrichment scores of the 50 Hallmark Gene Sets also identified the same outlier regions as not clustering with the corresponding tumor regions. Outlier regions showed enrichment (FDR<0.05) of metabolic, immune and epithelial to mesenchymal gene sets. When interrogating the expression of downstream targets of known HCC related transcription factors, outlier regions again showed marked derepression from counterpart regions. Fusion transcripts were identified in 8/10 patients. 6/8 patients had spatial discrepancies in detection of fusion transcripts. HBV integrations were identified in 4/5 infected patients. The integration of HBV showed a heterogeneous pattern, with no sites being detected in all samples of the corresponding tumor. Divergent somatic mutations were identified in 7/9 patients including known oncogenes and tumor suppressors such as TP53 (2/9), CTNNB1 (2/9) and JAK1 (1/9). Transcriptomic outliers showed an asymmetric distribution of somatic mutations affecting PDGFRB, CDK4/6, ARID2, BRF9, and PTEN.

Conclusion: Analysis of multi-region expression and mutation data using numerous metrics show concordant results in the measurement of molecular heterogeneity. There is substantial heterogeneity in 3/10 HCCs included in our study, as defined by transcriptomic outliers. These outliers show unique histological features and selective de-regulation of candidate HCC drivers (LNR28B1).

Disclosure of Interest: None Declared

O-011 ROLE OF THE TUMOR-INFILTRATING CELLS IN THE DEVELOPMENT OF CHEMORESISTANCE DURING ANTI-ANGIOGENIC THERAPIES IN HEPATOCELLULAR CARCINOMA


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Introduction: Neo-angiogenesis is frequently observed during progression of hepatocellular carcinoma (HCC) and associated with poor clinical outcome. Consequently, inhibition of neo-angiogenesis is an effective treatment strategy for advanced HCC. However, development of chemoresistance is observed in the majority of patients. Competing evidence suggest that stem-like tumor-infiltrating cells (TICs) may contribute to the acquisition of resistant properties in many solid tumors, but their exact role in this process for HCC remains to be defined. Here, we evaluate the importance of TICs in the development of resistance to different anti-angiogenic therapies in HCC and define the concomitant adaptive molecular changes.

Methods: Several HCC cell lines and primary HCC isolates were exposed to sorafenib and sunitinib for a total of 14-21 days. The treatment effects on TICs were estimated by sphere forming capacity in vitro as well as the side-population (SP) approach. Expression levels of key oncogenic and TIC markers were assessed by qRT-PCR and flow cytometry. Furthermore, whole transcriptome analyses were performed at different time points.

Results: Both treatment regimens effectively reduced oncogenic properties in all investigated HCC cell lines. However, sustained anti-proliferative effects were observed in only two cell lines whereas an initial treatment effect was subsequently followed by rapid re-growth in the majority of HCC cell lines thereby mimicking the responses observed in patients. While anti-angiogenic effects in sensitive cell lines were associated with significant reduction sphere forming capacity, TIC markers as well as SP cells, resistant cell line showed a transient increased in TIC properties. Importantly, acquired resistance to both drugs uniformly developed in the cell lines suggesting that common molecular mechanisms might be operative. These adaptive molecular changes involved signaling pathways known to be associated to cell survival (ERK, AKT, MHC), proliferation (TP53, CDKN1A) as well as angiogenesis (VEGF, PDGFR, HIF1α). Furthermore, the resistant cell lines showed compensatory upregulation of key oncopgenic molecules such as EGFR as well as multidrug resistance ABC transporters.

Conclusion: Our in vitro model recapitulates features of drug resistance observed in human HCC patients. Resistance to anti-angiogenic therapies might be fueled by transient expansion of TICs. Therefore, specific targeting of TICs as well as pro-angiogenic compensatory signaling pathways might be an effective therapeutic strategy to overcome resistance in HCC.

Disclosure of Interest: None Declared

Oral Communications

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General Session 3: Epidemiology and Diagnosis

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0-012 INCIDENCE OF CHOLANGIOCARCINOMA AND EXTRAPANCREATIC CANCER TAKING INTO ACCOUNT VIROLOGICAL CONTROL IN PATIENTS WITH COMPENSATED VIRAL CIRRHOSIS (ANRS C012 CIRVR PROSPECTIVE COHORT)

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Introduction: Excepted hepatocellular carcinoma (HCC), limited data about malignancies in viral cirrhosis are available. The multicentric CIRVR cohort aims to prospectively assess all clinical events in patients with compensated viral cirrhosis including all types of cancer.

Methods: Patients with the following inclusion criteria were enrolled in 35 French centers: biopsy-proven HBV or HCV cirrhosis; Child-Pugh A: absence of previous liver complications and cancer. Patients were followed-up every 6 months. Standardized mortality ratio (SMR) was calculated according to age and sex using 5 years period. The impact of sustained viral response for HCV patients and negative viral load for HBV patients was assessed using a time dependent analysis.

Results: 1671 patients were enrolled between 2006 and 2012 (age 56, men 67%, HBV 1323, HBV 317, HBV-HCV 31). Metabolic syndrome, previous alcohol and tobacco consumption were observed in 15%, 26% and 56% respectively. After a median follow-up of 59.7 months, 227 primary liver cancers (PLC) were diagnosed (216 HCC, 5-year Cumulative incidence (CumI): 12.9% and 11 cholangiocarcinoma (CC), 5-year CumI: 0.6%). Among the 11 patients with CC (10 intrahepatic CC, 1 extrahepatic CC), 81.8% were men with a median age of 59.6 years and most of them had hepatic failure (25%) and bacterial infection (12%). Among the 34 EHC patients who died, death was related to cancer progression in 68%. The CC 1-year survival was 71.6% (95% IC : 35-89.9).

Conclusions: At 5 year, the incidence of cholangiocarcinoma was 0.6% in patients with compensated viral cirrhosis. EHC is the second cause of non liver-related death. Higher risks of oral cancer and non Hodgkin lymphomas were observed when compared to the general population. A high risk of extrahepatic cancer development persists despite sustained viral response in HCV patients.

Disclosure of Interest: None Declared

0-013 NEW SUBCLASSIFICATION OF INTERMEDIATE STAGE HCC: ANALYSIS OF 46,997 JAPANESE HCC PATIENTS FROM A NATIONWIDE SURVEY OF THE LIVER CANCER STUDY GROUP OF JAPAN

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Introduction: Intermediate stage hepatocellular carcinoma (HCC) is a very heterogeneous tumor in terms of tumor size (over 3cm), tumor number (over 3 nodules) and liver function (Child-Pugh A to B9). Bolondi has proposed subclassification of intermediate stage HCC1 and this classification has been validated worldwide. On the other hand, the new classification (Kinki criteria) has been proposed from Japan as modified Bolondi’s classification.2

Methods: The overall survival (OS) of 46,997 Japanese HCC patients who were registered to Liver Cancer Study Group of Japan from 2000 to 2007 were analyzed using Kaplan-Meier method with comparison by log-rank test validated by Bolondi’s classification and modified Bolondi’s classification (Kinki criteria) which was classified by tumor burden and Child-Pugh (CP) score.

Results: The median OS of patients with BCLC 0, A, B, C and D were 74.7, 65.7, 60.9, 37.1, and 27.9 months, respectively (p<0.001). According to the Bolondi’s classification, the median OS of intermediate stage patients: with CP score 5-7, 5-7 and exceeding up-to-7 (B1), with CP score 6-7 and exceeding up-to-7 (B2) and with CP score 6-7 (B3) were 66.7, 56.7, 43.5, and 30.0 months (p<0.001). According to the Kinki Criteria proposed by Kudo as a modified Bolondi’s classification, the median OS of intermediate stage patients; with CP score 5-7 and within up-to-7 (B1), with CP score 6-7 and exceeding up-to-7 (B2), with CP score 6-7 and exceeding up-to-7 (B3) were 66.7, 55.0, 41.9, and 35.9 months, respectively (p<0.001).

Conclusion: The OS by Bolondi’s subclassification and modified Bolondi’s subclassification were both well stratified in Japanese HCC cohort. Modified Bolondi’s subclassification is more simple and easier to apply to clinical practice than Bolondi’s subclassification and gives the appropriate treatment indication according to each stage.


Disclosure of Interest: None Declared

0-014 COMPLIANCE TO HEPATOCELLULAR CARCINOMA SCREENING GUIDELINES IN PATIENTS WITH COMPENSATED VIRAL CIRRHOSIS INCREASES THE PROBABILITY OF CURATIVE TREATMENT AND SURVIVAL TAKING INTO ACCOUNT LEAD-TIME BIAS (ANRS C012 CIRVR COHORT)

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Introduction: Semi-annual surveillance for hepatocellular carcinoma (HCC) in patients with cirrhosis is recommended but has been recently challenged. The aim of this work was to assess the impact of compliance to HCC screening in intermediate stage at diagnosis, treatment procedures and survival in patients with compensated viral cirrhosis included in the ANRS C012 CIRVR prospective cohort.

Methods: Patients with the following criteria were enrolled in 35 French centers: a) biopsy-proven HBV or HCV cirrhosis; b) Child-Pugh A; c) absence of previous liver complications. Patients were...
**Oral Communications**

**Saturday, 10 September 2016**

**0-015 HOSPITAL VOLUME AND SURVIVAL AFTER HEPATOCELLULAR CARCINOMA DIAGNOSIS**

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**Introduction:** The association between hospital volume and outcome following high-risk low volume cancer surgery is well documented. However, this association is not well understood in cancer patients undergoing non-surgical therapies. We explored this association in a cohort of newly diagnosed patients with hepatocellular carcinoma (HCC).

**Methods:** Data from the 2000 through 2011 in Texas Cancer Registry were used to study adults with newly diagnosed HCC (17,233 patients from 322 hospitals). Hospital volume was stratified into low and high volume using Contal’s outcome-based method. A multivariable Cox regression with shared frailty was used to evaluate the association between hospital volume, over a continuous scale, and overall survival. The relationship between treatment modality and hospital volume was explored using mixed effects logistic regression.

**Results:** The majority (61%) of HCC patients were seen in 21 high volume hospitals. An annual hospital volume cutoff of 24 patients was determined to stratum between high and low volume hospitals. Patients at high volume hospitals presented more commonly with localized disease (56% versus 50%, p=0.01) and were more likely to receive curative therapies, including surgical resection, liver transplantation, or ablation (22% versus 12%, p=0.01). High volume hospitals were significantly associated with improved survival (HR = 0.96, 95% CI = 0.94 - 0.98). In multivariable analysis, hospital volume was associated with increased overall treatment utilization (HR = 1.3, 95% CI = 1.2 - 1.4).

**Conclusion:** In this prospective cohort of patients with histologically proven compensated viral cirrhosis, compliance to screening is independently associated with HCC diagnosis at an early stage, implementation of first-line curative treatments and better lead-time adjusted overall survival.

**Disclosure of Interest:** None Declared

**0-016 RANDOMIZED CONTROLLED TRIAL OF OUTREACH STRATEGIES TO IMPROVE HEPATOCELLULAR CARCINOMA SCREENING RATES**

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**Introduction:** Hepatocellular carcinoma (HCC) surveillance is associated with early tumor detection and improved survival in patients with cirrhosis, but its effectiveness is limited by underuse, particularly among racial/ethnic minorities and socioeconomically disadvantaged patients. There have been few data evaluating interventions to increase HCC surveillance rates. Our study’s aim was to compare the clinical effectiveness of mailed outreach and patient navigation strategies to increase HCC surveillance rates in a racially diverse and socioeconomically disadvantaged cohort of patients with cirrhosis.

**Methods:** Patients with documented or suspected cirrhosis at a large urban safety-net health system in the United States were randomized in a 1:1:1 fashion to receive mailed outreach invitations for surveillance ultrasound, mailed outreach plus patient navigation, or usual care with opportunistic, visit-based screening. Documented cirrhosis was defined using ICD-9 codes for cirrhosis or cirrhosis-related complications, and suspected cirrhosis was defined as an AST/ALT ratio >1.5 or an aminotransferase level >100 U/L. Surveillance rates were compared using the χ2 test. Logistic regression was used to determine predictors of surveillance uptake and compare rates of uptake among the three groups.

**Results:** Baseline characteristics were similar among the three groups. Surveillance rates were higher among patients with documented and suspected cirrhosis, with 20.4% having suspected cirrhosis. Cirrhosis was due to HCV in 51.0%, alcohol in 17.6%, and hypertension in 16.6%, and HBV in 3.4% of patients. Using intent-to-treatment analysis, rates of imaging-based HCC surveillance were significantly higher in the outreach/patient navigation arm (247/600, 41.2%) and outreach alone arm (229/600, 38.0%) than usual care arm (105/600, 17.5%) (p<0.001 for both comparisons); however, surveillance rates did not significantly differ between outreach arms (p=0.26). Diagnostic contrast-enhanced CT/MRI had been recently performed in 6.7%, 6.8%, and 7.0% of patients in the three arms, respectively, so repeat ultrasound for surveillance purposes was not required/ordered. An additional 4.3%, 15.7%, and 16.2% of patients in the usual care, outreach alone, and outreach/navigation arms, respectively, scheduled an ultrasound but missed or cancelled their appointment. Among all responders in both outreach arms, the median time to response was 27 days. There were 27.4% “early responders” who called to schedule an ultrasound for HCC screening, whereas only 10.8% of usual care patients responded within 21 days.

**Conclusion:** Outreach strategies doubled HCC surveillance rates in patients with cirrhosis. Adding patient navigation to telephone surveillance reminders provided no significant additional benefit.

**Disclosure of Interest:** None Declared
0-017 COMPARISON OF CLINICAL FEATURE OF NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) ASSOCIATED HEPATOCELLULAR CARCINOMA WITH VERSUS WITHOUT LIVER CIRRHOSIS

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Introduction: Nonalcoholic fatty liver disease (NAFLD) is one of major etiologies of hepatocellular carcinoma (HCC) in Western countries. Clinical characteristics of NAFLD induced HCC in the absence of cirrhosis remained to be known. We aimed to investigate the proportion of NAFLD induced HCC in the absence of cirrhosis and compare the clinical features of NAFLD induced HCC with and without cirrhosis.

Methods: The Global HCC BRIDGE (Bridge to Better Outcomes in HCC) study was a large multiregional longitudinal cohort study designed to describe the global practice patterns and outcomes in patients with HCC diagnosed between January 2005 and September 2012. Data from participating sites in North America and Europe was obtained for analysis.

Results: Of 5079 HCC patients, 323 (6.4%) had NAFLD induced HCC. Mean age at HCC diagnosis (76 vs 63, P<0.01) and proportions of females (31% vs 21%, P<0.01), noncirrhosis (77% vs 15%, P<0.01) and diabetics (78% vs 33%, P<0.01) were higher in patients with NAFLD compared to patients with all other etiologies combined. The proportion of patients with early stage HCC (33% vs 32%, P=0.70) were similar, but the proportion of patients receiving potentially curative treatment (53% vs 61%, P<0.01) was lower in patients with NAFLD than in patients with other etiologies. The overall survival was similar in patients with NAFLD compared to patients with other etiologies [hazard ratio (HR) 1.0, P=0.82]. Comparing the clinical features of NAFLD induced HCC patients with vs. without cirrhosis (Table), males, ever smoker, and non-diabetics were associated with lack of cirrhosis. In multivariable analysis, age (OR: adjusted odd ratio; 1.04, 95% CI [confidence interval] 1.01-1.08, P=0.03) and ever-smoker (AOR: 1.95, 95% CI: 1.04-3.74, P=0.04) were independently associated with lack of cirrhosis without diabetes while diabetes were inversely associated with HCC without cirrhosis (AOR: 0.35, 95%CI: 0.18-0.68, P<0.01). Although mean tumor size was larger in non-cirrhotics (6.5 vs 4.0, P<0.01), a higher proportion of non-cirrhotics were treated by surgical resection. Overall survival was similar in non-cirrhotics compared to cirrhotics (HR 0.8, 0.6-1.2, P=0.25).

Conclusion: In a large Western HCC cohort, a higher proportion of NAFLD induced HCCs occurred in the absence of cirrhosis. NAFLD induced HCC is associated with older age at diagnosis and a higher proportion of females. Among NAFLD induced HCC patients, diabetic patients were more likely to have cirrhosis associated HCC while old age and ever smoker were associated with NAFLD induced HCC in the absence of cirrhosis. Tumors were larger and surgical resection was performed more frequently in non-cirrhotics than in cirrhotics.

Disclosure of Interest: None Declared

0-018 UNEXPECTED HIGH RATE OF TUMOR RECURRENCE IN PATIENTS WITH HEPATITIS C VIRUS-RELATED HEPATOCELLULAR CARCINOMA UNDERGOING INTERFERON-FREE THERAPY

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Introduction: The success of direct acting antivirals against hepatitis C is a major breakthrough in Hepatology. Until now, however, there are very few data on the effect of HCV eradication in patients who have already developed hepatocellular carcinoma.

Methods: The study included patients with HCV infection and prior history of treated hepatocellular carcinoma who achieved complete response and lacked ‘non-characterized nodules’ at the time they underwent anti-HCV treatment with all-oral direct acting antivirals in 4 hospitals. Patients receiving interferon as part of the antiviral regimen were excluded. The baseline characteristics, laboratory and radiologic tumor response were registered in all patients before starting antiviral therapy and during the follow-up according to the clinical practice policy.

Results: Between 2014 and 2015, 103 patients with prior HCV received DAAs, 58 of them met the inclusion criteria. After a median follow-up of 5.7 months, 3 patients died and 16 developed radiologic tumor recurrence (27.6%). The pattern of recurrence was: intrahepatic growth (3 patients), new intrahepatic lesion (1 nodule in 5 patients, up to 3 nodules less or equal to 3 cm in 4 cases and multifocal in one patient) and infiltrative ill-defined hepatocellular carcinoma and/or extra-hepatic lesions in 3 patients.

Conclusion: Our data show an unexpected rate and pattern of tumor recurrence coinciding with HCV clearance and, though based in a very small cohort of patients, should be taken as a note of caution and prime a large scale assessment that exceeds the individual investigators capacity.


0-019 SAFETY AND ANTITUMOR ACTIVITY OF NIVOLUMAB (NIVO) IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC): INTERIM ANALYSIS OF DOSE-EXPANSION COHORTS FROM THE PHASE 1/2 CHECKMATE-040 STUDY

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Introduction: HCC tumors are associated with chronic inflammation that can promote an immunosuppressive environment; anti-PD-1 therapy may counter this inhibition. Nivo, a fully human IgG4 monoclonal antibody PD-1 inhibitor, was initially evaluated in a multiple ascending-dose, phase 1/2 study in patients (pts) with advanced HCC; it was well tolerated with antitumor activity in different etiologies, across lines of therapy, justifying an expansion phase. interim results are presented.

Plenary Session
**Methods:** Pts had histologically confirmed, advanced HCC and Child-Pugh class A. Dose expansion at nivolumab 3 mg/kg was occurred in 4 cohorts: uninfected sorafenib (sof) naive/intolerant, uninfected sof-progressors, HCV-, and HBV-infected. Primary endpoint was confirmed overall response rate (ORR) by RECIST 1.1. Secondary endpoints included OS, PFS, time to progression, and biomarker assessment.

**Results:** Dose expansion enrolled 206 pts; 75% had extrahepatic metastasis, 7% vascular invasion, and 64% prior sor. Across cohorts, pts received a median of 5–6 doses (range: 1–19). Treatment-related AEs (TRAEs) occurred in 104 pts (50%); the most frequent were fatigue (17%) and pruritus (12%). Grade 3/4 TRAEs were seen in 28 pts (14%). Most common were ALT and AST increases (23 each); 68 of 174 evaluable pts (39%) had a decline in tumor burden. Preliminarily, 91 pts (55%) had >18 wks follow-up and/or PD. ORR for these pts was 9% (9/91) [14% (3/22) uninfected sor/naiive/intolerant, 7% (2/27) uninfected sor progressors; 14% (3/21) HCV-infected, 6 mos OS rate was 69% (95 CI, 0.43–0.85). Responses were observed in pts with and without quantifiable PD-1 measured by HCV. Anti-CD8 responses in HCV- and HBV-infected pts have been observed as declines in HCV RNA and quantitative anti-tumor antigen.

**Conclusion:** AEs were consistent across nivo cohorts and similar to profiles in other tumor types. Results are preliminary and may underestimate response; data indicate activity across all etiologic subtypes and lines of therapy, supporting ongoing study of nivo in HCC. © 2016 American Society of Clinical Oncology (ASCO)

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**Disclosure of Interest:** B. Sangro Consulting of: Bristol-Myers Squibb, MedImmune and Bayer.

**General Session 4: Staging and Curative Treatments**

**Saturday, 10 September 2016**

**Oral Communications**

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**O-020 CLASSICAL AND NOVEL HISTOLOGICAL SUBTYPES OF HEPATOCELLULAR CARCINOMA ARE RELATED TO GENE MUTATIONS AND TRANSCRIPTOMIC CLASSIFICATION**


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**Introduction:** Our increasing understanding of hepatocellular carcinoma (HCC) biology holds promise for future personalized care of the patients, however translation of the HCC molecular classification into clinical practice requires a precise knowledge of its relationship to tumor phenotype. Here, we aimed at investigating molecular-phenotypic correlates in a large series of HCC.

**Methods:** Exhaustive pathological features of 343 HCC surgically resected in France in two centers (Créteil and Bordeaux) were reviewed by 2 specialized liver pathologists. Mutational status of 16 oncogenes and tumor suppressor genes involved in HCC development was determined by next generation sequencing. Transcriptomic subgroups of the tumors and expression levels of 60 genes related to various oncogenic pathways, hepatocellular differentiation and function were assessed by real time PCR. Cytokeratin 19, N001, ARD1A, Glutamine Synthetase and c-catenin expression were assessed by immunohistochemistry.

**Results:** Large tumor size (p<0.001), well-differentiation (p<0.001), microvascular (p<0.001) and pseudoglandular (p<0.001) architectural patterns, tumor chromatinosity (p<0.001) and lack of inflammatory infiltrates (p<0.001) were associated to CTNNB1 mutations. Poor differentiation (p<0.001), macrovascular (p=0.004) and microvascular (p=0.02) invasion, compact architectural pattern (p=0.02), multicentric (p=0.01) and pleomorphic (p=0.02) cells were associated to TP53 mutations.

**Conclusion:** Histological subtypes were strongly related to molecular features. The scirrhous subtype was related to the presence of TSC1/TSC2 mutations (p<0.005), the lack of CTNNB1 mutations (p<0.001), an epithelial to mesenchymal transition and progenitor features (CK19 expression p=0.001). The steatohepatitic subtype of HCC was associated to G4 transcriptomic group (p<0.003) and lack of CTNNB1 (p<0.01), TERT (p<0.01), and TP53 (p=0.02) mutations. Two novel histological subtypes, comprising approximately 20% of the analyzed tumors, were identified during the pathological review: (1) the hepatocytic subtype, which designates well-differentiated HCC with microtrabecular, pseudoglandular pattern and chromatinosis, was associated to HCV infection (p<0.001), low alphafeto protein serum levels (<100ng/ml, p=0.01), TERT promoter mutations (p<0.001), Wnt5c-pathway activation (nuclear ß-catenin p<0.001, high G2 expression p<0.001) by CTNNB1 mutations (p<0.001), bile salts transporters expression dysregulation and G566 transcriptomic subgroups (p<0.01); and (2) the macrotrabecular massive subtype, characterised by a predominant macrotrabecular architectural pattern, was associated to HBV infection (p<0.01), African (p<0.001) and Asian (p=0.04) geographic origin, high alphafeto protein serum levels (>100ng/ml p<0.02), satellite nodules (p<0.001), macrovascular and microvascular invasion (p<0.001), angioinvasion activation via angiopeptin 2 overexpression (p=0.007), G3 transcriptomic subgroup (p<0.001), TP53 mutations (p<0.001) and FGFl9 amplifications (p=0.02).

**Conclusion:** Altogether, our study provides a comprehensive overview of the relationship between HCC phenotype and its molecular characteristics. We have showed that histological features already recognized by the World Health Organisation of Tumors are related to particular gene mutations and oncogenic pathways, and further unraveled novel homogeneous histological subtypes linked to molecular alterations that may have clinical relevance. We thus believe that implementation of these subtypes in HCC classification should be considered.

**Disclosure of Interest:** None Declared

**O-033 LACK OF EVIDENCE OF AN EFFECT OF DIRECT ACTING ANTIVIRALS ON THE RECURRENCE OF HEPATOCELLULAR CARCINOMA: DATA FROM THREE PROSPECTIVE FRENCH COHORTS (ANRS C022 HEPATHER, C012 CIRVIR AND C023 CUPILT)**

*Nathalie Ganne-Carrié* for The ANRS collaborative study group on hepatocellular carcinoma (ANRS C022 HEPATHER, C012 CIRVIR and C023 CUPILT cohorts)

**Background and aims:** Sustained virological response following antiviral interferon-based treatment of chronic hepatitis C is associated with decreased long-term risk of hepatocellular carcinoma (HCC) in advanced liver fibrosis. An unexpected high rate of HCC recurrence following antiviral treatment using direct acting antiviral (DAV) has been recently reported.

**Methods:** We analyzed data individually from three French prospective multicenter ANRS cohorts including more than 6,000 patients treated with DAA and we focused on HCC patients who underwent curative procedures before DAA treatment. The aim was to assess the rates of HCC recurrence in these patients according to antiviral treatment regime.

**Results:** In the ANRS C022 HEPATHER cohort, 267 patients with CHC who were previously treated for HCC were analyzed, among whom 159 received DAA and 78 did not. The rates of recurrence were 0.73/100 and 0.65/100 person-months, respectively. In the ANRS C012 CIRVIR cohort, 79 cirrhotic patients in whom HCC was diagnosed and treated, 13 received DAA and 66 did not. The rates of recurrence were 1.11/100 and 1.73/100 person-months, respectively. In the ANRS C023 CUPILT Cohort, 314 liver transplant recipients for HCC who were subsequently treated with DAA were analyzed. Seven HCC recurrences were reported after a median time of 70.3 months after liver transplantation. The rate of recurrence was 2.2 %.

**Conclusion:** In three distinct prospective cohorts, we did not observe an increased risk of HCC recurrence after DAA treatment, notably in patients who underwent curative HCC treatment including liver transplantation.

**General Session 4: Staging and Curative Treatments**

**O-021 THE DETECTION OF CIRCULATING TUMOR-INITIATING CELLS FOR DIAGNOSIS, PROGNOSIS AND THERAPEUTIC RESPONSE EVALUATION IN HEPATOCELLULAR CARCINOMA: A LARGE-SCALE, MULTICENTRE STUDY**

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**Introduction:** The lack of effective methods for timely diagnosis, prognosis prediction, monitoring anticancer treatment response is the main obstacle to further improving the prognosis of hepatocellular carcinoma (HCC) patients. Accumulating evidences indicated that the spread of circulating tumor cells (CTCs) is an early event in tumor progression as well as plays an important role in the initiation of tumor metastases and recurrence. However, although thousands of tumor cells

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unleashed into circulation from primary tumor, only a small population with stem cell-like properties, namely circulating tumor-initiating cells (CTICs), which are the driving force of tumor progression and resistance to classical therapies. Thus, identifying the CTICs subpopulations will provide more clinically relevant information than total CTC counts. Meanwhile, our recent studies and the results for other labs suggest that CTICs in HCC are phenotypically diverse. Therefore, our study constructed a novel CTIC detection panel based on negative enrichment and multimarker qRT-PCR analysis, and the clinical utility for the diagnosis, prognosis and surveillance in hepatitis B virus (HBV)-related HCC were further explored.

Methods: Differing subsets of CTCs in HCC patients, including EpCAM+, CD133+, CD24+, ABCG2+, CD44+, Nestin+, CD133+, CK19+ and ICM+, CTCs, were systematically investigated, and a multimarker diagnostic panel was constructed to target CTICs in a multicenter-patient study with independent validation (total n=1006), including healthy individuals, patients with chronic hepatitis B infection, liver cirrhosis (LC), benign hepatic lesion (BHL) and HBV-related HCC, with area under the receiver operating characteristic curve (AUC-ROC) reflecting diagnostic accuracy. The role of CTIC detection panel in treatment response surveillance as well as its prognostic significance was further investigated.

Results: Four CTIC markers (EpCAM, CD133, CD90, and CK19) were established, with a cutoff of 0.57 by ROC curve after logistic regression training. AUC=0.98, 95% CI 0.94-0.99, sensitivity, 72.5%; specificity, 95.0%; validation: AUC=0.92, 95% CI 0.89-0.94; sensitivity, 82.1%; specificity, 94.5%). Results were similar for early-stage HCC (training: AUC=0.87, 95% CI 0.83-0.90; sensitivity, 71.8%; specificity, 95.0%; validation: AUC=0.93, 95% CI 0.89-0.95; sensitivity, 85.1%; specificity, 94.5%). Compared with all controls, the panel performed equally well in detecting α-fetoprotein (AFP)-negative HCC (including early-stage tumors), also distinguishing HCC from CHB, LC and BHL. Using an optimal cutoff point of 0.80, the prognostic significance of preoperative CTIC detection in predicting tumor recurrence after operation was further confirmed in two independent cohorts (all p <0.001), and its prognostic potential was also retained in AFP-negative and early-stage groups. More importantly, the CTIC load was decreased significantly after resection in 78% of HCC patients with blood sample collection 1 month after surgery, and the positive rate decreased from 76.00% to 51.00% and 34.00%. Compared with CTC persistent negative patients, the patients with persistently high CTIC load showed high tumor recurrence rate after surgery (70.6% vs. 13.3%).

Conclusion: The CTIC panel showed high sensitivity and specificity in the diagnosis of HCC, especially for patients with AFP negative or early stage disease. It could also be a real-time parameter for risk prediction and treatment monitoring, enabling early decision-making to tailor effective antitumor strategies.

Disclosure of Interest: None Declared

0-022 RECURRENCE PATTERNS AND DISEASE FREE SURVIVAL AFTER RESECTION OF INTRAHEPATIC CHOLANGIOCARCINOMA: PREOPERATIVE AND POSTOPERATIVE PROGNOSTIC MODELS

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Introduction: Liver resection is the most effective treatment for intrahepatic cholangiocarcinoma (HCC). Recurrent disease is frequent, however, recurrence patterns are ill-defined, and prognostic models are lacking.

Methods: A primary cohort of 189 patients who underwent resection for HCC was used for recurrence patterns analysis within and after 24 months. Based on independent factors for disease free survival (DFS) identified upon Cox regression analysis, preoperative and postoperative models were developed using a recursive partitioning method. Models were externally validated using a multicenter cohort of 522 selected patients (Association Française de Chirurgie-HCC study group).

Results: Recurrence within 24 months most often involved the liver (82.7%) while most recurrences after 24 months were strictly extrahepatic (61.1%). In multivariable analysis of the primary cohort, independent preoperative factors for DFS were tumor size and multifocality (based on imaging), while tumor size, multifocality, vascular invasion and lymph node metastases (based on pathology) were independent postoperative factors. The preoperative model (Figures 1A, 1B, 1C) allowed patient classification in low risk and high risk groups of recurrence. In the validation cohort (n=522), high risk patients had a greater likelihood of recurrence (HR=2.17, 95% CI 1.74-2.72; p<0.001). Postoperative model (Figures 2A, 2B, 2C) included tumor size, vascular invasion and positive nodal disease on pathology and classified patients in low, intermediate and high risk groups in the primary cohort. As compared to low risk patients in the validation cohort, intermediate and high risk patients were more likely to experience recurrence (HR=1.9, 95% CI 1.41-2.47; p<0.001 and HR=2.99, 95% CI 2.08-4.31; p<0.001, respectively).

Image:

Conclusion: Recurrence patterns are time dependent. Both models as developed and validated in this study classified patients in distinct recurrence risk groups, which may guide treatment recommendations.

Disclosure of Interest: None Declared

0-023 EARLY DETECTION AND CURATIVE TREATMENT OF HEPATOCELLULAR CARCINOMA: A COST EFFECTIVENESS ANALYSIS BASED ON PROSPECTIVE FRENCH COHORTS (ANRS C012 CIVIR-2014)

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Introduction: Hepatocellular carcinoma is the leading cause of death in patients with cirrhosis. As the international guidelines on screening for hepatocellular carcinoma in patients with cirrhosis are not universally admitted and followed, the objective of this study was to estimate the cost-effectiveness of full compliance.
Methods: We compared screening as recommended by the guidelines ("gold standard monitoring") to "real life monitoring" using a Markov model describing the history of the disease and treatment course. Patients entered the model in the "compensated cirrhosis" state and could be diagnosed with nodules or with liver cancer and transit to "non-malignant nodules" or "HCC" states. Curative HCC treatments included: surgical liver resection, percutaneous radiofrequency ablation and liver transplantation. Patients who required palliative care received chemomobilization, systematic therapy (Sorafenib) or other palliative care. After liver resection or radiofrequency ablation treatment, patients could be successfully treated or relapse. Transition probabilities were derived from two French cohorts. Costs were computed in € using French tariffs. Effectiveness was measured in life years gained. An incremental cost-effectiveness ratio was calculated for a 10-year horizon. We performed one-way and probabilistic sensitivity analyses.

Results: The cost difference between the two groups was €530 ($71,627 in the gold standard monitoring group versus €71,097 in the real life monitoring group) and survival increased by 0.37 years (7.16 versus 6.81 years). The global incremental cost-effectiveness ratio was €1,436 per life year gained (LYG). It was €3,250 per LYG for a patient undergoing radiofrequency ablation in first line curative treatment, €2,474 per LYG gained for a patient undergoing radiofrequency ablation in first line curative treatment and €19,319 per LYG for a patient undergoing liver transplantation in first line curative treatment. The gain in life expectancy was obtained by earlier detection and better treatment results. Gold standard monitoring allowed more patients to gain access to curative treatments, and among those to the cheaper options (radiofrequency ablation or resection) while later detection not only reduced the likelihood of curative treatment but also increased the proportion of liver transplant among the curative treatments.

Image:

Conclusion: Gold standard monitoring for patients with cirrhosis is life saving and cost-effective, due to a higher probability of benefiting from a curative treatment and a higher survival probability. These results highlight the pivotal role of interventions aimed at improving HCC surveillance rates both at the health-care providers and patients’ levels.

References: Trinchet, J.C; Chaffut, C; Bourcier V; Degos F et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6- month periodicities. Hepatology 2011

H4; Surveillance des malades atteints de cirrhose non compliquée et prévention primaire des complications", Sept. 2007.


Disclosure of Interest: None Declared

O-024 A PROPENSITY SCORE ANALYSIS ON SURVIVAL BENEFIT OF LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA ASSOCIATED WITH PORTAL VEIN INVASION USING NATIONAL SURVEY DATA IN JAPAN.

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Introduction: Portal vein tumor thrombosis (PVT) is one of the most significant prognostic factors in patients with hepatocellular carcinoma (HCC), and when present, only sorafenib is recommended according to BCLC guidelines endorsed by AASLD/ESOAS. There have been a number of case series reporting survival benefit of liver resection in this subgroup of patients, however, there have been no randomized controlled trials nor even large scale registry data analysis to address this issue. To provide a second best level of evidence for this clinical question, we have conducted a propensity score analysis using a large scale national registry data in Japan.

Methods: We analyzed data for 6,474 HCC patients with PVT registered between 2000 and 2007. Of these patients, 2,093 patients who underwent LR and 4,381 patients who received other treatments were compared. The propensity scores were calculated for 1,786 patients in the LR group and 3,758 patients in the non-LR group and we successfully matched 1,229 patients (88.8% of the LR group).

Results: The median survival time (MST) in the LR group was 1.93 years longer than that in the non-LR group (2.74 years vs 0.81 years; P < 0.001). Cox proportional hazards model revealed that LR provides a survival benefit regardless of the Child-Pugh grade, etiology of HCC, and tumor number. The survival benefit was not statistically significant only in patients with PVT invading the main trunk or contralateral branch in the LR branch, the postoperative mortality rate was 1.4% (29 patients) and the multivariate analysis identified liver cirrhosis grade (HR 1.31), Child-Pugh class B (HR 1.69), and R2 resection (HR 1.60) as significant risk factors for the overall survival other than tumor related factors.

Conclusion: LR is associated with a longer survival outcome than non-surgical treatment in HCC patients with PVT. As long as the PVT is limited to a first-order branch, LR should be the first treatment of choice, especially in patients with good liver function.

Disclosure of Interest: None Declared

O-025 TEN-YEAR OUTCOMES OF RADIOFREQUENCY ABLATION FOR HEPATOCELLULAR CARCINOMA: A NOMOGRAM STUDY OF THE ALBUMIN-BILIRUBIN GRADE

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Introduction: Tumor factor and liver functional reserve are both crucial in determining the prognosis of patients with hepatocellular carcinoma (HCC). Albumin-bilirubin (ALB-BIL) grade is a newly-developed serum marker for determining the outcomes of HCC patients, but is not well validated for those who undergo radiofrequency ablation (RFA). This study aimed to investigate the 10-year outcomes of RFA for HCC with an ALB-BIL grade-based nomogram.

Results: The median survival time (MST) in the LR group was 1.93 years longer than that in the non-LR group (2.74 years vs 0.81 years; P < 0.001) and 1.03 years longer than that in the non-LR group (2.41 years vs 1.36 years; P < 0.001) in a propensity score-matched cohort (Figure). A subgroup analysis revealed that LR provides a survival benefit regardless of the Child-Pugh grade, etiology of HCC, and tumor number. The survival benefit was not statistically significant only in patients with PVT invading the main trunk or contralateral branch in the LR branch, the postoperative mortality rate was 1.4% (29 patients) and the multivariate analysis identified liver cirrhosis grade (HR 1.31), Child-Pugh class B (HR 1.69), and R2 resection (HR 1.60) as significant risk factors for the overall survival other than tumor related factors.

Conclusion: LR is associated with a longer survival outcome than non-surgical treatment in HCC patients with PVT. As long as the PVT is limited to a first-order branch, LR should be the first treatment of choice, especially in patients with good liver function.

Disclosure of Interest: None Declared
Methods: We enrolled 622 treatment-naïve HCC patients who underwent RFA at Taipei Veterans General Hospital from May 2002 to September 2013. Prognostic factors were analyzed in terms of overall survival after RFA. Multivariate Cox proportional hazards model was used to construct the nomogram from significant predictors, including the ALBI grade which calculated as −0.085×(albumin g/l) + 0.66×log(bilirubin μmol/l). The performance of the nomogram was evaluated by concordance indices and calibration tests.

Results: After a median follow-up of 42.6 months, 190 patients died and 432 patients were still alive in their last visit. The cumulative 5- and 10-year overall survival rates were 63.1% and 48.7%, respectively. Stratified by the ALBI grade, the cumulative 5- and 10-year survival rates were 80.0% and 67.9% for patients with grade 1, and were 48.6% and 35.1% for those with grade 2-3, respectively (p<0.001). Multivariate analysis disclosed that age >65 years (p<0.001), prothrombin time international normalized ratio >1.1 (p=0.014), alpha-fetoprotein (AFP) >20ng/ml (p=0.010), multiple tumor (p=0.043) and ALBI grade 2 or 3 (p<0.001) predicted overall mortality. A nomogram with a scale of 0–260 was developed with these five variables, and the predicted survival rates at 3 and 5 years were calculated. Internal validation with 100 sets of bootstrap samples had a good concordance index of 0.770 (95 % confidence interval: 0.633-0.876) and the calibration plots well-matched the 45-degree line for 3- and 5-year survival prediction. Furthermore, the ALBI grade had a good predictive accuracy for overall survival in comparison to other prognostic factors.

Conclusion: Ten-year survival outcomes of hepatocellular carcinoma after radiofrequency ablation were acceptable, indicating RFA could be served as a curative treatment modality for early-stage HCC. This easy-to-use nomogram with the ALBI grade offers individualized survival at 3 and 5 years for HCC patients undergoing curative RFA.

Disclosure of Interest: None Declared

O-026 SUBSTAGING OF BARCELONA CLINIC LIVER CANCER STAGE C HEPATOCELLULAR CARCINOMA BY TUMOR FACTORS AND LIVER FUNCTION

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Introduction: It has been known that prognosis of advanced hepatocellular carcinoma (HCC) is grave. Advanced HCC principally denote Barcelona Clinic Liver Cancer (BCLC) stage C, but this stage encompasses a wide range of diseases with various prognoses. Therefore, we aimed to subclassify the BCLC stage C for prediction of more accurate prognosis in HCC patients

Methods: From January 2004 to December 2012, data of 564 patients with newly diagnosed HCC BCLC stage C of the three tertiary hospitals affiliated with Korea University were analyzed retrospectively. The variables affecting overall survival (OS) were analyzed and the sub-classification was performed.

Results: The mean follow up duration was 8.73 months [standard deviation (SD) = 12.36]. Tumor factors such as size more than 10cm (T, HR 1.77, p=0.001), major portal vein invasion (PVI, HR 1.38, p=0.005), and distant metastasis (M, HR 1.43, p=0.004) as well as Child-Pugh grade (HR 1.76, p<0.001) were proved to be independently associated with OS by multivariate analysis.

Conclusion: Substaging of BCLC stage C by tumor size, major portal invasion, distant metastasis and underlying liver function might be useful for discriminating patient prognosis.

Disclosure of Interest: None Declared
O-027 PROSPECTIVE RANDOMIZED CONTROLLED PHASE III TRIAL COMPARING THE EFFICACY OF SORAFENIB VERSUS SORAFENIB IN COMBINATION WITH LOW-DOSE CISPLATIN/FLUOROURACIL HEPATIC ARTERIAL INFUSION CHEMOTHERAPY IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Nataliya Rohr-Udilova5, Paulette Bioulac-Sage6, 7, Gabrielle Couchy1, 2, 3, 4, Bettina Grasl-Kraupp8, Fumihiko Kanai2, Kohei Akazawa9 and SILIUS Study Group

Introduction: Hepatic arterial infusion chemotherapy (HAC) using low-dose cisplatin and 5-fluorouracil (LDDP) is one of the treatment options for patients with unresectable advanced hepatocellular carcinoma (HCC). This study was designed to assess whether HAC in combination with sorafenib (S+HAC) improves overall survival (OS) compared with sorafenib alone (S).

Methods: This multicenter, open-label, randomized, phase 3 study enrolled uHCC patients who progressed to TACE failure, portal vein invasion, or extrahepatic spread. Patients were randomized (1:1) to receive sorafenib 400 mg BID orally or sorafenib 400 mg BID orally in combination with HAC using LDDP (20 mg/m², on days 1 and 8, and 5-FU 330 mg/m², continuously on days 1–5 and 8–12 via an implanted catheter system). The primary endpoint was OS. Key secondary endpoints were progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), disease control rate (DCR), and safety.

Results: Among 210 randomized patients (85.8% males), 44.7% had HCC infection, 87.4% had ECOS-PG of 0, 69.5% had vascular invasion, 26.3% had extrahepatic spread, and 88.4% had Child-Pugh A liver function. S+HAC did not meet the primary endpoint of significantly improving OS compared with S, but showed improvement in TTP and DCR, and S+HAC improved OS in patients with MPVI. The responders who achieved CR or PR in both groups showed significantly better OS than non-responders (p=0.001). Grade 3–4 adverse events with S and S+HAIC were anemia, neutropenia, and thrombocytopenia.

Conclusion: In this study, S+HAC did not significantly improve OS in uHCC patients compared with S. However, in uHCC patients with MPVI, S+HAC significantly improved OS and the 1- and 2-year survival rates compared with S. The higher ORR of S+HAC resulted in a much higher fraction of the enrichable patient population who had survival benefit from treatment with S+HAC compared with S (ClinicalTrials.gov identifier NCT01214343).

Disclosure of Interest: None Declared

O-028 PROLIFERATION MARKERS ARE ASSOCIATED WITH MET EXPRESSION IN HEPATOCELLULAR CARCINOMA AND PREDICT TIVANTINIB SENSITIVITY IN VITRO

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Introduction: Tivantinib has shown promising clinical benefits in a subgroup of hepatocellular carcinoma (HCC) patients with MET overexpressing tumors and is currently under phase III evaluation in HCC selected on high MET expression. However, although tivantinib was first reported as a highly selective MET inhibitor, its antitumor mechanism has been recently challenged, raising some concerns about the rational to use MET as a reliable predictive biomarker of response. We aimed to better characterize tivantinib pharmacological activity and its relationship with MET signaling by combining analyses of large collections of human HCC cell lines and primary tumors.

Methods: We tested 36 liver cancer cell lines for pharmacological response to 5 compounds: tivantinib, two selective MET inhibitors (UNJ-38877605 and PHA-665752) and two antimitotic compounds (paclitaxel and vinblastine). Drug sensitivity was assessed by measuring cell viability using the MTS assay. Western blot and mitotic index analyses were performed to investigate drug effect. We searched for biomarkers predicting tivantinib sensitivity, by analyzing the expression of 50 genes using qRT-PCR and searching for mutations in 5 major genes, including MET, in all the cell lines and in a large series of 281 HCC primary tumors.

Results: Tivantinib inhibited efficiently cell viability in more than half of the liver tumor cell lines at clinically achievable concentrations (GSI ≤ 6µM). However, no relationship between MET expression/activation and tivantinib antitumor activity was identified in cell lines. In addition, pattern of tivantinib sensitivity across the 36 cell lines was similar to those obtained with antimitotic drugs (r=0.57, P=0.0003 for paclitaxel; r=0.6, P<0.0001 for vinblastine) but not with MET inhibitors (r=0.13, P=0.4 for PHA-665752; r=0.29, P=0.1 for UNJ-38877605). In contrast to MET inhibitors, tivantinib was not able to inhibit MET activity and the phosphorylation of downstream proteins AKT and ERK1/2. However, tivantinib induced mitotic arrest similar to antimitotic agents. We identified a good correlation between expression level of cell proliferation markers and tivantinib antitumor efficacy in the whole panel of cell lines. In addition, serum starvation, that decreases cell proliferation, reversed tivantinib response in highly sensitive cell lines, while no or opposite effect was observed with MET inhibitors. Interestingly, in HCC we found a strong correlation between mRNA level of MET and proliferation markers including KI67 (r=0.52, P<0.0001), identifying MET as a surrogate marker of cell proliferation in primary tumors.

Conclusion: We showed that tivantinib does not act as a MET inhibitor but as an antimitotic agent and we identified cell proliferation markers as predictors of its antitumor efficacy. Moreover, we found that MET behaves as a proliferation marker in HCC thereby reconciling experimental results with previous clinical findings that have demonstrated greater therapeutic activity of tivantinib in “MET-high” HCC patients. Finally, KI67 assessment may help to refine patient selection who may benefit from tivantinib therapy.

Disclosure of Interest: None Declared
compared to ICB alone (40%) or with RT alone (49%) as shown in tumor mean diameter (p<0.01). Survival was significantly improved in combination group compared to ICB alone or RT alone (7-week survival rate: 50% vs. 10% or 30%, respectively, p<0.001). Increased level of apoptosis was observed in combination therapy compared to ICB alone (2-fold, p< 0.001) or RT alone (2.9-fold, p< 0.001), which suggests that combination of ICB and RT deactivates tumor growth in vivo by increasing apoptosis. 

Conclusions: Our study demonstrated that RT induced immunogenic modulation and enhanced expression of ICD inducers in tumor, which could lead to immunogenic cell death. We also demonstrated that RT upregulated PD-L1 expression in tumor, which could facilitate antitumor effect of anti-PD-L1. The combination of RT and immune check point inhibitor, anti-PD-L1, significantly improved antitumor effect shown in tumor growth delay as well as in survival. Our findings provide the evidence to support combination strategy of immunoradiotherapy for malignant tumor therapy.


Disclosure of Interest: None Declared

0-030  
COST-EFFECTIVENESS OF SORAFENIB THERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA: AN ANALYSIS OF THE SEER-MEDICARE DATABASE

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Introduction: Sorafenib, a multikinase inhibitor, is the only chemotherapeutic approved for use in the US for the treatment of advanced HCC, however its cost-effectiveness has not been well described. We aimed to examine the cost effectiveness of sorafenib therapy elderly patients with advanced HCC in the US.

Methods: We performed a secondary analysis of continuously enrolled Medicare beneficiaries with HCC diagnoses from 2007-2009, based on SEER diagnosis codes. Our primary aim was to determine the cost-effectiveness of sorafenib therapy. We compared advanced stage patients with HCC (AJCC stage IV/VM) who received sorafenib within 6 months of diagnosis to advanced stage patients with HCC who received no therapy (control). We calculated the Charlon comorbidity index 12 months prior to diagnosis and an aggregate variable for decompensated cirrhosis (presence of esophageal varices or varical banding, ascites or paracentesis, hepatic encephalopathy or use of neomycin, lactulose, or rifaximin.) We also performed a propensity matched analysis of sorafenib treated and control patients. Total costs were compiled using Medicare Part A, B, and D data files from diagnosis to the end of follow-up. We compared costs for sorafenib-treated patient and control patients and calculated incremental cost-effectiveness ratios (ICERs) per life year gained, with a threshold of $100,000 in 2015 US dollars. To examine the cost effectiveness ratio, we used a sensitivity analysis where our empirical distribution was resampled using replacement, giving us a total of 500 bootstrap permutations of the data. To assess the variation of the sample we considered the 2.5% and 97.5% nonparametric percentiles along with the median value. We also conducted traditional one-way sensitivity analyses by varying survival of the sorafenib treated group by 10% and 40% to test the robustness of our ICER estimates.

Results: We analyzed cost differences between sorafenib-treated and untreated groups, as shown in Figure 1. Based on accepted thresholds, sorafenib therapy appears to be cost-effective in both the overall cohort (ICER: $84,250) and propensity-matched cohorts (ICER: $81,249). However, sorafenib is no longer cost-effective when analysis is limited to patients with decompensation, with an ICER of $224,914 per life year gained in the overall decompensated cohort and $188,065 per life year gained in the propensity-matched decompensated cohort. In a one-way sensitivity analysis of the overall cohort, we found varying the median survival seen with sorafenib 10% resulted in an ICER range of $72,005-$101,513 and 40% resulted in an ICER range from $50,142-$263,469. We created two different ICER bootstrap samples—one for the overall comparison and one for the propensity score sample. The median values of the distributions were higher than our observed statistic so the percent of times for which the ratio was less than the standard cutoff ($100,000) might be biased upwards. The median ICER for the overall set was $96,327 (95% CI: $70,253-$193,573) and $110,982 (95% CI: $67,701-$321,127) for the propensity score set. Given these ranges we cannot conclude that our realized estimates were significantly less than $100,000.

Conclusion: Although sorafenib appears cost effective among all comers based on our base case analysis, it is of modest survival benefit and not cost effective in those with hepatic decompensation. Therefore, our data suggest providers may consider best supportive care and earlier referral to palliative care for elderly patients with hepatic decompensation and advanced HCC.

Disclosure of Interest: None Declared

0-031  
TRANSCRIPTIONAL Deregulation in Hepatoblastoma Patients Points to a New Oncogenic Mechanism and Treatment

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Introduction: Hepatoblastoma (HB) is the most common paediatric liver cancer that develops on a normal liver (NL). HB diagnosis and tumour staging are based on histopathological assessment of biopsies, radio-imaging and serum alpha-fetoprotein (AFP) levels. Treatment of HB associates cisplatin-based chemotherapy (CT) with either the surgical resection of the primary tumour, or liver transplantation. This treatment is effective for 70-90% of patients. However, the outcome is less satisfactory for patients with high-risk tumours, poor response to CT and/or lung metastasis. There is an urgent need for new agents to address the issues of the unresponsive tumours and tumour relapse in HB management [1].

In this study we focused on over-expression of the Fancani Anemia (FAN) pathway that has been previously shown to be responsible for replication-dependent removal of interstrand DNA crosslinks and to participate in DNA damage response. Abnormal activity of FAN pathway has been reported in many cancers and is particularly elevated in highly proliferating cancers. Interestingly, FA pathway counteracts the effects of DNA-damaging drugs such as cisplatin [2], the chemotherapeutic drug used in routine for the treatment of patients with HB.

Methods: We completed polyA+ sequencing of HB and matching NL samples from 24 child patients and several tumoral hepatic cell lines. Five-gene signature was further validated by RT-qPCR in a larger collection of HB samples. Activation of the FA pathway was explored by Western blot and immunofluorescence. The viability and apoptosis of the cells in response to drugs was assessed by MTS assay and flow cytometry, respectively.

Results: This work yielded an unprecedented view of the HB transcriptome. We confirmed the abnormal activation of Wnt pathway in all HB tumours, but also the involvement of other oncogenic pathways. There are clear differences in transcriptome between HB and adjacent NL. C1 and C2 subgroups were distinct with particular down-regulation of liver-specific enzymes and overexpression of stem cell markers in C2. However, the published 16-gene signature was not sufficient to separate NL from HB. Studying the expression levels of only five genes effectively distinguishes among NT, C1 and C2 and also revealed two major subgroups among C2 patients (C2A and C2B). We focused on C2A group characterized by increased proliferation and typical mutations in beta-catenin gene. RT-qPCR analysis showed that C2A group is transcriptionally similar to HB-derived HuH-6 and HepG2 cell lines – they exhibit cell cycle and DNA repair genes overexpression with a strong activation of the FA pathway.

Our results showed that the treatment of HB C2A-derived HuH-6 and HepG2 cell lines with a combination of cisplatin and inhibitors of FA pathway had an additive effect and strongly impaired the proliferation and massively induced tumoral cell death. Alone FA pathway inhibitors totally blocked
the ubiquitination and activation of key components of the FA core complex, FANCD2 and FANCI, and the formation of irradiation-mediated nuclear foci of repair. Moreover, a persistence of histone H2AX phosphorylation after FA pathway inhibition was observed confirming the inability of irradiated cells to repair DNA damages.

**Conclusion:** FA pathway inhibitors sensitize cancer cells to cisplatin-mediated DNA damages by blocking the DNA repair mechanisms. Our data support an important role of FA core complex in HB carcinogenesis and raises the possibility that FA pathway inhibitors can be used for HB treatment in combination with cisplatin.

**References:** 1. PMID:23831416, 2. PMID:26194820.

**Disclosure of Interest:** None Declared

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**O-032 MTOR INHIBITOR FOR THE TREATMENT OF AKT/YAPS127A DRIVEN CHOLANGIOCARCINOMA IN MICE**

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**Introduction:** Intrahepatic cholangiocarcinoma (ICC) is one of the most lethal cancers with limited treatment options. INK128, a second generation ATP competitive mTOR inhibitor, shows efficacy for multiple tumor types in vitro and in preclinical models.

**Methods:** Activated forms of AKT (myr-AKT) and Yap (YapS127A) were hydrodynamically transfected into mouse liver. The requirement of mTOR pathway for tumor development were analyzed using genetic approaches (shRaptor or conditional Rictor knockout mice). Gemcitabine or INK128 was administered to tumor bearing mice to study the efficacy of these drugs for the treatment of ICC in mice.

**Results:** Co-expression of the activated forms of AKT and Yap (AKT/YapS127A) led to ICC development in mice. Tumor tissues showed activated AKT/mTOR, Ras/MAPK and Notch cascades, increased glycolysis as well as profound desmoplastic response. Using genetic approaches with either shRaptor or Rictor knockout mice, we found that both mTORC1 and mTORC2 were required for AKT/YapS127A driven ICC formation in vivo. Next we determined the therapeutic effects of INK128 in comparison to Gemcitabine in this murine ICC model. We found that Gemcitabine had no efficacy in AKT/YapS127A induced ICC, consistent with the clinical observation that Gemcitabine has only very limited efficacy in a small subset of CCA patients. In contrast, when INK128 was orally administered to treat late stage AKT/YapS127A tumor bearing mice, the treatment resulted in partial tumor regression. Mechanistically, INK128 was able to efficiently inhibit AKT/mTOR signaling both in vivo and in vitro.

**Conclusion:** AKT/YapS127A induced mouse ICC represents a novel murine model to study ICC. Our study suggests that INK128 may be a superior drug than Gemcitabine for the treatment of ICC, especially in patients whose tumors show activated AKT/mTOR cascade.

**Disclosure of Interest:** None Declared
Clinical Posters

P-001 ASSESSMENT OF RISK FOR RECURRENCE OF HEPATOCELLULAR CARCINOMA: AN EXTENDED SURVEILLANCE INTERVAL 1 YEAR AFTER CURATIVE TREATMENT

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Introduction: The guidelines recommend surveillance for hepatocellular carcinoma recurrence be performed 3-monthly during 1 year after curative treatment, and 6-monthly thereafter in all patients. This strategy did not reflect individual risk based on patients’ tumor biology. We aimed to identify patients who can extend surveillance intervals 1 year after treatments.

Methods: We retrospectively analyzed 1,490 patients treated with hepatectomy/radiofrequency ablation in the Barcelona Clinic Liver Cancer stage I/D and well-preserved liver function. In patients under 3-month surveillance in total periods, a new model for survival was developed using multivariable analysis: the derivation (n=892)/validation set (n=598). Survival rates in low-risk patients by the new model were compared according to surveillance intervals 1 year after treatments: 3-monthly vs. 6-monthly (n=467) after propensity score matching and late time bias correction.

Results: Albumin levels, MELD score, tumor size, alpha-fetoprotein levels, and 1-year recurrence were independent factors for survival odds ratios (OR) of 0.33, 1.12, 1.06, 1.09, and 0.99 respectively (all P<0.01). One-year recurrence showed significantly higher OR than other durations (1–2, 2–3, and >3 years, P<0.01). A new model showed AUROC of 0.81 (the derivation set) and 0.77 (the validation set). Survival rates in low-risk patients of the new model under 3-month surveillance 1 year after treatments were not superior to those under 6-monthly surveillance (P=0.958).

Conclusion: Surveillance interval 1 year after treatments in patients with favorable tumor biology can be extended to 6-monthly interval. Surveillance schedules can be optimized to reduce radiation hazard and cost without compromising benefits in low-risk patients.

Disclosure of Interest: None Declared

P-002 INSULIN RESISTANCE INCREASES RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS

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Introduction: To date, few data are available whether insulin resistance (IR) increases hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B virus (HBV) infection. We investigated whether IR is associated with the development of HCC in patients with chronic HBV infection.

Methods: A total of 2,119 hepatitis B surface antigen positive patients (age: 50.2 ± 7.7, male: 1,266 (59.7%), diabetes = 149 (7.0%), obesity ≥ 25 kg/m2 = 722 (34.0%) with IR status) at baseline were analyzed for the development of HCC during follow-up. IR was estimated with HOMA2-IR [0.6%, 1.4%, 3.7% and 4.0% for 1st (<0.93), 2nd (0.93-1.25), 3rd (1.25-1.68) and 4th (≥1.68) quartile of HOMA2-IR, respectively]. During a median of 5.1 years of follow-up (min-max: 1.0 – 10.5 years), 57 patients (2.7%) had HCC. The incidence of HCC was 0.6%/year (95% CI): 0.6% (0.1-3.1), 3.6% (2.1-6.8) and 4.7% (2.1-9.2) for 1st, 2nd and 4th quartile of HOMA2-IR, respectively (P<0.01).

Conclusion: The incidence of HCC increased with HOMA2-IR. A new model is a better total prognostic scoring system for predicting long-term survival in patients with HCC.

Disclosure of Interest: None Declared

P-003 RISK OF HEPATOCELLULAR CARCINOMA IN KOREAN PATIENTS WITH METABOLIC SYNDROME: A BIG DATA ANALYSIS

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Introduction: The metabolic syndrome (MetS) and/or its individual components have been linked to the development of various cancers. Recent studies have suggested MetS as a risk factor of hepatocellular carcinoma (HCC). However, the association between MetS and HCC is in controversial especially in an HBV- and HCV-endemic area. We evaluated the association between the MetS and HCC in Korea.

Methods: The HCC incidences according to the MetS were analyzed in general population by using the Health Examination Cohort data of National Health Insurance. We followed all 112,794 people who were 40-79 years old and had health examination in 2002 or 2003. According to limited source justification, the criteria for MetS are as follows: BMI ≥ 25, hypertension SBP 130+ or DBP 85+, fasting blood glucose (FBG) 100mg/dL+ and total cholesterol (TC) 240 mg/dL+. Cox proportional hazard regression models were used.

Results: Out of 112,794 people, 40,443(35.9%) had one, 26,410(23.4%) had two, 19,674(17.6%) had three, and 16,601(4.1%) had four components of MetS. HCC incidence rates for 10 years were 1.3% for one, 1.7% for two, 2.0% for three, and 3.0% for four components of MetS. Univariate analysis on risk of HCC showed significant results with hypertension (HR: 1.18, FBG (HR: 1.25) and TC (HR: 0.67)). However, after adjusting for age, sex, alcohol drinking, and viral hepatitis (B and/or C), only TC (HR: 0.71) showed a significant result. After excluding TC which showed protective effect, adjusted HRs of BMI, FBG, and hypertension were not significant (1.016, 1.046, and 1.038, respectively).

Conclusion: MetS may not be a significant risk for HCC development in a Korean population-based study. A subsequent analysis of the HCC risk and MetS is currently under way in the second set including data of triglyceride and HDL-cholesterol.

Disclosure of Interest: None Declared

P-004 ASSESSMENT OF PRESURGICAL HEPATIC RESERVE AND PREDICTION OF PROGNOSIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA BY A NEWLY PROPOSED ALBI MODEL

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Introduction: The Child-Pugh (CP) classification has been widely adopted as an assessment tool for presurgical hepatic reserve. Recently the Albumin-Bilirubin (ALBI) scoring model has been proposed as a new and simple method of assessing liver function. This new model eliminates the need for subjective variables such as ascites, encephalopathy and prothrombin time, those are requirements in CP scoring. We retrospectively evaluated the efficacy of ALBI model for grading surgically resected HCC patients based on postoperative complications and their prognosis.

Methods: From 2005 to 2014, 512 patients of resected naïve HCC (67.4 ± 10.1 years old) with CP class A were enrolled. The formula of ALBI score was [(Log10 Serum bilirubin value x 0.66) + Serum albumin value x -0.085] and ALBI score was stratified into 3 grades: A1: ≤–2.60, A2: >–2.60 to –1.39, and A3: <–1.39. The incidences of postoperative morbidity and mortality were compared between ALBI grade and CP score. International Study Group of Liver Surgery (ISGLS) definition of posthepatectomy liver failure was applied for the assessment of postoperative liver dysfunction.

Results: Among 512 patients of CP class A, 406 had a CP score of 5 and 106 had a score of 6. These patients were stratified into A1 (n=273), A2 (n=239) and A3 (n=40) in ALBI model. The proportion of A1 and A2 was equally distributed. There were no mortality in this study. The incidences of postoperative liver dysfunction of Grade B in ALBI A1 and A2 were 11% and 16%, respectively. Those in CP score 5 and 6 were 12% and 19%, respectively. These differences were not significant between ALBI and CP models. There were no patients of liver dysfunction of Grade A and C. The morbidity in ALBI A1 and A2 were 27% and 29%, respectively. Those in CP score 5 and 6 were 27% and 33%. The morbidity were not different between ALBI and CP model. 5 and 10 years OS were 73% and 55% in ALBI A1 and 61% and 28% in A2, while 70% and 44% in CP A5 and 55% and 26% in CP 6. The population of 10 years survivor was high in A1P (<0.001).

Conclusion: A new and simple scoring model of ALBI was at least similar to CP score to evaluate risk of postoperative liver dysfunction and other complications. Further, ALBI model was found to be superior to distinguish patients with mild liver disorder who showed a better 10 years survival. ALBI model is a better total prognostic scoring system for predicting long-term survival in patients with HCC.


Disclosure of Interest: None Declared
P-005  RISK PREDICTION MODEL FOR THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS RECEIVING ENTECAVIR FOR CHRONIC HEPATITIS B

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Introduction: Although oral antiviral treatment reduces the development of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB), the risk of HCC remains still high. The aim of this study was to develop and validate the risk prediction model for the development of HCC in patients receiving entecavir for CHB.

Methods: We investigated 2,061 Korean patients with CHB and no HCC at baseline who treated with entecavir for at least 6 months. Risk prediction of HCC was developed using multivariate Cox proportional hazards model for a derivation cohort in single center (n=990) and we validated risk prediction model using a validation cohort in other three centers (n=1,071) in Seoul, Korea. Also, we compared the time-dependent area under receiver operating characteristic curve (AUROC) for predicting HCC development between our model and other previous published models (REACH-B, GAG-HCC, and PAGE-B).

Results: The cumulative incidence rates of HCC at 5 years were 11.2% and 8.9% in the derivation and validation cohort, respectively. Risk factors for HCC development were age, gender, and liver cirrhosis in the derivation cohort. The time-dependent AUROCs at 1 year, 3 years, and 5 years were 0.60, 0.79, and 0.77 in the derivation cohort and 0.92, 0.81, and 0.81 in the validation cohort. The time-dependent AUROCs of our model were significantly better than those of REACH-B, GAG-HCC, and PAGE-B (p<0.05) but there was no significant difference of AUROCs between our model and PAGE-B.

Conclusion: The risk prediction model for HCC development for CHB patients receiving entecavir is based on age, gender, and liver cirrhosis. It could be helpful for predicting the development of HCC in CHB patients receiving oral antiviral treatment.

Disclosure of Interest: None Declared

P-006  COMPARISON OF PROGNOSTIC STAGING SYSTEMS FOR HEPATOCELLULAR CARCINOMA IN A HEPATITIS B VIRUS ENDEMIC AREA

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Introduction: Many staging systems have been developed for hepatocellular carcinoma (HCC), however, it is uncertain which model provides better information. We aimed to compare performances of 7 prognostic classifications in the prediction of survival among patients with HCC.

Methods: Data of 4,596 randomly selected patients out of 38,176 HCC registrants of the nationwide statistic Korea Central Cancer Registry for 2008 to 2010 were used. A total of 3,962 patients were enrolled and stratified according to the following 5 staging systems and 2 survival prediction models: modified International Union against Cancer (mUICC), Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), Japanese Integrated Staging (JS), Tokyo Score, Model to Estimate Survival in Ambulatory HCC patients (MESIAH), and Korean version of MESIAH (K-MESIAH). Each model’s performance was assessed and compared.

Results: Most patients had preserved liver function (Child-Pugh class A, 71.8%), and 28.2% received curative treatment. As a cause of HCC, 62.2% had hepatitis B virus infection and 10.5% had hepatitis C virus infection. Overall, the MESIAH score had the highest C-statistics (0.797), followed by K-MESIAH (0.792), CLIP (0.762), JS (0.760), Tokyo Score (0.743), mUICC (0.728), and BCLC (0.727). Both MESIAH and K-MESIAH showed good homogeneity ability (likelihood ratio χ²: 2.286.04 for MESIAH and 2.365.88 for K-MESIAH) and the best fit (Akaike information criterion score: 36.127.10 for MESIAH and 36.047.24 for K-MESIAH). Each model’s performance was assessed and compared.

Conclusion: The MESIAH and K-MESIAH models provided better prognostic stratification for patients with HCC in South Korea.

Disclosure of Interest: None Declared

P-007  PRETREATMENT GLUCOSE STATUS DETERMINES HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CHRONIC HEPATITIS C PATIENTS WITH MILD LIVER DISEASE AFTER ANTI-VIRAL THERAPY

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Introduction: Diabetes mellitus (DM) may increase the risk of hepatocellular carcinoma (HCC). However, the impact of glucose status on HCC occurrence in chronic hepatitis C (CHC) patients receiving antiviral therapy is unclear in a long-term fashion.

Methods: A total of 1,112 CHC patients receiving peginterferon/ribavirin were consecutively enrolled. Both pretreatment and post-treatment glucose status, including 75 g oral glucose tolerance test (OGTT), were measured to evaluate the association between glucose status and the development of HCC.

Results: Ninety-three (8.4%) developed HCC over 5,183 person-years of follow-up and the annual incidence was 1.79%. Among patients with mild liver disease (F0-2) and a sustained virological response (SVR), the 1-, 3-, and 5-year cumulative incidence of HCC in DM patients was 0%, 2.8%, and 11.7%, respectively. The features were significantly higher than those non-DM patients with the 1-, 3-, and 5-year cumulative incidence of HCC of 0.2%, 1.3%, and 1.9%, respectively, hazard ratio (HR): 5.2, 95% confidence interval [CI]: 1.97-13.69, p < 0.001. Cox-regression analysis demonstrated that the strongest factor associated with HCC in patients with mild liver disease and SVR was the presence of DM (HR/95% CI: 3.78/1.42-10.136, P=0.039), followed by age (HR/95%CI: 1.06/1.001-1.117, P=0.046) and platelet count (HR/95%CI: 0.980/0.979-1.000, P=0.09).

Conclusion: DM contributes to the development of HCC in SVR patients with mild liver disease. HCC surveillance is of particular importance in this patient group.

Disclosure of Interest: None Declared

P-008  A COMPARISON OF HEPATOCELLULAR CARCINOMA OUTCOMES ACROSS PRACTICE SETTINGS IN THE UNITED STATES

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Introduction: Hepatocellular carcinoma (HCC) surveillance is recommended in patients with cirrhosis but few studies have evaluated the impact of system-level factors on HCC surveillance effectiveness in clinical practice. The aim of our study was to compare HCC surveillance effectiveness and outcomes between tertiary care academic centers and safety net health systems.

Methods: We identified all patients diagnosed with HCC between June 1, 2012 and May 31, 2013 at four centers in the United States – two tertiary care academic centers and two safety net centers. Authors adjudicated HCC cases to confirm they met diagnostic criteria, based on AASLD criteria. Patients were considered as detected by surveillance if HCC diagnosis was prompted by surveillance ultrasound and/or alpha fetoprotein (AFP). Wilcoxon rank-sum and Chi-square analysis was used to compare continuous and categorical variables, respectively, between academic center and safety-net patients. HCC staging was determined by the Barcelona Clinic Liver Cancer (BCLC) system, with early stage defined as BCLC stage A. Curative treatments included liver transplant, resection, or local ablation. Survival was determined by Kaplan-Meier analysis and Cox regression was performed to identify associated factors. Statistical significance was defined as p<0.05.

Results: We identified 380 HCC patients – 163 patients from safety net systems and 217 from academic centers. Patients at academic centers were significantly older (mean 64 vs. 56 years, p<0.001), less likely racial/ethnic minority (23% vs. 78%, p<0.001), and less likely to have HCV-related cirrhosis (49% vs. 68%, p<0.001). Despite having a lower proportion of Child B or C cirrhosis (46% vs. 59%, p=0.01), patients at academic centers were more likely to be receiving Hepatitis care prior to HCC diagnosis (53% vs. 23%, p<0.001). Patients at academic centers were significantly more likely to have HCC detected by surveillance (47% vs. 35%, p=0.02), diagnosed at an early stage (BCLC stage A 52% vs. 40%, p=0.03), and undergo curative treatment (25% vs. 13%, p=0.002). Despite similar rates of multidisciplinary care (66% vs. 63%, p=0.55), curative treatment rates were lower at academic centers. Patients at academic centers were significantly more likely to have HCC detected by surveillance (47% vs. 35%, p=0.02), diagnosed at an early stage (BCLC stage A 52% vs. 40%, p=0.03), and undergo curative treatment (25% vs. 13%, p=0.002). Despite similar rates of multidisciplinary care (66% vs. 63%, p=0.55), curative treatment rates were lower at the safety net health systems, even among the subset diagnosed at an early stage by surveillance. Only 11 (29%) of 37 BCLC A patients detected by surveillance at the safety net systems underwent curative treatment, compared to 30 (48%) of 62 at academic centers. Patients at academic centers had prolonged survival compared to safety nets (median 11.5 vs. 7.1 months, p=0.02). This association remained significant on multivariable Cox regression (HR 0.81, 95%CI 0.39-0.98) after adjusting for patient demographics, liver dysfunction, and tumor stage but became insignificant after adjusting for receipt of curative treatment (p=0.12) suggesting this may be a potential mediator.

Conclusion: Significant disparities exist between patients followed at academic centers and those followed at safety net health systems. HCC patients at safety net health systems have worse survival.
Conclusion: Conclusion: Increasing risk score while under repeated locoregional therapies may represent a warning signal toward prompt LT especially in case of 6 points or higher. This risk scoring system based on baseline tumor characteristics and treatment response can be served as a surrogate marker of tumor biology for the decision of LT timing, which requires further validation in a larger cohort including different etiologies.

Disclosure of Interest: None Declared

P-010 DUAL-TRACER 18F-FLUOROCHOLINE AND 18F-FDG PET/CT CAN IMPACT BCLC CLASSIFICATION AND TREATMENT ALLOCATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Conventional imaging allows staging of hepatocellular carcinoma (HCC) according to the BCLC classification, which links staging to therapeutic modalities. The aim of our study was to assess the impact of dual tracer 18F-Fluorocho line and 18F-FDG PET/CT on tumor staging and treatment allocation.

Methods: 154 dual tracer PET/CT were performed in 138 patients with HCC between 2012 and 2015 in two institutions. Diagnosis of HCC was based on histological (n=108) and/or radiological findings. For these patients, we retrospectively reviewed HCC staging according to the BCLC classification based on the conventional imaging and treatment proposition. Then, we collected any new lesion detected, as well as any change in BCLC classification and treatment allocation based on the dual-tracer PET/CT. Modification of BCLC classification and treatment allocation according to the dual tracer PET/CT were defined in a multidisciplinary meeting.

Results: Patients were mostly men (n=122; 88%) with cirrhosis in 106 patients (77%). The cause of the underlying liver disease was alcohol(MFHD (n=57; 41%), hepatitis B or C virus (n=77; 52%) and other (n= 9, 7%). At the time of the 154 dual tracer PET/CT, BCLC staging according to conventional imaging was O or A in 52 patients (34%), B in 32 patients (23%), C in 25 patients (16%). No active tumor was identified with conventional imaging in the remaining 45 patients (29%).

PET/CT with 18F alone detected new lesions in 21 patients (14%), upgraded BCLC staging in 15 patients (10%) and modified the treatment in 17 patients (11%). Dual-tracer 18F-Fluorocho line and 18F-FDG PET/CT detected new lesions in 30 patients (19.4%). BCLC staging was upgraded in 22 patients (14%), and dual tracer PET/CT had an impact on treatment decision in 23 patients (15%).

New inapthological lesions were detected in 7 patients, extrahepatic lesions in 16 patients and both intra and extrahepatic lesions in 7 patients. Ten patients had new bone lesions, 6 vascular invasion, 8 tumoral nodes, 3 lung metastasis and 1 adrenal metastasis.

Using dual-tracer PET/CT, in patients waiting liver transplantation, staging was modified in 8% of the patients with active lesion (n=34) and in 4% of patients without tumor remaining after curative treatment (n=28). BCLC staging was modified in 19% of the patients assessed before percutaneous treatment or resection (n=36), in 10% of the patients assessed before palliative treatment (n=35).

Staging was modified in 23% of the patients with doubtful extra-hepatic lesions (n=17) and in 36% of the patients with increased AFP without typical lesions at conventional imaging (n=11).

Conclusion: In our population, dual-tracer 18F-Fluorocho line and 18F-FDG PET/CT allowed the upstaging in the BCLC classification in 13.6% of the patients with HCC and treatment modification in 14.9% of the cases.

Disclosure of Interest: None Declared
Disclosure of Interest: None Declared

P-012 HEPATOCELLULAR CARCINOMA WITH MAIN PORTAL VEIN TUMOR THROMBUS: DOWNSTAGE LIVER RESSECTION WITH RADIOTHERAPY

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Introduction: The role of surgical resection in the treatment of hepatocellular carcinoma (HCC) with main portal vein tumor thrombus (mPVTT) is controversial and associated with poor survival outcomes. This study aimed to evaluate the efficacy of using neoadjuvant radiotherapy on patients with resectable tumor compared with using hepatectomy alone.

Methods: A non-randomized comparative study was carried out. Patients with resectable HCC with mPVTT were assigned into neoadjuvant radiotherapy group and surgery group according to the patients’ own choice. Radiotherapy was given with 300 cGy per fraction/day for six consecutive days, with a total dose of 1800 cGy to cover the HCC and PVTT. Treatment, either the radiotherapy in the neoadjuvant group, or partial hepatectomy in the surgery group was given within 3 days after completion of all investigations. Hepatectomy was carried out 4 weeks after irradiation AR-SA→> to evaluate the efficacy of using neoadjuvant radiotherapy on patients with resectable tumor compared with using hepatectomy alone.

Results: From January 2010 to December 2013, 116 consecutive HCC patients with mPVTT who were suitable to be treated with surgical resection in our department 108 patients met the selection criteria, in which 95 were enrolled in the study with a drop-out rate of 13.7% (13/95). Finally, a total of 95 patients were analyzed in this study, with 45 patients in the neoadjuvant radiotherapy group and 50 patients in the control group. There was no significant difference between liver function before and after 4 weeks after irradiation. The surgical and postoperative complications were also similar between the groups. Compared with receiving surgical treatment alone, the use of neoadjuvant radiotherapy significantly reduced both HCC recurrence and HCC-related death with a hazard ratio of 0.244 (95% CI, 0.143–0.415) and 0.329 (95% CI, 0.194–0.559). The 1- and 2-year DFS rates were 30.2% and 28.2% for the neoadjuvant radiotherapy group vs. 12.0% and 10.0% for the control group (P = 0.087, 0.026). The 1- and 2-year OS rates were 71.1% and 42.2% for the radiotherapy group vs. 32.0% and 18.0% for the control group (P = 0.0001, 0.0097).

Conclusion: The neoadjuvant radiotherapy was effective in reducing PVTT extent and improving the rate of curative resection with limited adverse reaction. Neoadjuvant radiotherapy combined with surgery offered a better survival than conventional hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus invaded the main trunk.

Disclosure of Interest: None Declared

P-013 PREDICTORS OF ADEQUATE ULTRASOUND QUALITY FOR HCC SURVEILLANCE IN PATIENTS WITH CIRRHOSIS

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Introduction: Ultrasound is the primary modality for hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis but fails to detect one-fourth of HCC at an early stage in clinical practice. Identifying patients in whom ultrasound is of inadequate quality can inform interventions to improve surveillance effectiveness. Our study’s aims were to evaluate and identify predictors of inadequate ultrasound quality among a cohort of patients with cirrhosis undergoing HCC surveillance.

Methods: We performed a retrospective cohort study among 941 patients who underwent an ultrasound exam at a large academic center between April 2015 and October 2015 for evaluation of cirrhosis and HCC surveillance. One of three ultrasound-experienced, fellowship-trained radiologists reviewed images for each ultrasound exam and determined ultrasound adequacy for HCC surveillance based on visualization and clarity of the entire liver, penetration, and any other exam limitations. Ultrasound quality was categorized as definitely adequate, likely adequate, likely inadequate, and definitely inadequate to exclude liver lesions. We used univariate and multivariate logistic regression to determine patient characteristics associated with inadequate ultrasound quality.

Results: We identified 941 eligible patients and at least one ultrasound exam performed for an indication of cirrhosis. Median age was 57 years and 64% were men. Over one-third (39%) was obese, with 9% having morbid obesity. The most common etiologies of cirrhosis were hepatitis C (49%), alcohol (18%), and nonalcoholic steatohepatitis (NASH) (12%). Child Pugh scores were 69% A, 24% B, and 7% C. Ultrasounds were inadequate for HCC surveillance in 191 (20.3%) cases – 134 definitely inadequate and 57 likely inadequate. On multivariate analysis, inadequate ultrasound quality was directly associated with male gender (OR 1.70, 95% CI 1.51–2.58), BMI category (OR 1.64, 95% CI 1.43 – 1.89), inpatient status (OR 1.56, 95% CI 1.02 – 2.40), Child-Pugh score (OR 1.47, 95% CI 1.10 – 1.98), alcohol-related cirrhosis (OR 1.85, 95% CI 1.19 – 2.86), NASH-related cirrhosis (OR 2.65, 95% CI 1.64 – 4.27). Ultrasounds were inadequate quality in 16.1% of patients with Child Pugh A cirrhosis, 26.4% of Child Pugh B cirrhosis, and 39.1% of patients with Child Pugh C cirrhosis. Inadequate quality was observed in 9.3% of normal-weight patients, 16.9% of overweight patients, 22.8% of patients with obesity level 1, 25.5% with obesity level 2, and 39.3% of patients with morbid obesity. Ultrasounds were inadequate in 31.4% of patients with alcohol-related cirrhosis and 34.6% of patients with NASH cirrhosis, compared to only 15.0% of patients with other etiologies of cirrhosis. Among the 55 patients with BMI >30, alcohol of NASH etiology, and Child Pugh B or C cirrhosis, 25 (45.5%) had inadequate ultrasound quality. In contrast, ultrasounds were inadequate in only 4.4% of patients without any of these characteristics. I.e., normal weight patients with Child Pugh A cirrhosis due to etiologies other than alcohol or NASH.

Conclusion: Over 1 in 5 ultrasounds are of inadequate quality for exclusion of HCC lesions, which can contribute to HCC surveillance failure. Alternative surveillance modalities are needed in subgroups with high rates of inadequate ultrasound quality including obese patients, those with Child Pugh B or C cirrhosis, and those with alcohol- or NASH-related cirrhosis.

Disclosure of Interest: None Declared

P-014 STEREOTACTIC BODY RADIATION THERAPY FOR SMALL HEPATOCELLULAR CARCINOMA: LONG-TERM PATIENT OUTCOMES

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Introduction: Even with early stage hepatocellular carcinoma (HCC), patients are often ineligible for curative treatments due to advanced cirrhosis, donor shortage, or difficult location of the tumors. Stereotactic body radiation therapy (SBRT) has emerged as an alternative, non-invasive local treatment option for patients with HCC when established curative treatment modalities cannot be applied. In our present study, we report our long-term clinical experiences with SBRT as an alternative treatment for small HCC.

Methods: A total of 292 patients (332 lesions) with HCC who were treated with SBRT were registered between March 2007 and July 2013 at our institution. A dose of 10-15 Gy per fraction was given over 3-4 consecutive days, resulting in a total dose of 30-60 Gy. Local failure was defined as the recurrence of the treated lesion; intrahepatic recurrence was defined as recurrence within the liver outside the treated lesion. Overall and recurrence-free survivals were estimated from the date of the start of SBRT to the date of death, the last follow-up examination, or to the date of tumor recurrence, respectively.

Results: The median overall survival was 22.2 months and a range of 22 to 98 months. On univariate analysis, factors associated with shorter overall survival were AFP at OLT (P=0.004), poorly differentiated histology and vascular invasion (P=0.002), maximum AFP (P=0.016), and AFP at OLT (P=0.004), cold ischemia time, and vascular invasion (P=0.002) were associated with time to tumor recurrence.

Conclusion: Both lower donor age and shorter cold ischemia time were independently associated with improved tumor-free survival after liver transplant. If confirmed in larger cohorts, these represent potentially modifiable factors in liver transplant patients with liver cancer.

Disclosure of Interest: None Declared
Results: The median follow-up period of all patients was 69.6 months (range, 2.1–220.3 months). The study population was mostly male (79.5%), demonstrating a median age of 61 years. Two-hundred and fifty-two (86.3%) patients had liver function of Child-Pugh class A, and median size of tumors was 1.7 cm (range, 0.7-6.0 cm). Only 7 patients (2.4%) were treatment-naive, and all other patients had received various courses of chemotherapy, targeted therapy, and immunotherapy, respectively before receiving SBRT. Overall survival rates at 3 and 5 years were 63.7% and 44.9%, respectively. Local control rate at 3 and 5 years were 94.0% and 91.8% in all treated lesions, respectively. Intratumoral recurrence was the main cause of failure and intratumoral recurrence-free survival rates at 3 and 5 years were 26.4% and 19.0%, respectively. The Child-Pugh class before SBRT had significant effects on overall survival (Child-Pugh A: Hazard ratio = 0.322; 95 CI, 0.219-0.472; p<0.001).

Conclusion: SBRT was an excellent ablative treatment modality for patients with small HCC over a long period of time. SBRT can be a good alternative treatment for patients with small HCCs that are unsuitable for surgical resection or local ablative therapy.

Disclosure of Interest: None Declared

P-015 TRUNK VS BRANCH DRIVERS: DISSECTING MOLECULAR HETEROGENEITY IN HCC

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Introduction: Molecular heterogeneity in HCC has been underexplored. The importance of molecular heterogeneity relies on the fact that a) it might compromise precision medicine (aimed at providing each patient with a tailored-specific treatment), and b) it might be difficult to assess if multiple biopsies are required. Our hypothesis is that trunk drivers in HCC are present in all malignant cells (clonal) in early stages of the disease, whereas branch mutations (subclonal) occur at more advanced stages. In oncology, molecular therapies are mainly targeting trunk drivers. We aimed to characterize molecular heterogeneity in HCC through the study of trunk and branch driver copy-number variations (CNVs) and mutations.

Methods: We explored a total of 165 samples for assessment of gene expression, CNV by SNP array and mutations by exome deep-sequencing (~850a) targeting 6 most frequent oncogene drivers (ERT promoter, TP53, CTNNB1, ARID1A, AXIN1, CTNND1). Clonality was defined based on significant range of similarity in CNV profiles (p<0.05). Trunk mutations were defined as present in all pre-neoplastic or very early HCC (eHCC) or b) all regions of the same tumor or c) all multinodular clonal tumors of the same patient. The rest of alterations were defined as branch. The spectrum of samples included a) tumors (10 LS/lung) and 20 HCC), b) 11 module-inodule samples (trinions of cirrhosis/ HCC/eHCC), 32 single HCC tumors <cm comprising 16 eHCCs (no satellites, no vascular invasion) and 6 early HCs (eHCC, no satellites); d) 21 single large tumors (size>4cm), for which we explored intratumor heterogeneity (2 samples of distinct regions/tumor), and e)17 multinodular (2-3 nodules/patient, 39 samples).

Results: CNV analysis in premalignant and early HCC showed that chromosomal instability increases from premalignant (6.6% aberrations) to eHCC (9%) and HCC (25%). Broad 1q (1/28) and 8q (2/28) gains and 8q deletions (2/28) gains containing oncogenes (MYC, ARID1A or PARPi) occurred in premalignant nodules suggesting a trunk role. Focal VEGFA and MYC amplifications and NMYC amplifications and CNDK2A homozygous-deletions were early trunk events in eHCCs (2/16). Among 21 single large tumors >4cm, 2 did not present any mutation. The remaining 19 tumors showed 63 mutations; 56 (89%) of which were identical/trunk in different tumoral regions. The rest of alterations were defined as branch. The spectrum of samples included a) tumors (8 LS/lung) and 20 HCC), b) 11 module-inodule samples (trinions of cirrhosis/ HCC/eHCC), 32 single HCC tumors <cm comprising 16 eHCCs (no satellites, no vascular invasion) and 6 early HCs (eHCC, no satellites); d) 21 single large tumors (size>4cm), for which we explored intratumor heterogeneity (2 samples of distinct regions/tumor), and e)17 multinodular (2-3 nodules/patient, 39 samples).

Conclusion: Curative liver resection offered superior overall and disease-free survival to RFA in patients with BCLC stage 0/HCC. The ALBI grade could identify those patients with worse liver function who did not gain any survival advantage from curative surgery.

References:

Disclosure of Interest: None Declared

P-017 HEPATIC ARTERIAL INFUSION CHEMOTHERAPY FOR PROGRESSIVE HEPATOCellular CARCINOMA WITH VASCULAR INVASION WITH GOAL OF 5-YEAR SURVIVAL

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Introduction: We have previously reported on the usefulness of hepatic arterial infusion chemotherapy (HACI) using CDDP-fluorouracil (NPH1.2) therapy for progressive unresectable hepatocellular carcinoma (HCC) with vascular invasion. Response to NFP achieved long-term survival, so we retrospectively studied 5-year survival rates and related factors.

Methods: We evaluated 198 patients with unresectable HCC with visible vascular invasion and no extrahepatic metastasis out of 299 patients who received NFP via the reservoir system at our institution and affiliated Kurume University Hospital between January 2004 and December 2015 (mean age: 68.9 years; Child-Pugh Class A/B/C: 120/69/9 cases; PVT second/first/trunk: 90/62/46 cases; mean main tumor diameter: 66.4 mm).

Conversion therapy such as hepatectomy was performed when partial response (PR) or better was achieved with NFP in order to achieve cancer-free status. Antitumor effects of NFP were evaluated according to best overall response using m-RECIST. Cumulative overall survival (OS) after NFP was estimated using Kaplan-Meier and compared using log-rank tests with regard to cancer-free status. Factors related to patients with 5-year survival were analyzed with multivariate logistic regression analysis.

Results: A total of 143 patients (72%) responded to NFP, of whom 63 (32%) achieved cancer-free status. Of these 63 patients, 18 were treated exclusively with HACI, while 14 underwent hepatectomy, 22 adjuvant radiotherapy, and 4 adjuvant RFA. There were 111 patients with at least 5 years of observation; of these, 12 (10.8%) reached 5-year survival (8 received adjuvant hepatectomy and 2 adjuvant radiotherapy, while 2 patients received HAIC alone). Overall median survival time (MST) for all patients following HACI initiation was 16 months, while MST for cancer-free patients was 51 months (P<0.001). The only factor related to 5-year survival was cancer-free status (P=0.012). Factors related to cancer-free status were antitumor effects of NFP and extrahepatic metastasis.

Conclusion: NFP results in excellent response rate for progressive HCC with vascular invasion, with long-term survival possible if cancer-free status is achieved. Conversion therapy such as hepatectomy or radiotherapy is effective for achieving 5-year survival.

References:

Disclosure of Interest: None Declared

P-018 A MULTICENTER PHASE II STUDY OF STEREOTACTIC BODY RADIATION THERAPY FOR HEPATOCELLULAR CARCINOMA

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Introduction: The purpose of this study is to evaluate the toxicity and treatment outcomes of stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC).

Methods: A total of 73 patients with unresectable HCC showing an incomplete response after 1-5 sessions of transcatheter chemembolization were enrolled in a phase II clinical trial of SBRT from 6 institutions between January 2012 and April 2015. SBRT was delivered with a total dose of 45-60 Gy in 3 fractions within 14 days, with ≥48 hour intervals between each fraction. The treatment response was evaluated using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Radiation-induced liver disease (RILD) was analyzed at 2 months. Survival outcomes were analyzed with the Kaplan-Meier method. This trial is registered with Clinical Trials.gov, number NCT01850667.

Results: Sixty-seven patients were evaluable with a median follow-up of 19 months (range, 2-42 months). Local control rate at 2 years and 3 years were 94.0% (95% confidence interval [CI], 76.1%-98.6%) and 89.0% (95% CI, 67.8%-98.6%), respectively. Overall survival rate at 2 years and 3 years were 83.5% (95% CI, 68.5%-91.7%) and 75.1% (95% CI, 50.9%-98.6%), respectively. Progression-free survival rate at 2 years and 3 years were 47.2% (95% CI, 32.8%-60.4%) and 37.2% (95% CI, 21.1%-53.3%), respectively. Intrahepatic failure-free survival rate at 2 years and 3 years were 51.1% (95% CI, 36.8%-63.8%) and 41.3% (95% CI, 24.9%-57.0%), respectively. 

Conclusion: In conclusion, rapid normalization of post-LT AFP level at 1 month is a useful clinical marker for HCC recurrence. Therefore, an adjuvant strategy and/or intensive screening are needed for patients who do not show rapid normalization.

Disclosure of Interest: None Declared
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**P-020**

**PARTIAL SPLENIC EMBOLIZATION WITH TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) IN PATIENTS WITH HEPATOCELLULAR CARCINOMA ACCOMPANIED BY THROMBOCYTOPENIA: CHANGE OF PLATELET COUNT AFTER TACE FOR 2 YEARS COMPARED TO THE CONTROL GROUP**

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**Introduction:** Partial splenic embolization (PSE) has been introduced for the treatment of thrombocytopenia caused by secondary hypersplenism in patients with liver cirrhosis. We retrospectively evaluated the effects and safety of PSE and platelet changes with transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) accompanied by thrombocytopenia.

**Methods:** Twenty HCC with cirrhotic patients were treated with TACE and PSE due to severe thrombocytopenia (platelet count <45×10^3/mm^3). Twenty HCC with cirrhitc patients were treated with TACE without PSE as control group. Serial transverse images of the enhanced abdominal CT scan were obtained. The splenic volume was calculated by multiplying height in PSE group. The laboratory data was examined to evaluate the therapeutic effects and the complications.

**Results:** The platelet value after PSE was significantly increased at 12 months (p=0.001). The average platelet count of PSE-TACE group was 38.9×10^3/mm^3, 107.9×10^3/mm^3, 92.5×10^3/mm^3, 93.1×10^3/mm^3, 98×10^3/mm^3 each other at baseline, 6 months, 1 year, 1.5 year and 2 years after TACE. The average platelet count of control group was 56.8×10^3/mm^3, 57.4×10^3/mm^3, 58.9×10^3/mm^3, 70×10^3/mm^3, 56.4×10^3/mm^3 each other at baseline, 6 months, 1 year, 1.5 year and 2 years after TACE. The causes of HCC with cirrhosis were similar in both groups (p=0.326). Even though platelet counts of PSE-TACE group was lower than the control group’s one, platelet count of PSE-TACE group was elevated until 2 years after TACE. But it was nearly not changed in the control group. The CTP and MELD score were similar between groups after PSE.

**Conclusion:** PSE with TACE proved to be effective at maintaining platelet count after TACE for 2 years compared to control group for treating thrombocytopenia in patient with hypersplenism and HCC. Liver function and Child-Pugh score after PSE was similar with non-PSE patients at 2 years, concurrent PSE with TACE for HCC can maintain hepatic functional reserve. PSE may be considered to patients of HCC with thrombocytopenia before TACE.

**Disclosure of Interest:** None Declared

**Molecular Posters**

**P-021**

**EXOME SEQUENCING IN EARLY-STAGE HEPATOCELLULAR CARCINOMA IDENTIFIES PTENP1 AS A TUMOUR SUPPRESSOR**

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**Introduction:** Hepatocellular carcinoma (HCC) is the second leading cause of cancer mortality and carries a dismal prognosis. The present study aimed to identify early mutations implicated in HCC tumourigenesis and progression.

**Methods:** We sequenced the whole exomes of 5 hepatitis B virus-related early-stage HCC and identified the tumour suppressor PTPN13 as an alternative therapeutic target for HCC.

**Results:** Amplification and activation of c-Myc is one of the leading genetic events in HCC pathogenesis. The oncogenic potential of c-Myc is validated that overexpression of c-Myc in the mouse liver leads to liver tumor formation. mTORC1 cascade is one of the major signaling pathways involved in HCC development. However, whether mTORC1 signaling is required for c-Myc driven HCC development has not been investigated.

**Conclusion:** MTORC1 is required for c-Myc driven hepatocarcinogenesis.

**Disclosure of Interest:** None Declared
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P-023 ULTRA-DEEP SEQUENCING OF CIRCULATING TUMOR DNA IDENTIFIES ACTIONABLE MUTATIONS: EXPLORING APPLICATIONS OF A LIQUID BIOPSY IN HCC

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Introduction: Tumor by-products such as nucleic acids are released to the circulation of patients with solid malignancies. However, evidence on circulating DNA in hepatocellular carcinoma (HCC) is scarce, specifically for the detection of potentially actionable mutations. This study aimed to identify mutations in the blood of HCC patients by comparing tumor-tissue (multiregional sampling) and matched plasma/serum.

Methods: This pilot study analyzed 43 samples collected in 8 patients, including multiregional tissue sampling (22 regions, average of 2.7 regions per tumor), peripheral blood mononuclear cells (PBMC, n=8), plasma (n=8) and serum (n=5). Circulating DNA was extracted from 5 ml of plasma or serum using the QIAamp Circulating Nucleic Acid Kit (Qiagen). Ultra-deep DNA sequencing of 93 relevant genes in HCC (as per prevalence and therapeutic actionability) was performed after targeted exon capture using SureSelectXT method (Agilent). Stringent pre-processing steps prior to variant discovery were implemented. Both heuristic and statistical algorithms were used in VarScan2 to call variants in solid tumor samples with control DNA from matched PBMC. Somatic status of variants was classified as: germline, somatic, or loss of heterozygosity. Somatic mutations categorized as high confidence in tissue were further used as a standard to evaluate liquid biopsy efficacy for the detection of point mutations.

Results: Patients enrolled were all males (8/8), average age of 61 years. All patients had single-nodule HCC, underwent surgical resection, and had an average tumor size of 4.2 cm (SD: 3.7). HBV was the etiology of the underlying liver disease in 3/8 patients. DNA extraction from plasma and serum yielded a median concentration of 12 ng/ml (IQR: 7-15), with a median DNA fragment size of 171 base pairs (IQR: 168-174). Median sequencing coverage was 1,500X and 5,500X for tissue and plasma, respectively. Overall, 23 somatic mutations were detected in the tissue samples of 6/8 patients. Tissue mutations included well-known HCC oncogenes and tumor suppressors such as TERT promoter (4/8 patients), TP53 (3/6), CTNNB1 (2/6), TP53N (1/6). Some mutations (e.g., PIK3CA) were only detected in a subset of tissue regions. Among the 6 patients with mutations detected in tissue, corresponding mutations in plasma DNA were identified in 5 patients (83%). Out of the 23 somatic mutations detected in tissue, 16 (70%) were also present in circulating DNA. 10/23 (43%) mutations were confidently detected in plasma whereas 6/23 (26%) were detected in serum but at allele frequencies indistinguishable from background noise. Detected somatic mutations in plasma included both potentially actionable genes (e.g., JAK1) as well as sub-clonal mutations (e.g., PIK3CA). Comparative analysis of mutation detection performance in plasma and serum (n=5 patients, total of 14 tissue mutations) indicates a trend towards higher detection rate of high confidence mutations in plasma vs. serum (5/14 vs 2/14, p=0.1). Mutations in ctDNA were also detected in a patient with a small HCC (2 cm, BRAF).

Conclusion: Ultra-deep coverage targeted sequencing of circulating DNA in plasma is feasible, and confidently identifies somatic mutations in patients with surgically resected HCC. ctDNA was detected in 5/8 (83%) of HCC patients, while 16/23 (70%) of tissue-corresponding mutations were identified in plasma. Circulating mutations involved known HCC genes (e.g. TP53), actionable candidates (e.g., JAK1) and sub-clonal mutations (e.g., PIK3CA). Liquid biopsy is a promising tool for non-invasive interrogation of HCC genomic data.

Disclosure of Interest: None Declared

P-024 INTEGRATIVE GENOMIC ANALYSIS OF HEPATOBLASTOMA REVEAL NOVEL MOLECULAR DRIVERS

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Introduction: Hepatoblastoma (HB) is the most frequent liver cancer in children, but it is considered a rare disease due to its low incidence (1-2 cases/10 6 children). Curative treatment is achieved by combining chemotherapy and surgery. However, around 20% of HB patients do not survive the disease. We previously defined two transcriptomic-based subclasses, named C1 and C2, where the latter defines the most aggressive phenotype (1). Nonetheless, so far aside for CTNNB1 mutations present in 70% of cases, the molecular characterization of the disease is poorly defined. We aimed to identify novel molecular drivers and tumor suppressors by performing a comprehensive integrative analysis using high-throughput techniques.

Methods: A total of 79 samples (training set) from 32 patients with paired HB and non-tumoral liver, 3 recurrences and 13 Patient Derived Xenografts (PDX) were first assessed. Mean age of patients was 2.5 years, 23 had liver-only disease and 9 had also extrahepatic metastases. In term of molecular class, 16 belong to C1 and 15 to C2, sera AFP range 341-2,186,461 ng/ml. After a mean follow-up of 26.2 months, 5 patients died due to cancer.

All tumor samples were subjected to transcriptome and SNP array analyzes HTA and CytoScanHD from Affymetrix and RNA sequencing (RNA-seq). As controls, 18 NL samples were included in the transcriptomic analysis. The data was analyzed by Chromosome Analysis Suit and Transcriptomic Analysis Console software. Key findings were further validated by RT-PCR and Sanger sequencing using an independent series of 21 patients (validation set).

Results: Mutational analysis confirmed CTNNB1 as the main mutated gene (39/53, 70%), followed by mutations in NEF2L2 (2/4, 5%), and a new gene related to developmental processes- in 2/54 (4%), all in 5 tumors belonging to the C2-subtype. By RNA-sequencing we identified 18 fusion events with perfect alignment, 4 of which were validated at low incidence (TERF2, ALH, DNAJC15-TP1, T1PM, and TMEM36C). C2 subclass revealed significantly more de-regulated genes than average HB (C2/NT: 6052 genes; all HB/NT: 2133 genes, p<0.0001). Pathway analysis revealed deregulation of IGF2 signaling (80%) and NEF2L2-related MIF2 pathway in HB with a clear enrichment of pathways activation in C2 tumors. SNP array confirmed most frequent chromosomal aberrations: +1q (50%), +2q (45%), +8 (40%), +20 (5%), and losses of -1p (-20p) and -4 (25%). Interestingly, high-level amplifications (CN>4) associated with gene overexpression were identified in chromosome 1q (3/5, 62%), 2q (2/6), 3p (2/6), 6p (2/6), whereas the most frequent LOH involved the locus 11p15 (13/30, 43%). Interestingly, HSF4 oncogene is upregulated in the two samples having the 10q40 amplification of the 1q region, where it is mapped, whereas LOH of MSH5 tumor suppressor gene is found in 2 cases. Conclusion: By performing an integrative molecular analysis of HB, we identified new targetable mutations and deregulated pathways in aggressive tumors. Discovered drivers need to be validated in functional studies.


Disclosure of Interest: None Declared

P-025 THE MIR-200B-3PB2 CIRCUIT REGULATES THE DIFFERENTIAL STEMNESS OF HUMAN HEPATOCELLULAR CARCINOMA

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Introduction: The microRNA 200 (miR-200 family)-ZEB circuit regulates epithelial-mesenchymal transition (EMT) of cancer cells. EMT-ongoing cancer cells usually present with the biological and functional characteristics similar to those of cancer stem cells (CSC), which contribute to tumor initiation, invasion, metastasis, recurrence and resistance to anti-cancer therapies of cancers. The role and underlying molecular mechanisms of miR-200 in the regulation of cancer stemness remain largely unknown.

Methods: Profiling the expression of microRNAs in clinical liver tumor and paratumor samples was performed using a human v2 MicroRNA Expression Profiling kit targeting 1146 human microRNAs (Illumina, San Diego, CA).

Results: We demonstrate here that the miR-200B-3PB2 circuit plays a crucial role in the initiation and maintenance of two discrete CSCs of human hepatocellular carcinoma (HCC). We found that a large proportion (74/5%) of HCCs had miR-200b downregulation and ZEB1 upregulation (miR-200B-3PB2). More than 90% of the miR-200B-3PB2 HCC presented with CD13+ and/or CD24+. Both CD13 and CD24 were functional stemness molecules per se, because inhibition of CD13 or CD24 directly decreased tumorigenicity of HCC, including anchorage independent growth and tumor sphere formation. Interestingly, CD24 and EpCAM were exclusively expressed in the 1q region, where it is mapped, whereas LOH of MSH5 tumor suppressor gene is found in 2 cases. Conclusion: By performing an integrative molecular analysis of HB, we identified new targetable mutations and deregulated pathways in aggressive tumors. Discovered drivers need to be validated in functional studies.

Disclosure of Interest: None Declared
Promoter activity and CDIP assays evidenced that CD13 and CD24 were upregulated by ZEB1, while EPcam was suppressed by ZEB1, which further strengthened the pivotal role of the miR-200b-ZEB1 circuit in orchestrating the discrete CSCs in HCC.

Conclusion: We provide molecular link between the miR-200b-ZEB1 circuit and CSCs in human HCC. The miR-200b-ZEB1-C123224/EPcam regulatory pathways are potential targets in treatment and prevention of recurrence of the disease.


Disclosure of Interest: None Declared

P-026 DIFFERENTIAL HEPATOCARCINOMA POTENTIALS BETWEEN KRAS SPlicingVARIANTS

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Introduction: In humans, three RAS genes encode four RAS proteins with a high degree of sequence homology: HRAS, NRAS, KRAS4A and KRAS4B, with the latter two resulting from alternative splicing of exon 4 of the KRAS gene. Activation of RAS signaling pathways is considered a key oncogenic circuit in orchestrating the discrete CSCs in HCC. One unresolved question is whether there are differential oncogenic potentials among activated RAS isoforms.

Methods: Hydrodynamic transfection was performed with transposons expressing short hairpin RNA down-regulating p53 and each of activated RAS isoforms, and livers were harvested at 23 days after gene delivery to investigate the presence of tumors. Also, survival of mice expressing different RAS isoforms were compared following hydrodynamic transfection.

Results: No differences were found in hepatocarcinogenic potentials among RAS isoforms as determined by both gross examination of livers and liver weight per body weight ratio. LW/BW of mice expressing KRAS4A, KRAS4B, and KRAS5, respectively, however, tumorigenic potentials were significantly different between KRAS splicing variants. The LW/BW ratio in KRAS4A[mice was significantly lower than that in KRAS4B[lower group (p < 0.001) and KRAS5[mice lived significantly longer than KRAS4B[mice (p < 0.001). Immunoblotting revealed that tumors from KRAS4A[mice had an elevated expression of p16INK4A compared with KRAS4B[29/32 tumors. Co-expression of p16INK4A with KRAS5[4/5 mice led to retardation of tumor development driven by KRAS5[29.

Conclusion: Oncogenic potentials differed significantly between the two KRAS splicing variants; KRAS4A being more tumorigenic than KRAS4B in the liver. Thus, it is presumed that when an activating mutation arises in KRAS, KRAS5 will predominantly lead to the tumorigenic processes.

Disclosure of Interest: None Declared

P-027 DISSECTING THE CROSSTALK BETWEEN MESENCHYMAL StromAL CELLS AND HEPATOCELLULAR Carcinoma: CLUES TO IMPROVE THE USE OF CELLS AS CARRIERS FOR THERAPEUTIC GENES.

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Introduction: The recruitment of other cells to the tumor microenvironment. MSC therapy did not affect HCC growth in a cooperative way. In addition, HCC soluble factors increase MSC chemotactic potential, and modulate their gene and protein secretion profile. Moreover, HCC-stimulated MSCs could encourage the recruitment of other cells to the tumor microenvironment. MSC therapy did not affect HCC growth in vivo after in vitro transplantation. MSC as carriers of therapeutic genes for HCC is a challenging strategy and warrants further investigations.


Disclosure of Interest: None Declared

P-028 CHANGES IN TISSUE AND BLOOD BIOMARKERS UPON EXPOSURE TO SORAFENIB IN PATIENTS WITH RESECTABLE HCC: TRANSLATIONAL EVALUATION IN THE BIOSHARE TRIAL

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Introduction: BIOSHARE phase 2 study evaluated the activity of 4 weeks neoadjuvant treatment with sorafenib in patients with resectable HCC. Herein, we report the analysis of tissue and blood changes in this population of patients treated with sorafenib and evaluated in more details.

Methods: The translational endpoints of the study were pathological and immunohistochemical (IHC) changes on tumor biopsies for CD31, VEGF, E-cadherin, vimetin, MET, HGF, FGF19 and TGFβ2 at baseline, during, and on surgical specimen along with plasma biomarkers assessment for VEGF-A, VEGF-C, PIGF, HGF, FGF, TGF-β1, FGF19.

Results: Among 29 treated patients, 25 were evaluable for pathological assessment, and 19 for translational analysis and correlations with radiological assessment. All patients being stable by RECIST on CT scans (Bouattour et al. ILCA 2015), radiological evaluation of sorafenib activity was based on 4 weeks after treatment by RECIST on CT scans. Of the 19 patients who were evaluable by RECIST, 13 (68%) had a complete response, 6 (32%) had a partial response, while 10 (53%) had stable disease. VEGF-A, VEGF-C, PIGF, HGF, FGF, TGF-β1, FGF19 was significantly increased in plasma samples from baseline to day 28. No significant changes were observed for CD31, VEGF, E-cadherin, vimetin, MET, HGF, FGF19 and TGFβ2 at baseline, during, and on surgical specimen along with plasma biomarkers assessment for VEGF-A, VEGF-C, PIGF, HGF, FGF, TGF-β1, FGF19.
observed upon short exposure to sorafenib. However, within individual patient, sorafenib induced increased expression of VEGFRI/II ligands VEGF-A and PIGF. We observed significant differences in PLGF(p<0.03) and TGF-Beta(p<0.002) plasma levels after sorafenib exposure between responders and non-responders by Chi.

Conclusion: Short-time preoperative exposure to sorafenib yields radiological hypodensity associated with significant necrosis in patients with resectable HCC with no induction of epithelial-to-mesenchymal transition. Large throughput screening for changes in transcriptional analysis and signaling pathway activation may be of interest to further deciphering sorafenib-induced effects in HCC.


Disclosure of Interest: None Declared

P-029 GENETIC ALTERATIONS IN COMMONLY UTILIZED HEPATOCELLULAR CARCINOMA CELL LINES: EVIDENCE OF BIAS TOWARD HBV BACKGROUND

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Introduction: Cell lines and in-vitro studies are important tools for assessment of various biological aspects of carcinogenesis including genomic based targeted therapy. Several hepatocellular carcinoma (HCC) cell lines are available and they have been widely utilized in research laboratories. Given the genetic heterogeneity of HCC the aim of this study was to evaluate genetic alterations in commonly used HCC cell lines to assess how they represent the spectrum of the genetic alterations that are present in primary tumors.

Methods: We carried out a secondary analysis of the genetic data available in the Catalogue for Somatic Mutations in Cancer (COSMIC) database for HCC cell lines. Seven cell lines available through ATCC, SNU-475, Huh-7, SNU-423, SNU-3849, SMU-387, Cia and SK-HEP-1 were obtained and validation of selected genetic alterations was performed by direct sequencing. We also investigated alterations in the promoter region of TERT, which was not reported in COSMIC, in a subset of the cell lines. Prometic studies was carried out utilizing Western blot analysis. Antiproliferation activity of different compounds were tested in vitro against a subset of tumor cell lines in a three-day assay using the tetrazolium dye-based CellTiter reagent.

Results: Genetic data were available for the following 17 cell lines: Huh-7, Huh-6- clone 5, JHH-1, JHH-1, SNU-475, JHH-2, Huh-7, SNU-182, SNU-423, SNU-499, SNU-387, Huh-6, CIA, HLE, SNU-398, SK-HEP-1 and JHH-4. The average number of genetic mutations was 705.6 (range 336 to 1264). Of these the average number of truncating mutations (frameshift and nonsense) was 31.6 (range 12 to 55) while the average number of missense mutations was 269 (range 200 to 763). The average number of mutations in the COSMIC cancer genes was 20.5 (range 10 to 35). In regards to genes commonly affected in HCC, mutations in TP53 were detected in 14/17 (82%) of the cell lines, activating mutations in CTNNB1 in only 2/17 (11.8%) and TERT promoter mutations in 3/5 (60%).

Conclusion: The commonly utilized HCC cell lines represent only a small subset of the genetically heterogeneous HCC (mostly the HBV related etiology). Development of other tumor cell lines from patients with other etiologies in particular HCC related HCV is highly needed. Correlation of genomic, proteomic and response to selected molecular target-based therapy in seven cell lines will be presented.

Disclosure of Interest: None Declared

P-030 S49076, A NOVEL KINASE INHIBITOR OF MET, AXL AND FGFR, DEMONSTRATES MARKED IN VITRO AND IN VIVO EFFICACY IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) is the second cause of cancer-related deaths worldwide. Besides sorafenib new therapies are needed to improve patient outcome in advanced HCC. Both preclinical and clinical data support a role of MET and AXL receptor tyrosine kinases in HCC progression. We thus evaluated S49076, a novel MET/AXL/FGFR inhibitor in HCC cell lines in vitro and in a transgenic mouse model of HCC.

Methods: MET and AXL expression levels were assessed in a panel of HCC cell lines by western blot. Downstream signaling activities and cell invasion on matrigel assays were investigated in the presence or absence of HGF, GAS6 and S49076. Transgenic mice developing stage-defined HCC were treated with S49076 (50mg/kg) or placebo. Tumor response was evaluated by measuring the liver volume by echo-doppler and the number of tumor nodules at interim (12 weeks) and final sacrifices (16 weeks).

Results: Both MET and AXL were expressed in the majority of HCC lines screened. Notably, high levels of AXL and MET expression were observed in the SK-HEP1 cells which were therefore selected for further investigation. MET and AXL pathways were strongly stimulated by their respective ligands, HGF and GAS6. Combination of HGF and GAS6 led to marked activation of ERK protein kinase phosphorylation. S49076 inhibited MET and AXL pathway activation as well as HGF- and GAS6- induced invasion at nanomolar concentrations. In vivo anti-tumor efficacy of S49076 was demonstrated in a transgenic mouse model of HCC expressing increasing level of MET and AXL during progression. Whole liver volume and liver weight were significantly decreased by 42% and 54% in the S49076 treated mice compared to placebo. Tumor growth inhibition was confirmed by a 66% decrease in the number of micronodules, as well as a ~50% reduction in the number and size of microtumors in S49079 treated mice. S49079 also affected the blood flow in the caudal trunk that was linked to a normalization of the vascularization. On HPS section, S49076 treated-tumor displayed a 69% decrease in the number of CD31 positive vessels compared to placebo.

Conclusion: S49076 displayed strong MET and AXL pathway inhibition and anti-invasive properties in SK-HEP1 HCC cells. Moreover, S49076 demonstrated antitumor activity as a single agent in a mouse model of HCC. Together, these results would support development of S49076 as an innovative treatment in HCC patients.


P-031 SPECIFIC MOLECULAR SPECIES OF PHOSPHATIDYLCHOLINE DIFFERENTIATE LIVER TUMORS DETECTED BY 18F-FLUOROCHOLINE PET/CT

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Introduction: PET/CT imaging with fluorine-18 fluorocholine (18F-choline) is a molecular imaging modality for cancer detection that is based on depicting the initiating steps of tissue phosphatidylcholine (PC) synthesis. The cytidine-diphosphate choline (CDP-choline) pathway for PC synthesis has been shown to be upregulated in many cancers, including hepatocellular carcinoma (HCC). This study examined the relationship between 18F-choline uptake and PI3K composition in liver tumors, using tissue metabolomics to provide radiopathologic correlation in patients undergoing hepatectomy for liver cancer who were imaged pre-operatively by 18F-choline PET/CT.

Methods: Patients with resectable liver tumors were enrolled to this clinicaltrials.gov-registered IRB-approved study following written informed consent. All patients underwent 18F-choline PET/CT of the liver within 2 weeks of surgery. Tumor and liver standardized uptake value (SUV) measurements were obtained from static PET images. Upon resection, tumor and adjacent parenchymal tissue samples were collected in liquid nitrogen (20 hepatocellular carcinoma, 3 intrahepatic cholangiocarcinoma, 3 freeze-dried, homogenized and extracted with methanol/CH32O water containing BHT as preservative. Tumor and liver tissue profiling was performed using a high-resolution liquid chromatography mass spectrometry (LC/MS) system. Positive-mode electrospray ionization results were queried by exact mass using the human metabolome database (hmdb.ca) to identify tissue phospholipids by their m/z ratios. This revealed 54 potential PC species containing highly-saturated fatty acids (HSA) 14 to 18 carbons long (potential products of the CDP-choline pathway) and over 100 PC species composed of long chain poly-unsaturated fatty acids (PUFA).

Results: Tumors differed significantly from adjacent liver tissue in the ratio of HSA:PUFA-PIC concentrations (2.75 vs 1.91, p=0.0015). PET SUV measurements of tumor 18F-choline uptake correlated significantly with HSA:PUFA-PIC levels and total PIC (r = 0.71, p = 0.0005 and r = 0.72, p = 0.0004, respectively), but not PUFA-PIC levels. Using principal components (PC) analysis, the results were reduced to 3 PC factors accounting for 75% of total profile variation. PUFA-PICs were the only significant (p < 0.01) contributors to PC factor 1, which also reliably distinguished intrahepatic
cholangiocarcinoma from HCC tumors in our study. HSFA-PICs were the only significant contributors (p = 0.01) to PC factor 2, correlating significantly with tumor 18F-choline uptake on PET (P = 0.03, p = 0.0012). Overall, the detection rate of 18F-choline PET/CT for malignant tumors was 94% based on tumors demonstrating increased or decreased 18F-choline uptake. The detection rate for HCC was 84% if a positive PET finding was defined only by an increase in tumor 18F-choline uptake, in which case tumors showing decreased 18F-choline uptake were associated with lower HSFA levels. All intrahepatic cholangiocarcinoma tumors demonstrated low uptake of 18F-choline.

Conclusion: PIC composition varies in primary liver cancer and is associated with tumor detectability on 18F-choline PET/CT. These findings support the CDP-choline pathway as a molecular imaging target for differentiation of liver tumors, and 18F-choline PET/CT as a potential means to monitor anti-cancer treatments targeting phospholipid metabolism.

Disclosure of Interest: None Declared

P-032 ADENOMATOUS POLYPOSIS COLI-BINDING PROTEIN EB1 PROMOTES PROLIFERATION AND INVASION OF HEPATOCELLULAR CARCINOMA CELLS VIA DELTA-LIKE 1

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Introduction: We previously reported that adenomatous polyposis col-binding protein EB1 (EB1) is overexpressed in hepatocellular carcinoma (HCC) cell lines and HCC tissues by proteomics (Fujii et al. Proteomics 2005, Orimo T, et al. Hepatology. 2008). Recent studies suggest that EB1 might be involved in tumorgenesis in addition to its role in regulating microtubule dynamics and related activities, such as cell division, migration, and cell polarity. Here, we investigated the correlation between the expression of EB1 and the malignant behavior of HCC using (1) immunohistochemistry (IHC) of HCC tissues, and (2) proliferation and invasion assay of HCC cell lines. Moreover, we investigated which gene is involved in EB1 overexpression by microarray analysis.

Methods: (1)HCC tissues were obtained from 235 HCC patients who underwent curative surgery at Hokkaido university hospital and subjected to IHC. Informed consent was obtained from all patients in this study. (2)HLE and HuH7 which are HCC cell lines were used for proliferation and invasion assay. The EB1 expression of these cells was inhibited by using two different EB1 specific siRNAs. Furthermore, the EB1 expression of HuH7 was knocked out with CRISPR/Cas9 technology and re-expression of EB1 was performed by lentiviral gene transduction. (3)Microarray analysis was performed with EB1-knockout HuH7 compared with EB1 re-expressed EB1-knockout HuH7.

Results: (1)The tumor was considered EB1-positive if more than 30% of tumor cells showed a stronger staining intensity than the bile duct epithelium. According to the criteria, 24 HCC tumors were classified as EB1-positive, and 211 HCC tumors were EB1-negative. EB1 expression significantly correlated with the degree of histological differentiation, alpha-fetoprotein, vascular invasion status and related activities, such as cell division, migration, and cell polarity. Here, we investigated the correlation between the expression of EB1 and the malignant behavior of HCC using (1) immunohistochemistry (IHC) of HCC tissues, and (2) proliferation and invasion assay of HCC cell lines. Moreover, we investigated which gene is involved in EB1 overexpression by microarray analysis.

Conclusion: Our results indicated that PDX model could accurately reproduce patient tumors and could aid in the discovery of new treatments to advance precision medicine.

Disclosure of Interest: None Declared

P-033 ESTABLISHMENT OF A HUMAN HEPATOCELLULAR CARCINOMA PATIENT-DERIVED XENOGRAFT PLATFORM AND ITS APPLICATION IN PRECLINICAL DEVELOPMENT

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Introduction: Hepatocellular carcinoma (HCC) is the most lethal malignancy worldwide. Surgery remains the most effective curative treatment, but only 30 to 40% of HCC patients are suitable for surgical intervention (1). Although the multikinase inhibitor sorafenib was recently approved as a standard treatment for patients with advanced HCC, the survival benefits remain modest (2, 3) due to a lack of suitable preclinical models that faithfully recapitulate the pathologic, biological, and genetic features of HCC (4).

Results: Using a method optimized in hepatocellular carcinoma (HCC), we established patient-derived xenograft (PDX) models with an increased take rate (42.2%) and demonstrated that FBS +10% dimethyl sulfoxide exhibited the highest tumor take rate efficacy. Among 166 HCC patients, 59 stably transplantable xenograft lines that could be serially passaged, cryopreserved, and revived were established. These lines maintained the diversity of HCC and the essential features of the original specimens at the histological, transcriptomic, proteomic, and genomic levels. Tumor engraftment was associated with poor tumor differentiation and overexpression of cancer stem cell biomarkers, and was an independent predictor for tumor recurrence after resection. To confirm the preclinical value of the PDX model in HCC treatment, several antitumor agents were tested in 16 randomly selected PDX models. The results revealed a high degree of pharmacologic heterogeneity in the cohort, as well as heterogeneity to different agents in the same individual. The sorafenib responses observed between HCC patients and the corresponding PDXs were also consistent. Following molecular characterization of the PDX models, we explored the predictive markers for sorafenib response and found that MAP3K1 might play an important role in sorafenib resistance because tumor tissues with high MAP3K1 expression exhibited a superior response to sorafenib in PDX models and HCC patients (P < 0.05).

Conclusion: The preclinical research platform established in this study provides a powerful tool to investigate the pharmacologic heterogeneity and predictive markers of HCC patients. Furthermore, the platform may aid in the discovery of new treatments to advance precision medicine.

References:

Disclosure of Interest: None Declared

P-034 INTEGRATED ANALYSIS OF MULTIPLE RECEPTOR TYROSINE KINASES IDENTIFIES AXL AS A THERAPEUTIC TARGET AND MEDIATOR OF RESISTANCE TO SORAFENIB IN HEPATOCELLULAR CARCINOMA (HCC).

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Introduction: Axl receptor tyrosine kinase (RTK) is implicated in the progression of HCC. We explored the biologic significance and clinical efficacy of Axl as a therapeutic strategy in HCC using sorafenib (SOR)-naive and resistant cell lines.

Methods: We evaluated Axl expression in a panel of sorafenib-naive and in 2 sorafenib-resistant (SR) clones from epithelial (HuH7) and mesenchymal cell lines (SHep-1) using phospho-RTK arrays and confirmed tissue expression by immunohistochemistry (IHC). We tested the effect of Axl inhibition with RNA interference and pharmacologically with R428 on a number of phenotypic assays including effects on cell survival, motility, and invasion capacity and performed downstream pathway analysis by western blotting.

Results: Axl mRNA overexpression was found in 13/28 HCC cell lines and correlated negatively with E-cadherin and positively with Slug, Vimentin and F-cadherin, consistent with epithelial-to-mesenchymal transition (EMT) (p<0.001). Analysis of RNA-sequencing datasets (n=373) confirmed these associations. IHC confirmed an Axl overexpression gradient in HCC samples compared to background cirrhosis and normal liver tissue (n=10 in each group). In SOR-naive cells, treatment with R428 induced cytotoxicity with GI50 values between 1.5-3.6 μM. In Axl-overexpressing SHep1-5R cells, R428 induced G1-cycle arrest and reduced cell viability. We confirmed SR resistance to be associated with EMT and enhanced motility in both HuH7 and SHep-1-SR clones and found a 4-fold increase in Axl phosphorylation as a late adaptive feature of chronic SOR treatment in SHep1-5R SR cells compared to parental clones. siRNA-mediated Axl inhibition reduced motility and enhanced sensitivity to sorafenib in SHep1-5SR cell clones.

Conclusion: Suppression of Axl-dependent signaling modulates several aspects of the transformed phenotype in immortalized HCC cell lines including proliferation, motility and survival and contributes to adaptive resistance to sorafenib. Our data provide a pre-clinical rationale for the development of Axl inhibitors as a novel therapeutic strategy to overcome sorafenib-resistance in HCC.


Disclosure of Interest: None Declared

P-035 SELECTIVE TARGETING OF THE LIVER WITH NUCLEOSIDE PRODRUGS FOR THE TREATMENT OF LIVER CANCERS

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Introduction: Systemic chemotherapy treatments have failed in many clinical trials for hepatocellular carcinoma (HCC), often because systemic toxicity prevents efficacious exposures levels of the drug from being reached in the liver. This has resulted in alternative strategies to deliver effective concentrations of chemotherapeutic agents to the liver while reducing systemic toxicity e.g. TACE. TACE is a chain terminating nucleoside for cancer treatment that was evaluated in a number of clinical trials. Despite showing some signs of clinical activity, its development was halted due to limited efficacy at the maximum tolerated dose, driven by systemic exposure to troxacitabine. We have generated phosphorylatable nucleotide prodrugs of troxacitabine, designed to overcome a number of limitations of troxacitabine, with improved cellular uptake, improved metabolic conversion to the active triphosphate, and to have selective targeting to the liver with reduced systemic exposure after oral dosing.

Methods: Cell proliferation and viability of liver cancer cell lines was assessed using Cell Counting Kit-8 reduction of the tetrazolium salt WST-8 by viable cells. DNA damage induction was assessed using WestScale Discovery assays for phosphorylated p53. Metabolic activation of prodrugs and nucleosides was assessed in liver and intestinal S9 fractions, hepatocytes and liver cancer cell lines using LC-MS/MS. Anti-proliferative synergy was assessed using MacSynergy II software.

Results: Diverse phosphonamidate prodrugs of troxacitabine monophosphate were designed, synthesized and extensively profiled in vitro. Several of these prodrugs show potent inhibition of HCC cell line growth, with EC50 ranging from 20-500nM and up to 20-fold increased potency relative to the parent nucleoside troxacitabine. Anti-proliferative activity correlates with potent induction of DNA damage markers in HCC cell lines. The most active prodrugs have >1000-fold lower DNA damage inducing activity in primary human hepatocytes. Combination studies with troxacitabine prodrugs show synergistic anti-proliferative activity with sorafenib in a number of HCC cell lines in vitro. Comprehensive metabolic profiling of prodrugs incubated in Hep3B cells or human hepatocytes shows greatly improved conversion to the active triphosphate compared to troxacitabine itself. Compounds were selected for stability in intestinal S9 fractions, and rapid activation in liver S9 fractions, with multiple examples showing good ratios and properties consistent with liver targeting.

Conclusion: Phosphonamidate prodrugs of troxacitabine have been identified that show greatly improved in vitro properties compared to the parent nucleoside, including potent inhibition of HCC cell line growth, increased formation of the active triphosphate, and induction of DNA damage. These compounds are stable in intestinal S9 fractions, and rapidly metabolized to the active triphosphate in liver S9 fractions, with in vitro properties designed to be orally bioavailable and targeted for metabolism and activation in the liver. These compounds are synergistic with sorafenib, suggesting that they might prove efficacious in combination treatment. Further preclinical profiling of these agents is ongoing with the intention of initiating clinical trials to evaluate their potential as new orally delivered agents for the treatment of HCC and other liver cancers.

Disclosure of Interest: M. Alberelli: None Declared, R. Bethell: Stocks of: Stockholder of Medivir AB.

P-036 HCC-SPECIFIC RNA REPLACEMENT OF HTERT-TARGETING TRAN-SPLICING RIBOZYME ENHANCED BY POST-TRANSCRIPTIONAL AND MICRORNA REGULATION DISCLOSES MORE EFFICACY AND SAFETY OF HCC-TARGETING GENE THERAPY

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Introduction: An adenoviral vector harboring human telomerase reverse transcriptase(TERT) RNA-targeting trans-splicing ribozyme(TSR) and liver-specific promoter PEPCK for HCC-specific gene therapy has been developed, successfully. The ribozyme can mark cancer cells expressing hTERT and sensitize them to ganciclovir treatment by expression of therapeutic thymidine kinase(TK) gene[Ad-PEPCK-TERT-Ribo-TK: PRT]. To overcome two hurdles, weaker transcriptional activity of PEPCK promoter and possible TERT-targeting to non-hepatic hepatocytes, we designed a next generation by insertion of splice donor(5’splice acceptor)GA site and woodchuck hepatitis post-transcriptional regulatory element(WPRE) for post-transcriptional regulation, inducing enhanced expression, and insertion of antisense target sequence of liver-specific microRNA122a, which will suppress expression in non-hepatic hepatocytes. In this study, we investigated enhanced efficacy and safety of Ad-PEPCK-5’CSA-Ribo-TK-WPRE-miR122aT[EPRT-122aT].

Methods: Adenoviral vectors(PT, PRT, PRT-122aT, EPRT-122aT) were constructed. Hep3B and HepG2(TERT+, miR122aT), Huh7(TERT+, miR122aT) and SKLU1(TERT+, miR122aT) were used. In vitro cytotoxicity was examined, following in vivo toxicity and antitumor efficacy studies through systemic delivery of vectors. Intrahepatic multilocal HCC model in nude mice was made by splenic subcapsular injection of cells.

Results: When cells injected with EPRT-122aT, prominent cytotoxicity of HepG2 and Hep3B cells was observed, more than PRT-122aT, but not in Huh7 and SKLU1 cells. Least hepatotoxicity was noted in normal mice when injected with decreasing doses, 10, 2, 1, 0.5x10⁷VP of EPRT-122aT, similar to 10x10⁷VP of PRT group (n=5, each). In multilocal HCC xenograft, treatment with 10, 2, 1, 0.5x10⁷VP of EPRT-122aT, tumor weights were 0.11±0.29g, 0.14±0.14g, 0.21±0.22g and 0.77±0.98g, and with PRT10x10⁷VP, 0.38±0.31g, representing remarkably enhanced efficacy with 1/10 dose of PRT, compared with PBS group (n=4, 1.21±0.43g). In vivo.

Conclusion: These results represent that post-transcriptional expression regulation of ribozyme discloses remarkably enhanced antitumor efficacy, resulting in lowering adenoviral dose, leading to more safety as well as efficacy. Concurrently, liver-specific microRNA regulation role evasion of non-tumoral liver cells, endowing enhanced safety. HCC-specific gene therapy by enhanced hTERT targeting TSR promises highly specific, efficient and safe HCC gene therapy.

Disclosure of Interest: None Declared
Introduction: Drug resistance is the major factor that limits the application of chemotherapy for hepatocellular carcinoma (HCC). It has been reported that Histidine-rich glycoprotein (HRG), an abundant plasma protein produced by liver, has antitumor activity and involves in antitumor response[1, 2]. Hence HRG may be an ideal enhancer for chemotherapy regimen of HCC.

Methods: The expression of HRG mRNA was detected in 32 fresh paired cancerous and noncancerous tissues by quantitative real-time PCR. HRG protein was examined in 10 fresh paired tumor and non-tumor samples by western blot. The association between HRG expression and overall survival rate of patients with HCC was analyzed in Cancer Genome Atlas project (TCGA) and GSE14520 of Gene Expression Omnibus (GEO) dataset. The effect of HRG overexpression on cellular proliferation was determined by CCK-8, EDU assay, and athymic nude mice xenograft models. Chemosensitivity was evaluated by calculating the percentage of apoptotic cells using Annexin V/7-AAD staining and detecting the level of apoptosis-related proteins by western blot. The significance of the difference between groups was calculated using Student’s t test or ANOVA test. A value of p< 0.05 indicated a significant difference.

Results: Our study found that HRG expression was remarkably down-regulated in HCC tissues compared with adjacent non-tumor liver tissues detected by qRT-PCR and western blotting. This results was confirmed by analysis of TCGA (n=351; p< 0.0001) and GSE14520 (n=152; p= 0.0001) datasets. In addition, the patients with lower expression of HRG showed significantly shorter overall survival (OS, p= 0.003 and p= 0.0056 for TCGA and GSE14520, respectively). Ectopic HRG expression significantly inhibited cellular proliferation as determined by CCK-8 and EDU assays. In vivo experiments further confirmed that HRG overexpression suppressed the growth of SMMC-7721 xenograft tumors in nude mice (n= 6). Moreover, FCM data showed that HRG overexpression significantly increased the percentage of apoptotic cells after 5-fluorouracil treatments in comparison with control cells (p= 0.0003 and p= 0.0001, respectively). Consistent with FCM data, after 5-fluorouracil treatments, the expressions of apoptotic related proteins, cleaved caspase-3 and cleaved PARP, were remarkably increased in HRG-overexpressing SMMC-7721 and HuH7 cells compared with the controls. Meanwhile, we found that p38/MAPK pathway was responsible for the chemotherapy enhancement effect of HRG.

Conclusion: Our results demonstrated that low expression of HRG is associated with a poor prognosis of HCC patients. HRG functions as a tumor suppressor and enhances 5-fluorouracil chemosensitivity in HCC through p38/MAPK-mediated apoptosis pathway, which proposes the therapeutic value of HRG in HCC chemotherapy.


Disclosure of Interest: None Declared
Conclusion: These findings indicated that negative regulation occurred in the exhausted NK cells as a result of the increased expression of inhibitory receptor NKG2A from cancer nests and suggesting that NKG2A blockade has potential to restore immunity against tumor by reversing NK cell exhaustion.

References:

Disclosure of Interest: None Declared

P-039 PROGRAMMED DEATH LIGAND 1 AS AN INDICATOR OF PREEXISTING ADAPTIVE IMMUNE RESPONSES IN HUMAN HEPATOCELLULAR CARCINOMA

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Introduction: It is well known that the aberrant expression of programmed death ligand 1 (PD-L1) on tumor cells impairs antitumor immunity. To date, in hepatocellular carcinoma (HCC), the relationship between PD-L1 expression and host-tumor immunity is not well defined. This study characterized the PD-L1 expression in HCC and further elucidated the associations between PD-L1 and tumor-infiltrating CD8+ T cells.

Methods: The expression of PD-L1 and tumor-infiltrating CD8+ T lymphocyte count were assessed by immunohistochemistry (IHC) in paraffin-embedded specimens from 167 HCC patients undergoing resection. The mRNA of PD-L1, CD8 and INF-γ was quantified by qPCR in 45 HCC tissues. PD-L1 expression on three HCC cell lines was detected by western blot assay. The prognostic significance of PD-L1 expression and CD8+T cell infiltration was evaluated using the Kaplan–Meier method and compared by the log-rank test. The Cox-regression model was used to perform univariate analyses, and multivariate analysis was performed on all factors with p less than 0.10.

Results: Intratumoral PD-L1 expression was found to be significantly correlated with CD8+ T cells (r=0.38, P=0.01) and INF-γ expression (r=0.49, P=0.001). PD-L1 expression was not detected on HCC cell lines, but co-culture with INF-γ remarkably up-regulated PD-L1 expression. Both increased intratumoral PD-L1 and CD8 were significantly associated with superior DFS (CD8: P=0.03; PD-L1: P=0.023) and OS (CD8: P=0.001 and PD-L1: P=0.059), but PD-L1 expression was not independently prognostic.

Conclusion: PD-L1 up-regulation is mainly induced by activated CD8+ cytotoxic T cells pre-existing in the HCC milieu rather than being constitutively expressed in the tumor and is a favorable prognostic factor for HCC.

Disclosure of Interest: None Declared
**P-041** TARGETING ALPHA FETOPROTEIN WITH TCR ENGINEERED T CELLS IN HCC

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**Introduction:** Alpha fetoprotein (AFP), an oncofetal protein, is transcriptionally repressed after birth. Reappearance of AFP in adult circulation indicates liver regeneration, hepatitis, chronic liver diseases, or malignant growth. When AFP positive, expression in HCC tends to be very high and homogeneous, making it an attractive immunotherapy target.

**Methods:** A TCR specific for the HLA-A2-restricted peptide AFP158-165 (FMNKFIYEI) was identified and engineered to generate a panel of 12 affinity-enhanced TCRs. One clone (10µM KD), demonstrating enhanced potency against AFP-expressing liver tumor cell lines and no response to normal hepatocytes, was selected. Molecular mapping of each position of the target peptide was performed; the generated binding motif was searched against the human genome, identifying 165 potentially reactive peptides, which were synthesized, loaded onto T2 cells, and tested for reactivity by AFP-T engineered T cells (AFP-T).

**Results:** No safety concerns were identified. 126 normal cells and 42 tumor cell lines from various organ systems were screened for AFP-T reactivity. AFP-T showed colchicine secretion and cytotoxic activity against HCC cell lines in 2D culture and 3D microtissues, but no relevant response to any other HLA-A*0201-expressing cells. Alloreactivity was detected against a subset of HLA-A*0202 primary cells. A full alloreactive screen performed using a panel of 51 EBV- transformed B cell lines covering 38 HLA-A, 63 HLA-B and 28 HLA-C alleles, demonstrated enhanced responses against HLA-A*0204 and HLA-B*5103. AFP-T did not recognize the AFP peptide in the context of HLA-A*0203. Patients with HLA-C*0404 and B*5103 and A*0202 will be excluded.

**Conclusion:** A Phase I study will evaluate preconditioning- and cell- dose escalation to investigate the safety and anti-tumor activity of AFP-T in HLA-A*0201+ patients with AFP+ HCC and good residual liver function. Clinical safety measures for mitigating treatment-related hepatotoxicity include pre-treatment biopsy evidence of low AFP expression in non-cancerous liver, and monitoring/management strategies within the protocol. Three cell-dose cohorts at 1x10⁶, 1x10⁷, 5x10⁹ total transduced cells will be investigated.

**Disclosure of Interest:** None Declared

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**P-042** HISTONE ACETYLTRANSFERASE HMOF PROMOTES VASCULAR INVASION IN HEPATOCELULAR CARCINOMA, VIA H4K16 ACETYLATION.

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**Introduction:** We previously showed that an epigenetic modification of histone H4 acetylation on lysine 16, H4K16ac, was significantly overexpressed in hepatocellular carcinoma (HCC) with microvascular invasion (mVI), a major prognostic factor in HCC (1). H4K16 acetylation, mediated by the histone acetyltransferase hMOF (human Males absent On the First), plays a major role in transcriptional activation (2). Interestingly, several studies have shown that hMOF and/or H4K16 acetylation were deregulated in many cancers (3). However, the role of hMOF and H4K16 acetylation in liver carcinogenesis has not been investigated so far.

**Methods:** hMOF expression was assessed by immunohistochemistry (HC) and RT-qPCR in a panel of 55 HCC obtained from surgical resections (mVI+, n=29; mVI-, n=26). A semi-quantitative IHC score (0-300) was calculated (% of stained cells [0-100] staining intensity [1 weak; 2 intermediate; 3 strong]), blinded to the clinicopathological data. Genes specifically regulated by hMOF and H4K16 acetylation were identified by a microarray transcriptional analysis (Affymetrix® HTA 2.0) in hepatoma cell line PLC/PRF/5, using a TAP mining approach. Data were analyzed with GeneSpring® and Pathway STUDIO® softwares.

**Results:** hMOF was significantly overexpressed at the protein level in HCC/mVI+ compared to HCC/mVI- (median IHC score 198 vs 70, p = 0.002), but not at the mRNA level (p = 0.7). TAP-encoded hMOF knockeddown led to a significant H4K16ac overall decrease. Transcriptomic analysis showed that hMOF down-regulation was associated with repression of genes mainly involved in tumor cell migration/vasculatin (CD24, LAGALS1, ITGA1, ITGA4, ITGA4, ITGA4, and cell matrix organization (PECAM1, MMP19) (figure 1). Interestingly, AXL, a tyrosine kinase receptor specifically involved in transendothelial migration in HCC (4), was also found to be significantly downregulated (fold -1.43, p=0.016). Downregulation of AXL and LAGALS1 mRNA levels in PLC/PRF/5 cells was confirmed by RT-qPCR (p=0.05).

**Conclusion:** This study suggests a critical role for hMOF and H4K16 acetylation in vascular invasion in HCC via transcriptional activation of genes involved in this process, and paves the way for future therapies targeting chromatin-modifying enzymes in HCC.


**Disclosure of Interest:** None Declared

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**P-043** TOLL-LIKE RECEPTOR 3 REPRESSION DURING HEPATOCARCINOGENESIS AS AN ESCAPE FROM EXTRINSIC APOPTOSIS

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**Introduction:** TLR3 (Toll-like receptor 3) detects viral or endogenous double-stranded RNA, and promotes in primary human hepatocytes (PHH) an inflammatory response notably by interferon type I production (1). In cancer cells, TLR3 can also induce apoptosis by its ability to activate the extrinsic caspase pathway (2).

Our aim was to characterize TLR3 expression and functionality in hepatocellular carcinoma (HCC) in order to assess its potential antitumor effect.

**Methods:** 129 patients with resected HCC were analyzed to evaluate the prognostic impact of TLR3 expression at mRNA (RT-qPCR) and protein levels. In vitro TLR3 expression was evaluated in 6 human HCC cell lines (Hep G2, Hep 3B, Hep 7, PLC/PRF/5, SK-HEP1, Focus) as well as in a model of PHH transformation by the onxogenes SV40T12 and H-RasV12. The mechanisms underlying TLR3 invalidation in HCC cells were assessed at genetic and epigenetic levels. In vivo, transgenic mice expressing the onxogen SV40LT in the liver were crossed with TLR3 WT (TLR31/2) or TLR3 invalidated mice (TLR31) to assess the impact of TLR3 invalidation on hepatocarcinogenesis.

**Results:** In human resected HCCs, low levels of TLR3 mRNA in tumors was significantly associated with shorter time to recurrence (HR = 2.16 p = 0.006). Moreover TLR3 protein was under-expressed in tumor vs non tumor in more than 50% of cases. In vivo, TLR3 was poorly expressed in all HCC cell lines (Hep G2, Hep 3B, Hep 7, PLC/PRF/5, SK-HEP1, Focus) as well as in a model of PHH transformation by the onxogenes SV40T12 and H-RasV12. Two mechanisms were identified: one genetic by alicic loss and one epigenetic by a represive histone mark. TLR3 re-expression by lentiviral transduction in 3 cell lines tested (Hep G2, Hep 3B, PLC/PRF/5) led to apoptosis after activation with a TLR3 ligand (PolyC). Cancerous transformation of PHH by SV40T12 and H-RasV12 was associated with a drastic decrease of TLR3 expression at mRNA and protein levels. In the transgenic SV40 mouse model, nodules were significantly more prominent in SV40/TLR31 mice than in SV40/TLR3 mice at different lifetimes. 8, 10 and 12 weeks. In SV40/TLR31 mice, cleaved caspase 3 staining confirms a significant decrease of apoptotic events in the hepatic parenchyma without impact on proliferation (similar Ki67 proliferation index).

**Disclosure of Interest:** None Declared
Conclusion: These results suggest that TLR3 could represent the first receptor of innate immunity acting as a potential tumour suppressor gene in HCC. Expression level is more advanced than in normal liver tissues, cirrhosis to HCCs (p<0.05, one-way ANOVA with post-test for trend). In addition, HMGA1 expression levels in a cohort of HCC needle biopsies matched with corresponding non-neoplastic (cirrhosis) liver tissues (n=37 matched samples) and normal liver specimens (n=5). In addition, by using tissue microarray (TMA) we evaluated HMGA1 protein levels in a large collection of liver specimens (n=434) including normal, cirrhotic and tumoral tissues. Survival analysis was performed using the Kaplan-Meier method and compared using log-rank tests. Furthermore, liver cancer cell lines with low and high endogenous HMGA1 expression (PCL5 and SNU449, respectively) were transfected with stable induced shRNA knockdown expression of HMGA1 were subjected to in-vitro assays, including proliferation, invasion and soft agar assays to test the oncogenic properties of HMGA1.

Results: Our analysis revealed that compared to normal liver samples, HMGA1 RNA and protein levels were both significantly increased in HCCs (p<0.05) as well as in cirrhotic tissues (p<0.001). We observed a significant trend of increasing HMGA1 RNA and protein expression from normal liver tissues, cirrhosis to HCCs (p<0.05, way ANOVA with post-test for trend). In addition, HMGA1 expression was higher in female than male patients (p<0.001) and was higher in virus-infected than alcohol-related HCC specimens (p<0.05). High HMGA1 protein levels were associated with worse prognosis in terms of disease-free progression but not overall survival. Functional characterization in liver cancer in-vitro models showed that forced expression of HMGA1 resulted in increased cell growth and invasion compared to the cells transfected with the empty vector (p<0.05), while cells with HMGA1 knockdown displayed reduced growth and invasion compared to the cell transfected with the empty vector (p<0.05). Soft agar assays showed that cells with forced expression had increased foci formation, suggesting an oncogenic role of HMGA1 in hepatocarcinogenesis.

Conclusion: Here we provide evidence that the development of cirrhosis and HCC is associated with HMGA1 overexpression. Moreover, functional studies implicate an oncogenic role for HMGA1 in tumor growth and invasion potential in liver carcinogenesis.


Disclosure of Interest: None Declared
P-047 SYSTEMATIC EVALUATION OF CIRCULATING INFLAMMATORY MARKERS AND MODIFICATION OF THE INFLAMMATORY PROGNOSTIC INDEX FOR HEPATOCELLULAR CARCINOMA

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Introduction: A number of circulating inflammatory factors are implicated in the pathogenesis and prognostication of hepatocellular carcinoma (HCC). We aim to evaluate the prognostic potential of multiple serum inflammatory factors simultaneously and develop an objective inflammatory score for HCC.

Methods: A prospective cohort of 555 patients with HCC with paired serum samples was accrued from 2009 to 2012. The blood levels of conventional inflammatory markers, namely C-reactive protein, albumin, neutrophils, lymphocytes and platelet, were determined, and 41 other exploratory markers were measured by a multiplex assay. The prognostication and interaction of markers were determined by univariable and multivariable analyses.

Results: The cohort was randomly divided into training cohort (n=416) and validation cohort (n=140). There were no differences in baseline characteristics between the two cohorts. In the training cohort, independent prognostic factors for overall survival included C-reactive protein [hazard ratio (HR) 1.107; p=0.003], albumin (HR 0.953; p=0.032) and interleukin-8 (HR=5.816; p<0.001). We have modified the existing inflammation based index (IBI) by adding serum interleukin-8 level. The modified IBI could stratify patients into four groups with distinct overall survival (p=0.001) (Figure 1). The results were also validated in the validation cohort (Figure 2). When compared with IBI and other conventional inflammatory markers, the modified IBI had better prognostic performance with higher c-index and homogeneity likelihood ratio chi-square.

Image:

Figure 1: Kaplan-Meier plot of overall survival according to Inflammatory Based Index (IBI) and modified IBI (mIBI) in the training cohort.

Figure 2: Kaplan-Meier plot of overall survival according to Inflammatory Based Index (IBI) and modified IBI (mIBI) in the validation.

Conclusion: Amongst the conventional and exploratory circulating inflammatory markers, higher CRP, lower albumin and higher interleukin-8 were independent prognosticators. By combining these factors, a simple and accurate inflammatory index could be constructed.


Disclosure of Interest: None Declared

P-048 SUBCLASSIFICATION OF THE ADVANCED STAGE AMONG PATIENTS WITH UNTREATED HEPATOCELLULAR CARCINOMA

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Introduction: Subclassification of the Barcelona Clinic Liver Cancer (BCLC) early stage (BCLC A) and intermediate stage (BCLC B) have been proposed due to heterogeneous populations of patients with hepatocellular carcinoma (HCC). However, heterogeneity of the advanced stage (BCLC C) remains largely unknown. The need of subclassification of BCLC C has not explored yet.

Methods: We recruited a cohort of 345 HCC patients with BCLC C disease receiving best support care. Univariable and multivariable Cox regression was employed to identify independent prognostic factors predicting clinical outcome. A subclassification was established by using these independent factors.

Results: The univariable Cox regression showed that patient’s age, cirrhosis, Child-Pugh grade, tumor size, portal vein thrombosis, extrahepatic spread and serum alpha-fetoprotein predicted overall survival. After exclusion of these parameters with collinearity, the multivariable Cox regression identified Child-Pugh grade B (hazard ratio (HR) 1.32, 95% confidence interval (CI): 1.06-1.65, P=0.012), portal vein thrombosis (HR 1.89, 95% CI: 1.51-2.36, P<0.001) and extrahepatic spread (HR 1.75, 95% CI: 1.29-2.39, P<0.001) were independent prognostic factors. A subclassification was constructed based on the presence of these three parameters (C1: none; C2: any one factor; C3: any two factors; C4: all three factors). Median survival was gradually worsen from stage C1 (9.0 months; n=73, 21.0%) through stage C2 (9.0 months; n=159, 45.7%) and C3 (2.2 months; n=140, 29.9%) to stage C4 (1.0 months; n=3, 3.4%). There were significant differences between contiguous stages (C1 vs. C2, P=0.004; C2 vs. C3, P=0.002; C3 vs. C4, P<0.001).

Image:
Conclusion: The advanced stage (BCLC C) is a heterogeneous group. Subclassification of BCLC C predicted the prognosis of patients with untreated HCC.

Disclosure of Interest: None Declared

P-049 EVALUATION OF THE ALBI SCORE AS PROGNOSTIC INDICATOR IN EGYPTIAN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: The Child-Pugh (CTP) score for evaluation of liver function status has limitations as it relies on individual subjective variables as ascites and encephalopathy, that are scored based on arbitrarily defined points. The albumin-bilirubin (ALBI) score eliminates the need for the subjective variables required in the CTP grade and offers more precise selection of patients with HCC for treatment allocation and it is now considered a core for other scores.

Methods: This study was conducted on 415 patients with HCC in a tertiary referral center in Egypt. Baseline characteristics including CTP, BCLC & ALBI scores were determined. Patients were followed up from the time of diagnosis to the date of death or date of data collection if they remained alive. Overall survival and the received treatment were determined. Survival data were analyzed using Kaplan Meir Survival curves using log rank test and multivariate analysis.

Results: For 415 patients, the mean age was 57 years, 317 were males. At presentation, 65.5% were CTP A, 28% were CTP B and 6.5% were CTP C. Most of patients were ALBI grade 2 (63.6%), followed by grade 2B (35.9%) and grade 1 (0.5%). Kaplan-Meier survival curves were stratified with significant differences, suggesting that the Kinki Criteria were predicted the prognosis of patients with untreated HCC.

Conclusion: ALBI score was found to be an independent prognostic factor that classifies patients with HCC according to liver functions better than CTP score. Further sub-classification for ALBI grade 2, were found to be significant to identify patients with better liver reserve. In addition, ALBI score will help providing better treatment modalities to patients with HCC.


Disclosure of Interest: None Declared

P-050 VALIDATION OF A PROPOSED SUBSTAGING SYSTEM FOR PATIENTS WITH INTERMEDIATE HEPATOCELLULAR CARCINOMA

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Introduction: Barcelona Clinic Liver Cancer (BCLC) stage B, an intermediate stage, includes various conditions of hepatocellular carcinoma (HCC); such heterogeneity of the patients with intermediate-stage makes difficult to predict the survival. In the present study, we examined the validity of the modified Bolond’s classification (BCLC A) as a subclassification of BCLC stage B HCC patients.

Methods: Of 906 patients who underwent conventional Transarterial chemoembolization (cTACE) at Kinki University Hospital, 753 who meet the inclusion criteria were examined. Of these 753 patients, 425 (56.4%) with BCLC stage B were subclassified using the Kinki Criteria to examine the survival. For the determination of sub-stage based on the Kinki Criteria, the Child-Pugh scores are classified into 5 - 7 points or 8 - 9 points, and the beyond Milan and IN or OUT of the up-to-7 criteria were determined based on the number and diameter of tumors. The subclasses B1, B2, and B3 refer to Child-Pugh scores of 5 - 7 points and “IN” in terms of the up-to-7 criteria, subclass B2 refers to Child-Pugh scores of 5 - points with “OUT” of the up-to-7 criteria, subclass B3 refers to Child-Pugh scores of 8 - 9 points with either IN or OUT of the up-to-7 criteria, respectively.

Results: Using the Kinki Criteria, 158 (17.2%) were subclassified into BCLC subclass B1, 236 (26.5%) into B2, and 317 (37.2%) into B3. The comparisons of the survival showed that the median overall survival (OS) was 3.9 years (95% CI, 3.2–4.6) in the BCLC subclass B1 group, 2.5 years (95% CI, 2.2–3.1) in the BCLC subclass B2 group, and 1.7 years (95% CI, 0.8–1.5) in the BCLC subclass B3 group (P < 0.001). Pairwise comparisons confirmed a significantly longer OS in the BCLC subclass B1 group than in the BCLC subclass B2 group (P < 0.001). Similarly, OS was significantly longer in the BCLC subclass B1 group than in the BCLC subclass B3 group (P < 0.001), and significantly longer in the BCLC subclass B2 group than in the BCLC subclass B3 group (P < 0.001). In contrast, no significant differences in OS were detected between the BCLC stage A and BCLC subclass B1 groups (P = 0.24) or between the BCLC subclass B3 and BCLC stage C groups (P = 0.49).

Conclusion: When the BCLC stage B patients were subclassified according to the Kinki Criteria, survival curves were stratified with significant differences, suggesting that the Kinki Criteria were suitable for the subclassification of the intermediate stage of HCC patients.

Disclosure of Interest: None Declared

P-052 RISK PREDICTION MODEL FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDERGOING RADIOFREQUENCY ABLATION

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Introduction: We aimed to establish a simple-to-use risk prediction model for patients with hepatocellular carcinoma (HCC) undergoing radiofrequency ablation (RFA).

Methods: Patients receiving RFA as the first-line therapy between 2005 and 2014 were selected from the database (n = 757). The study population was randomly assigned into the derivation (n=505) and the validation (n=252) cohorts. Multivariate Cox-regression analysis for disease-free survival (DFS) was used to select the variables to generate the risk prediction model in the derivation cohort and then, the prognostic performance was assessed in the validation cohort.

Results: From multivariate Cox-regression analysis, tumor size, tumor number, baseline alpha-fetoprotein (AFP) level, baseline protein induced by vitamin K absence/antagonist-II (PIVKA-II) level and ascites were selected. The scores were allocated for each variable as follows: 0, 2, and 5 for tumor size<2 cm, 2–3 cm, and ≥3 cm, respectively, 0, 2, and 4 for tumor number 1, 2, and 3, respectively, 0 and 1 for AFP<20 mg/mL and AFP>20 mg/mL, respectively, 0 and 1 for PMMA≤40 mL/min, and PMMA>40 mL/min, respectively, and 0 and 1 for pressure and absence of ascites, respectively. The risk prediction model was defined as the sum of each score assigned to each variable. Time-dependent areas under receiver-operating characteristic curves of the risk prediction model for DFS at 3 and 5 years were 0.706 and 0.706 in the derivation cohort and 0.846 and 0.853 in the validation cohort, respectively. According to the score of the risk prediction model, patients were stratified into three groups: the low-risk (score 0–1), the intermediate-risk (score 2–3), and the high-risk (score ≥4) group, respectively. In the training cohort, the low-risk group had the longest median DFS (50.1 months), followed by the intermediate-risk group (24.8 months), and the high-risk group (9.9 months). Compared with the low-risk group, the intermediate-risk group (hazard ratio [HR] 2.419, P < 0.001) and the high-risk group (HR 8.499, P < 0.001) retained the significant higher risk of recurrence or death. Similar results were obtained in the validation cohort.

Conclusion: A simple-to-use risk prediction model for patients with HCC undergoing RFA might be helpful in appropriate prognostic stratification and guidance for decision of further treatment strategies.

Disclosure of Interest: None Declared
**FGF19 AS BIOMARKER FOR FGFR4 INHIBITOR TRIAL ENRICHMENT IN HEPATOCELLULAR CARCINOMA**

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**Methods:** We performed cDNA microarray analysis of SP cells isolated from the 2 cell lines and found 8 molecules, i.e., Jumos kinase and microtubule interacting protein 3 (JAKMIP3), Annexin A1 (ANXA1), G protein subunit gamma 11 (GNG11), VAC14, E74-like factor 3 (ELF3), Gualacinmin (N-Acetyl) Transferase 3 (GCNT3), Complement component 3 (C3), EPH receptor A2 (EPHA2), with increased gene expression in common. The real-time PCR analysis of the 8 molecules was performed in the 2 cell lines. In addition, we immunohistochemically examined the expression of some of the 8 molecules using 100 cases of HCCs (< 5 cm in diameter) obtained from the patients who undergone curative hepatectomy at Kurume University Hospital from 2007 to 2009. Immunoreactivity was evaluated with immunohistochemical (IHC) score obtained by multiplying intensity of positive cells (0, 1, 2, 3) by area of positive cells (0, 1, 2, 3). The relationship between each or sum of IHC score of 3 molecules and clinicopathological parameters (e.g., gross type, histological differentiation, portal vein invasion, intrahepatic metastasis, and so on) was examined.

**Results:** The real-time PCR analysis revealed that the expression of ANXA1, ELF3, and JAKMIP3 was significantly higher in SP cells than NSP cells in HAK-1B cells and was higher in HAK-1B cells than HAK-1A cells. Thus, we selected the 3 molecules for further IHC analysis. Each of IHC score of ANXA1, ELF3, and JAKMIP3 was significantly higher in poorly differentiated HCCs, in HCCs with high incidence of portal vein invasion, and in HCCs with intrahepatic metastasis. Sum of 3 IHC scores could show the same or more significant results. Regarding to gross type, IHC score of ‘contiguous multinodular type’ and ‘simple nodular type with extranodular growth’ were significantly higher than that of ‘simple nodular type’. When 100 cases were classified into 2 groups according to the sum of IHC score of 3 molecules, low IHC score (< 6) group showed significantly better overall survival rate than high IHC score (> 6) group.

**Conclusion:** As candidates for biomarker of aggressive HCC, we identified 8 molecules, in which ANXA1, ELF3, and JAKMIP3 may be useful to predict malignant biologic feature and poor prognosis of the HCCs.

**Disclosure of Interest:** None Declared
Conclusions: TPMT/height can be an effective and simple marker of sarcopenia and may predict mortality in HCC patients.


Disclosure of Interest: None Declared

P-057 REPROGRAMMING CELLULAR METABOLISM BY β-CATENIN AND ITS CLINICAL IMPLICATION IN HEPATOCELLULAR CARCINOMA

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Introduction: CTNNB1 (β-catenin) is a commonly activated oncogene in hepatocellular carcinoma (HCC). While β-catenin has been extensively studied in other cancers, its roles in HCC are less understood. We investigated roles of β-catenin in cancer metabolism and sensitivity to sorafenib in HCC.

Methods: We characterized gene expression profiles of human and mouse HCC tumors with activated β-catenin to uncover molecular traits associated with clinical outcomes and further developed a prediction model that can identify β-catenin-active HCC. We silenced and overexpressed glutamine synthetase (GS), a major target of β-catenin, and measured cell growth rate, cell cycle progression, metabolism, and autophagy rate in multiple HCC cell lines to characterize its roles in HCC development.

Results: We show that β-catenin increases the expression of GS and triggers a series of metabolic changes leading to a lag in tumor growth and induction of autophagy in HCC. Mechanistically, upregulation of GS by β-catenin reduces glutamine turnover and TCA flux by decreasing glutamate levels, which contributes to delayed cell cycle progression. Delayed tumor growth coincides with increased autophagy, which is also mediated by glutamine synthetase, for alleviating cellular stress. Moreover, a high basal level of autophagy in β-catenin-active HCC cells makes them more sensitive to sorafenib, suggesting a connection between β-catenin mutations and treatment. We also demonstrated significant association of β-catenin activation with good prognosis.

Conclusion: HCC with mutated β-catenin is distinct subtype with favorable prognosis and β-catenin is involved in cell metabolism leading to favorable prognosis. Significant sensitivity of HCC with activated β-catenin to sorafenib suggests that mutation status of β-catenin might be used to guide treatments and improve efficacy of standard treatment.

Disclosure of Interest: None Declared

P-058 BIOMARKER-DRIVEN INHIBITION OF MET AND EGFR PATHWAYS IN HEPATOCELLULAR AND CHOLANGIOCARCINOMA MODELS

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Introduction: High levels of c-MET and EGFR have been correlated with poor prognosis in hepatocellular carcinoma (HCC) and cholangiocarcinoma (CK). Moreover, MET and EGFR have been involved in drug resistance. Our study aimed to evaluate MET and EGFR inhibition on cell viability, invasion, MET and EGFR signaling, as well as on sorafenib sensitivity.

Methods: SU11274 and lapatinib are specific inhibitors of activated MET and EGFR/HGFR, respectively. Antiproliferative effects were evaluated in 12 HCC and CK cell lines using MTT assay. Protein levels were assessed by Western blot. Cell motility was investigated by wound-healing and matrigel invasion assays. Ex vivo experiments testing SU11274 were performed on surgical specimens from HCC patients that were cut into 300µM-thick slices and grown in specific media for 48h. Tumor samples were analyzed by F or H & I.

Results: Expression levels of MET and EGFR defined two subgroups of cells classified as high-MET/low-EGFR or low-MET/high-EGFR cell lines. These subgroups displayed differential sensitivity towards MET and EGFR inhibitors. High-MET/low-EGFR cells displayed high sensitivity to SU11274 (G50=[1.6-3.7]µM) but not lapatinib (G50≈20µM), whereas low-MET/high-EGFR cells were more sensitive to lapatinib (G50=[4.8-10.2]µM) than SU11274 (G50≈20µM). HGF-dependent invasion was more potently inhibited by SU11274 in high-MET/low-EGFR than in low-MET/high-EGFR cells. Cells sensitivity to receptor inhibition could be explained by intrinsic cell responsiveness to MET- and EGFR-pathway activation. Increased levels of high-MET/low-EGFR cells to HGF was translated into increased sensitivity to SU11274. Similarly, low-MET/high-EGFR cells were more responsive to EGFR and consequently more sensitive to lapatinib. Interestingly, SK-Hep1 cells resistant to sorafenib expressed increased level of MET and were subsequently more sensitive to MET inhibition. Ex vivo results would be detailed on the poster with c-MET, HE, KI67, and caspase 3 expression.

Conclusion: MET and EGFR expression profiles defined two subgroups of HCC and CK cell lines with differential inhibitory sensitivity towards MET and EGFR inhibitors. Our results suggest that high-MET/low-EGFR might be the candidate tumor types to evaluate MET inhibitors, whereas low-MET/ high-EGFR tumors may be preferentially tested for EGFR pathway inhibition. Moreover, these results suggest that MET could be an attractive target in sorafenib resistant HCC patients.

Disclosure of Interest: None Declared
P-061 COMBINING TUMOR GLYCAN-3 EXPRESSION AND CD16 EXPRESSION ON NK CELLS FROM PERIPHERAL BLOOD TO IDENTIFY PATIENTS RESPONDING TO CODRITUZUMAB/GC33/ RS0137382

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Introduction: Codrituzumab (GC33 or RS0137382), a monoclonal antibody targeting an oncofetal protein-glypican-3 (GPC3) expressed on the cell surface of hepatocellular carcinoma (HCC), induces antibody-dependent cellular cytotoxicity (ADCC) and inhibits tumor growth in preclinical studies. Based on this mechanism of codrituzumab, two biomarkers GC33 and CD16 of the NK cells, which are the effector cells of ADCC, were investigated to correlate with clinical efficacy of codrituzumab in patients with advanced HCC.

Methods: Data from a phase II clinical trial of codrituzumab were used for this analysis. GC33 expression was determined by immunohistochemistry (IHC) analysis of tumor biopsy samples, and CD16 expression on NK cells were quantified by a flow cytometry analysis of peripheral blood mononuclear cells. Overall survival of patients with high expression of codrituzumab or placebo (n = 113) was used to compare different patient subgroups stratified by high or low expression of GC33 and CD16.

Results: In individual-biomarker analyses, longer survival after codrituzumab treatment correlates with either high expression level of GC33 in tumors (n = 97, HR = 0.39, 95%CI = 0.21-0.70, p = 0.00081) or a relatively high level of CD16 expressed on NK cells (n = 80, HR = 0.44, 95%CI = 0.23-0.83, p = 0.0056) at baseline. Furthermore, joint analyses of the two biomarkers reveal that both high levels of GC33 and CD16 are required for patients to benefit from codrituzumab treatment (n = 67, HR = 0.29, 95%CI = 0.13-0.62, p = 0.00074), and lack of either one of them leads to a loss of codrituzumab therapeutic effect.

Conclusion: The retrospective analysis supports the mechanism of ADCC, in which the combination of high GC33 expression in tumors and high CD16 expression in NK cells from peripheral blood is associated with prolonged overall survival given treatment of codrituzumab. This result supports the usage of both GC33 and CD16 as potential biomarkers to select HCC patients for codrituzumab treatment.

Disclosure of Interest: None Declared

P-062 THE COMPARISON STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION WITH LAPAROSCOPIC RADIOFREQUENCY ABLATION ON OVERALL SURVIVAL AND RECURRENTNESS OF HEPATOCELLULAR CARCINOMA

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Introduction: Laparoscopic radiofrequency ablation (LRA) allows treatment of hepatocellular carcinoma (HCC) in difficult locations and more accuracy under real time imaging guidance compared with percutaneous RFA (P-RAF). However, there are still studies comparing the efficacy and survival outcome of LRA to P-RAF. This study aims to evaluate the comparative effectiveness of the two RFA modalities on the treatment outcomes for HCC.

Methods: From December 2008 to February 2015, clinical outcomes of 226 HCC patients treated with either P-RAF (n=169) or LRA (n=66) were analyzed and compared for baseline characteristics, overall survival, and disease-free survival, retrospectively.

Results: There was no significant difference of patient characteristics between two groups that received P-RAF or LRA, except minor differences of background liver disease and several tumor characteristics. Especially, the portion of hepatic cirrhosis patients was higher on LRA (83.4%) compared with P-RAF (73.3%) (p=0.023) and number of tumor node per patient and TNM stage of HCC was statistically higher on LRA compared with P-RAF (p=0.001, and p=0.001, respectively). On univariate analysis, previous transarterial chemoembolization (TACE) experience before P-RAF for HCC have statistical significance on disease-free survival of both groups (p<0.001). However, TACE experience before P-RAF between two groups were not shown significant difference (p=0.194) on baseline analysis. In addition, there was no significant difference between P-RAF (1379.9 days, 95% CI, 1194.0 – 1565.7) and LRA (1244.6 days, 95% CI, 1084.6 – 1504.6) in Kaplan-Meier Estimates of disease-free survival for HCC (p=0.580). However, there was significant difference between P-RAF (2203.0 days, 95% CI, 2044.6-2361.4) and LRA (2065.3 days, 95% CI, 2551.7 – 2778.8) on Kaplan-Meier Estimates for overall survival on HCC (p=0.021). In other words, the patients received LRA were shown higher overall survival compared with P-RAF on log-rank test.

Conclusion: In HCC treatment, the patients received laparoscopic RFA have higher overall survival compared with percutaneous RFA irrespective of previous therapeutic modality.

Disclosure of Interest: None Declared

P-063 INHIBITION OF CYCLIN DEPENDENT KINASE 5 SENSITIZES HEPATOCELLULAR CARCINOMA CELLS FOR SORAFENIB TREATMENT

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Introduction: In the treatment of advanced hepatocellular carcinoma (HCC) Sorafenib is the only approved systemic therapy. Unfortunately patients only gain a survival benefit of about 3 months and therefore there is a great need for novel systemic treatment option or combinational treatments.1 Recently we identified cyclin dependent kinase 5 (CDK5), an atypical kinase, as a novel target in HCC therapy.2 We found that CDK5 was frequently overexpressed in HCC and rendered HCC cells sensitive for the treatment with DNA damaging agents by regulating DNA damage response.2 The aim of this study was to investigate whether CDK5 inhibition could also sensitize HCC cells for Sorafenib treatment and thereby enhance the tumour growth inhibition and to elucidate the corresponding mechanism.

Methods: To evaluate the impact of CDK5 inhibition on Sorafenib treatment we used the pharmacological CDK5 inhibitors roscovitine and dinaciclib as well as genetic downregulation of CDK5 via shRNA in different cell based assays and mouse xenograft models. For the investigation of CDK5 function and signaling in the context of Sorafenib treatment we used a proteomics screen of whole cell lysates of Sorafenib treated HCC cells with or without CDK5 knockdown.

Results: In fact, the combination of Sorafenib with a functional ablation of CDK5 synergistically inhibited the proliferation and clonogenic survival of HCC cells in vitro. This synergism could also be confirmed in a xenograft mouse model, where a combinational treatment resulted in a significantly reduced tumour growth rate. Moreover, we could show that CDK5 inhibition not only reduced overall migration but also prevented the induced cancer cell migration caused by sub therapeutic concentrations of Sorafenib. The proteomics screen revealed on the one hand, that CDK5 knockdown cells showed altered expression of metabolic activity and on the other hand the epithelial growth factor receptor (EGFRI) is connected to CDK5. Our further investigations could show that CDK5 is involved in EGFR signalling and trafficking and prevents the activation of the PI3K/Akt pathway, which was shown to be caused by compensatory activation of EGR.

Conclusion: The pharmacological inhibition of CDK5 with drugs, which are already clinically used in the treatment of other diseases, offers a new concomitant therapy option for patients treated with Sorafenib. The combination has the benefit of not only inhibiting tumour cell growth to a greater extent but also impeding tumour cell motility compared to Sorafenib single treatment.

To conclude, our work provides evidence for CDK5 inhibition as a new promising strategy to improve the therapeutic effect of Sorafenib in HCC.

References:
development. Macrophages (MΦ) are key cells in chronic inflammation and crucial promoters of cancer initiation and progression. Thus, we hypothesized the existence of a particular MΦ-subset associated with CCA-CSC (CSC-associated MΦ), that may support CCA-initiation and control CSC expansion by regulating self-renewal pathways.

Methods: 3D-tumor sphere assay was used to identify stem-like cells in both CCA (CCLP-1) and PSC-patient derived cholangiocytes (BECS1). Obtained spheres (SPH) were characterized by RT-PCR Array. Then, monocyes were cultured in presence of SPH-conditioned medium (CM) to obtain macrophages (SPH-MΦ). MΦ differentiated with monolayer CM (MON-MΦ) were used as control. Impact of SPH-MΦ on CCLP-1 and BECS1 proliferation/viability was assessed by MTT- Assay. Additionally, acquisition/strengthening of tumor stem-like features was assessed by 3D-tumor spheres assay, RT-PCR Array, invasion assay and drug resistance.

Results: As expected, only tumorigenic CCLP-1 cells were able to form 3D spheres, suggesting an existence of a CSC-compartment in CCA. Concordantly, sphere-forming ability was accompanied by over-expression of large number of genes associated with CSC-pathway (69/84). Notably, CCLP-1 and BECS1 cells grown in presence of SPH-MΦ-CM showed a higher proliferation rate, enhanced/acquired sphere forming ability and up-regulation of genes linked to CSC-related markers (CCLP-1: 30/84, BECS1: 35/84) and EMT signalling (CCLP-1: 76/84, BECS1: 22/84). Interestingly, SPH-MΦ-CM conferred to both CCLP-1 and BECS1 cells invasive skills as well as augmented drug-resistance, as key features of tumor stem-like state.

Conclusion: In our study we used PSC and CCA cells as a model of inflammatory pre-cancerous conditions and established tumor, respectively. In both PSC and CCA cells we observed an increase of sphere-forming ability, invasiveness and drug resistance in presence of SPH-MΦ-CM, as well as an up-regulation of CSC and EMT genes. Indeed EMT program is intimately related with the acquisition of stem-like traits and its activation is essential for cancer progression and invasion. Interestingly, the effect on PSC-cholangiocytes, suggested a possible role of SPH-MΦ in the acquisition of CCA-initiating ability. We concluded that CSC-MΦ interaction may be decisive in CCA initiation, representing a possible target for new molecular therapies.


Disclosure of Interest: None Declared

P-065 NARDILYSIN, A NOVEL BIOMARKER FOR HEPATOCELLULAR CARCINOMA, ENHANCES DIETHYLNITROSAMINE-INDUCED MICE CARCINOGENESIS AND CANCER CELL PROLIFERATION VIA ACTIVATION OF STAT3 SIGNALING PATHWAY

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Introduction: Chronic inflammation is involved in the pathogenesis of hepatocellular carcinoma (HCC), in which tumor necrosis factor (TNF) and interleukin 6 (IL6) are associated with the progression of chronic hepatitis to HCC. Nardilysin (NRDc) is a metalloendopeptidase of the M16 family. We previously reported that NRDc promoted gastric cancer cell proliferation via upregulation of IL6 by activating TNFα signaling pathway (EMBO Mol Med 2012). The aim of this study is to clarify the role of NRDc in the progression of HCC.

Methods: Serum NRDc levels were measured by enzyme-linked immunosorbent assay in 215 patients who underwent hepatectomy for HCC and 112 healthy volunteers as the control to evaluate the diagnostic accuracy for HCC. Overall survival after hepatectomy was compared according to the serum NRDc levels. Histological NRDc expression of the surgically resected specimens was evaluated with immunohistochemistry and western blotting. Diethylnitrosourea (DEN)-induced mice carcinogenesis of liver was compared between heterozygous NRDc-knockout mice (NRDc+/-) and their wildtype littermates (NRDc+/-/+). NRDc was knocked down (KD) with micro RNA for liver cancer cell lines, Huh-7 and Hep3B, and the cell growth was evaluated by 2D cell proliferation assay and 3D spheroid formation assay.

Results: Serum NRDc level was significantly higher in HCC patients than healthy volunteers (median 358.1 vs. 539.8 pg/ml, P < 0.001). The area under ROC curve to diagnose HCC was 0.816. Among the patients with positive hepatitis C virus antibody, overall survival was significantly worse in the patients with higher serum NRDc levels (≥ 800 pg/ml) than the patients with lower levels (< 800 pg/ml) (median survival time 36.0 vs. 85.3 months, P = 0.004), and higher serum NRDc level was an independent prognostic factor for overall survival under the absence of extrahepatic metastasis (hazard ratio 1.97, 95% confidence interval 1.23-3.24). Histological NRDc expression was upregulated 3-fold in tumoral lesion compared to non-tumoral background liver. Tumor to non-tumor ratio of NRDc expression was positively correlated with serum NRDc level (r = 0.391, P = 0.044). In DEN-induced mice carcinogenesis model of liver, carcinogenesis at 36 weeks was suppressed by NRDc+/- mice compared to NRDc+/- mice assessed by the tumor number (median 2 vs. 4, P = 0.001) and the maximum tumor size (median 1.5 vs. 3.0 mm, P = 0.015). The number of Ki67-positive proliferating tumor cells was significantly lower in the tumor of NRDc+/- mice. NRDc-KD Huh-7 and Hep3B cells showed attenuated cell growth on both 2D cell proliferation assay and 3D spheroidal formation assay. Phosphorylation of STAT3 was suppressed in NRDc-KD Huh-7 cells, and inhibition of STAT3 abrogated the proliferative dominance of cells over NRDc-KD cells.

Conclusion: We demonstrated that NRDc enhanced carcinogenesis of HCC and HCC cell proliferation via the activation of STAT3 signaling pathway. NRDc could be a diagnostic marker and a novel therapeutic target for HCC.


Disclosure of Interest: None Declared

P-066 DOES TRANSARTERIAL CHEMOEMBOLIZATION PRIOR TO SURGICAL RESECTION IMPROVE CLINICAL OUTCOMES IN RESECTABLE HEPATOCELLULAR CARCINOMA?

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Introduction: The efficacy of transarterial chemoembolization (TACE) performed prior to surgical resection in patients with resectable hepatocellular carcinoma (HCC) is still a matter of debate. This study aimed to assess the impact of preoperative TACE in patients with resectable HCC.

Methods: A total of 117 consecutive HCC patients who received hepatectomy at the Incheon St. Mary's Hospital between 2008 and 2015 were enrolled. 19 patients who either received more than 3 sessions of TACEs prior to resection were excluded. 98 patients underwent resection after conventional staging work up (non-TACE group) and 19 patients received a single or two sessions of TACEs before resection (TACE group).

Results: The median follow up period was 30.9 months (range, 6.5-52.9). According to the modified UICC stage, 29 (23.9%) patients were diagnosed as stage 1, 73 (62.4%) as stage 2, and 16 (13.7%) patients as stage 3. No difference was observed in terms of the age, Child-Pugh score, level of alpha-fetoprotein, and tumor stage between the two groups. In the TACE group, three new HCC lesions which were not identifiable with MRI were found in 3 patients on angiography and resected with the original lesion together. No difference was observed in the disease-free survival (DFS) and overall survival (OS) between the two groups with the mean DFS of 56.1 vs. 53.4 months (p=0.278) and mean OS of 73.9 vs. 60.2 months (p=0.359) in the TACE group and the non TACE group, respectively. However when the tumor size exceed 5cm, longer DFS was achieved in the TACE group compared to the non TACE group (p=0.044).

Conclusion: TACE performed prior to surgical resection does not enhance DFS or OS in the patients with resectable HCC. However, preoperative TACE may be useful in patients with HCC exceeding 5cm and may aid in the discovery of new lesions that were not identifiable with conventional imaging studies.

Disclosure of Interest: None Declared
P-067 MULTIMODALITY TREATMENT OF HEPATOCELLULAR CARCINOMA: HOW FIELD PRACTICE COMPLIES WITH INTERATIONAL RECOMMENDATIONS

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Introduction: Management of patients with a hepatocellular carcinoma (HCC) is framed by standardized protocols released by international societies whose applicability and efficacy in field practice need validation and updated refinement. Aim of the study was to prospectively evaluate the applicability and effectiveness of 2005 practice guidelines of the American liver society (AASLD) stratifying patients according to BCLC stage.

Methods: 370 consecutive patients with a de novo HCC, 251 BCLC A, 66 BCLC B, 53 BCLC C, were enrolled. Treatment modality was guided by multidisciplinary clinic team (MDC), intention-to-treat according to AASLD 2005 recommendations. Discrepancies to guidelines, first-second-third-fourth line treatment were justified and recorded. Univariate and multivariate analysis according to Cox proportional hazard model were performed for each BCLC stage.

Results: During a mean follow up of 5 years, 105 patients died, 41 (16%) BCLC A, 25 (36%) BCLC B, 39 (72%) in early stage BCLC A, 95%, 55%, 42% in intermediate stage BCLC B, and 59%, 14%, 0% in advanced stage BCLC C. Adherence to AASLD recommendations was in 204 (81%) BCLC A patients, 36 (55%) BCLC B, and 27 (51%) BCLC C. By multivariate analysis, survival in BCLC A was predicted by maximum diameter of the nodule (HR 1.9, p<0.01), ascites (HR 2.3, p<0.016) and discordance to AASLD guidelines (HR 2.1, p<0.035), whereas in BCLC B the only independent predictors of survival were AFP >200 ng/mL (HR 2.7, p<0.001) and in BCLC C only discordance to AASLD guidelines (HR 0.4, p=0.032).

Conclusions: In clinical practice, applicability of AASLD recommendations largely depends on the wide heterogeneity of patients included in each BCLC stage. Half of BCLC C patients can be proposed for effective treatment off the guideline recommendations, suggesting to refine the stage classification for these patients.

Disclosure of Interest: None Declared

P-068 USEFULNESS OF ALBUMIN-BILIRUBIN-BASED JAPAN INTEGRATED STAGING (ALBI)-T SCORE IN CHINESE PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: The Albumin-Bilirubin (ALBI) grade is an emerging alternative of the Child-Pugh grade, and could substitute the Child-Pugh grade in some staging systems for hepatocellular carcinoma (HCC). Japan Integrated Staging (JIS) is one of the Child-Pugh-based staging systems, which has been extensively studied in hepatitis virus C-endemic Japanese population. The ALBI-based JIS (ALBI-T score) has not been fully validated outside Japan.

Methods: A cohort of Chinese patients with primary HCC was employed to evaluate the prognostic performance of ALBI-T scores by homogeneity likelihood chi-square, Harrell’s c-index and corrected Akaike information criterion (AIC).

Results: Total 1934 patients were recruited. 81.4% of patients had underlying hepatitis B. Curative and palliative treatments were offered for 39.4% and 60.6% of patients, respectively. The ALBI-T score showed superior prognostic performance to the JIS score, which were indicated by homogeneity likelihood chi-square (ALBI-T 784.66 vs. JIS 764.55), c-indices (ALBI-T 0.74 vs. JIS 0.73) and AICs (ALBI-T 15885.16 vs. JIS 15915.27).

Conclusion: The ALBI-T score was useful among Chinese patients with HCC to provide good prognostic information.

Disclosure of Interest: None Declared

P-069 VALIDATION OF THE INTERMEDIATE STAGE HEPATOCELLULAR CARCINOMA SUBCLASSIFICATION IN EGYPTIAN PATIENTS

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Introduction: The intermediate stage of HCC (Barcelona Clinic Liver Cancer, (BCLC) B) contains a wide range of different population with varying tumor burden and liver function (Child-Turcotte–Pugh (CTP) score of 5 up to 9), provided that there is no vascular invasion, extrahepatic spread, or compromised performance status. This makes it difficult to predict their outcome and allocate treatment. Beloboli et al., (ref) proposed a subclassification of intermediate stage HCC patients with good performance, yet, not validated in an Egyptian cohort.

Methods: This study was conducted on 701 patients with intermediate stage HCC in a tertiary referral center in Egypt. Baseline characteristics including CTP, performance status (PS), AFP, and treatment modalities were recorded. Patients were stratified from the date of diagnosis to date of death or date of data collection if they remained alive. Overall survival and the received treatment were determined. Patients were subclassified using the Beloboli subclassification. Survival data were analyzed using Kaplan- Meier Survival curves using log rank test and multivariate analysis.

Results: The mean age was 57 years, 81.8% were males, 43% had AFP>200 ng/mL and 91% received TACE. At presentation, 49.8% were CTP A and 50.2% were CTP B, and 21.2% were subclassified into subclass B1, 32.5% into B2, 19.8% into B3 and 26.6% into B4. The median overall survival was 18 months while median survival for BCLC B subclassification B1, B2, B3 and B4 were 33, 22, 15 and 14 months respectively (p<0.001). In addition, Multivariate analysis showed that BCLC B subclassification was an independent prognostic factor for OS (HR: 1.23, 95% CI: 1.23-1.59, p<0.001).

Conclusion: BCLC B subclassification is an independent prognostic factor and can distinguish intermediate stage HCC patients with favourable outcome, narrowing the wide heterogeneity of intermediate stage HCC and thus will offer more precise patient selection for treatment allocation.


Disclosure of Interest: None Declared

P-070 VALIDATION OF 2 EXPLANT-BASED RECURRENCE PROGNOSTIC MODELS AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN AN EXTERNAL COHORT

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Introduction: After liver transplantation (LT) for HCC, a standardized prediction of recurrence would be valuable to define patients who might benefit from adjuvant therapy or early changes in immunosuppressive regimens. We reported 2 explant-based recurrence models (ILCA 2015 abstract P-005) able to identify 4 distinct risk groups for 5-years recurrence. The aim of this study was to test these models in an external cohort.

Methods: Score 1 included all variables identified as independent predictors of recurrence in the training cohort of 372 French patients transplanted for HCC in 19 centers between 2003 and 2005 (number of nodules, size of the largest, tumor differentiation, micro-vascular invasion and tumor burden (unil or bilobar) and ranged from 0 to 9 points. Score 2 included all variables except tumor differentiation (not available if effective pre LT tumor treatment) and ranged from 0 to 11 points.
Posters

The 4 levels of risk for 5-years recurrence were tested and the accuracy of these 2 scores to predict 5-years recurrence assessed in an external cohort of 481 Italian patients transplanted for HCC in 4 centers from 2001 to 2011.

Results: The patients and explant characteristics in the training and the validation cohorts were as follows: viral related HCC 62% vs 83% (p=0.001), liver tumor 41.9% vs 35.6% (p=0.065), microvascular invasion 23.1% vs 24.5% (p=0.017), macrovascular invasion 7.3% vs 4.2% (p=0.068), tumor differentiation= insufficient 24.6% vs 57.9% (p=0.001); tumor differentiation= poorn 5.2% vs 32% (p=0.001); the two scores performed well in the external cohort (c-index 0.736 and 0.717 for score 1 and 2 respectively) and identified 4 distinct risk groups for 5-years recurrence, ranging from 7.8 to 73.3% with score 1 and 10.2 to 73.8% with score 2.

Using score 2, a nomogram was built, giving the probability of recurrence at 1, 3 and 5 years post transplantation, according to the score value [figure1].

Conclusion: The predictive value of the 2 explant-based models is reproducible in an external cohort differing from the test cohort by different HCC features, confirming robustness. These models could be used to propose guidelines for recurrence screening and adjust therapeutic strategies post LT.

Disclosure of Interest: None Declared

P-071 METABOLIC ACTIVITY ASSESSED BY 18F-FURODEOXYGLUCOSE PET-CT PREDICTS SURVIVAL AFTER RADIODEMBOLIZATION IN HEPATOCELLULAR CARCINOMA

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Introduction: To evaluate the predictive value of metabolic activity assessed by 18F-Fuoro-deoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) in patients with hepato-cellular carcinoma (HCC) undergoing Yttrium-90 radioembolization (Y-90 RE).

Methods: Between 2009 and 2013, a total of 40 patients with HCC were treated with Y-90 RE. 18F-FDG PET-CT was performed before treatment and maximum standardized uptake value (SUVmax) was obtained in each patient. Tumor response was evaluated in accordance with modified RECIST criteria every 3 months after Y-90 RE. Chi square tests, Kaplan-Meier method and Cox proportional hazards model were used for statistical analysis.

Results: The median age was 56.5 years, and 29 (72.5%) were males; 36 (90.0%) patients were in Child-Pugh class A. Patients with low SUVmax (<1.0) had a higher disease control rate than those with high SUVmax (≥1.0) (65.6% vs. 23.1%, respectively, P = 0.05). Median FPS was significantly longer in patients with low SUVmax than those with high SUVmax (22.1 vs. 6.5 months, respectively; P = 0.03). In addition, a longer FPS was observed in patients with BCLC stage A or B than those with BCLC stage C (P = 0.01). In multivariate analysis, low SUVmax was found to be a significant independent risk for better survival (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.17 – 0.95; P = 0.04), along with BCLC stage A or B (adjusted HR 0.27, 95% CI 0.10 – 0.76; P = 0.01).

Conclusion: A high SUVmax assessed by pre-therapies 18F-FDG PET-CT and initial BCLC stage independently predicts progression-free survival in patients with HCC undergoing Yttrium-90 RE. The simple method of SUVmax-based stratification into high (>6.1) and low (<6.1) SUVmax may be implemented in the treatment planning and could potentially modify strategies in subsequent therapies.

Disclosure of Interest: None Declared

P-072 LESS FIBROTIC BURDEN DIFFERENTIALLY AFFECTS LONG-TERM OUTCOMES OF HEPATOCELLULAR CARCINOMA AFTER CURATIVE RESECTION

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Introduction: The clinical features of HCC may differ according to whether cirrhosis is present or absent. Whether HCC patients without cirrhosis have a more favorable prognosis after curative resection than do those with cirrhosis is controversial. Several studies reported that non-cirrhotic HCC patients had better outcomes when treated surgically. We aimed to investigate the long-term surgical outcomes of HCC patients with non-cirrhosis after curative resection.

Methods: Consecutive HCC patients who underwent curative resection at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea between 1996 and 2012 were considered eligible. Tumor resectability was assessed by surgeons. Major resection was defined as the removal of three or more anatomical segments as described by Couinaud. The study population was stratified into cirrhotic and non-cirrhotic groups (n=387 [59.6%] vs. n=262 [40.4%]).

Results: The median age (511 men) was 54.7 years. The most common etiology of HCC was hepatitis B virus (HBV) (n=419, 64.6%). Non-cirrhotic HCC showed larger tumors and advanced TNM stage than cirrhotic HCC. Overall survival (OS) and disease-free survival (DFS) after resection were significantly longer in non-cirrhotic group than in cirrhotic group (median 64.9 vs. 56.0 months for OS and 48.9 vs. 31.0 months for DFS; all P<0.05). Even though non-cirrhotic HCC showed more aggressive presentations, DFS in non-cirrhotic patients was not compromised and even better at the later postoperative period. The presence of cirrhosis more affected the tumor recurrence at early TNM stage compared with advanced stage. The independent predictors for recurrence were cirrhosis (hazard ratio [HR] 1.665, 95% confidence interval [CI]1.172-2.339, P=0.004), tumor diameter (HR 1.162, 95% CI 1.076-1.255, P=0.001), tumor number (HR 1.519, 95% CI 1.557-2.163, P=0.024), portal vein invasion (HR 2.299, 95% CI 1.398-3.779, P = 0.001), and major surgery (HR 1.822, 95% CI 1.288-2.579, P<0.001).

Conclusion: The initial aggressive presentation of non-cirrhotic HCCs was counterbalanced by a higher rate of major hepatectomy. DFS was better in non-cirrhotic patients with stage 1 HCC, perhaps owing to the lower number of de novo HCCs. In contrast, post-recurrence OS was better in non-cirrhotic patients with stage II or III HCC, which might reflect greater reserved liver function. Better long-term outcomes for non-cirrhotic HCC were observed regardless of the HCC background.

Disclosure of Interest: None Declared

P-073 A PREDICTION FOR SURVIVAL PREDICTORS FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO FAILED TO SORAFENIB TREATMENT

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Introduction: Although sorafenib is the standard treatment of patients with advanced hepatocellular carcinoma (HCC), substantial patients experience failure of sorafenib therapy due to progression, adverse effect and clinical decompensation. We aimed to investigate the prognosis predictors and the role of 2nd-line systemic chemotherapy in patients with advanced HCC who failed by sorafenib therapy.

Methods: From 2007 to 2015, the medical records of 168 HCC patients who permanently discontinued sorafenib therapy with any cause were retrospectively reviewed. For further analysis of survival factors after sorafenib failure, we divided the 2nd-line treatment patients as systemic chemotherapy group, selected best supportive care (BSC) group consisted with favor general condition and liver function, and terminal supportive care group consisted with poor general condition and/or liver function.

Results: Mean age was 57.8 years and chronic hepatitis B (74.1%) was main attributable factor in development of HCC. After discontinuation of sorafenib, median overall survival (OS) was 2.8 (95% CI: 1.9-3.7) months. The survival in patients who discontinued sorafenib due to adverse effect, progression and poor clinical condition were 5.5 (95% CI: 2.4-8.6), 5.5 (2.2-8.9) and 0.9 (0.5-1.3) months, respectively (p<0.001). The independent predictive factors of survival after sorafenib failure were poor ECOG (HR 0.801), alpha fetoprotein >400ng/ml (HR 0.412) and discontinuation cause (HR 0.349). We further investigated the survival according to patients who received 2nd-line therapy or not. 48 patients were treated with systemic chemotherapy whereas 116 patients received supportive care. Systemic chemotherapy group showed better survival outcome compared to supportive care group (10.6 vs 1.6 months, p<0.001). When terminal supportive care group were excluded, systemic chemotherapy group showed also better survival outcome compared to selected BSC group (10.6 vs 4.2 months, p=0.023).
**Conclusions:** The survival after sorafenib failure of patients who discontinue sorafenib due to progression and adverse effect was significantly better than due to clinical deterioration. Moreover, patients who received 2nd-line therapy showed better survival than only supportive care after sorafenib failure.


**Disclosure of Interest:** None Declared

**P-074** HEPATIC FIBROTIC STATUS ASSOCIATED WITH STATIN AND ANTI-INFLAMMATION TREATMENT, DETERMINES THE RECURRENCE AFTER CURATIVE RESECTION OF HBV-RELATED HEPATOCELLULAR CARCINOMA: A HOSPITAL-BASED STUDY

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**Introduction:** The incidence of recurrence after resection of hepatocellular carcinoma (HCC) is high. The use of statin or anti-inflammation agents (including nonsteroidal anti-inflammatory drugs, NSAlDs; or aspirin, ASA) as a strategy for tertiary prevention of HCC recurrence is still uncertain in patients after curative resection of HCC. This study aimed to examine the effect of those drugs on chemoprevention of HCC recurrence.

**Methods:** From 2007 To 2014, consecutive patients undergoing curative resection of hepatocellular carcinoma by hospital-based study. The detailed medical records including the exposure of statin, NSAlD and aspirin for at least 30 days within 6 months of surgical resection of HCC were carefully reviewed. All the patients had regular image study surveillance after the surgery, and the recurrences were confirmed by contrast-enhanced image studies. Factors associated with recurrence were analyzed.

**Results:** A total of 457 patients with HBV-related HCC after curative surgical resection were analyzed. Of them, 64.9% were male, with a mean age of 58.4 years. There were 261 patients (57.1%) in BCLC stage A, and 42.5% had severe liver fibrosis or cirrhosis. During a median 40.8 months of follow-up, 232 patients (50.8%) experienced recurrence. The median time to recurrence was 859.8 days. Twenty-one patients had statin exposure and 22 patients had anti-inflammatory agents exposure. In the 37 patients exposed statin or anti-inflammatory agents, the fibrotic stage (#lank score) is significantly minor then the other group (p = 0.003) even after the propensity analysis (p = 0.024). In univariate analysis, the risk of recurrence was not associated with the exposure of statin (Hr:0.72; 95% CI:0.37-1.40), or NSAlD (HR:1.34; 95% CI:0.59-3.00). Interestingly, aspirin exposure was significantly associated with the risk of recurrence (HR:0.21; 95% CI:0.05-0.86, p = 0.03). In multivariate regression model, factors associated with recurrence were fibrosis stage, tumor size, tumor number and serum albumin level.

**Conclusion:** Statin and anti-inflammatory treatment are associated with minor hepatic fibrotic status, implying their potential anti-fibrotic effect, and may indirectly reduce the risk of recurrence after curative resection of HCC.

**Disclosure of Interest:** None Declared

**P-075** UNDERUTILIZATION OF STAGE-DIRECTED CURATIVE AND PALLIATIVE THERAPY IN CORHETF OF 3954 US VETERANS WITH CIRRHOSIS: TUMOR BOARDS ASSOCIATED WITH IMPROVED REFERRAL AND OVERALL SURVIVAL

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**Introduction:** Few studies have reported on hepatocellular carcinoma (HCC) outcomes in non-tertiary North American populations. This was a retrospective study of clinical outcomes among a national cohort of US Veterans.

**Methods:** Patients with incident HCC between 2008 and 2010 were identified using ICD9 codes from a national health system database then 100% confirmed with medical chart review. Curative therapy was defined as resection or percutaneous/laparoscopic radiofrequency, microwave or cryoablation. Palliative therapy was defined as receipt of chemothermodulation in absence of curative surgery. Logistic regression, Cox proportional hazards, and time-varying competing risk models evaluated the associations between independent and dependent variables.

**Results:** Of 7008 cases, 5500 (78%) were confirmed by chart review as HCC. 1548 cases were diagnosed managed outside the VA or outside the 2008-2010 timeframe, leaving 3954 patients with 8407 person-years of follow-up for analysis. Mean age was 62 years, 99% were male; 54% were White, 23% Black, 9% Hispanic, and 1.4% Asian; 92% had cirrhosis. Etiology of liver disease was hepatitis C (HCV) in 67%, alcohol abuse in 59%, hepatitis B (HBV) in 4%, and 2% had HIV. At diagnosis, 36% were within Milan criteria. BCLC 0/AB/C/D stage was present in 63/30/21/15%, respectively. Overall, 75% received any HCC treatment (25% received no treatment). Of the entire cohort, only 10% were treated with curative resection or ablation, and only 3% received transplant. Among BCLC stage 0 or A, 5% received liver transplant and 23% received curative therapy. Factors associated with not receiving any therapy were older age (OR 1.04, 95% CI: 1.02-1.06), Child Pugh B/C/D (OR 2.3, 95% CI: 1.7-3.0), largest tumor >5 cm at presentation (OR 1.5, 95% CI: 1.2-1.8), ECOG 3 (OR 3.9, 95% CI: 2.8-5.3), and lack of tumor board discussion (OR 1.5, 95% CI: 1.3-1.8). The overall transplant-free survival was 13% and the median survival was 1.1 years. In multivariable models adjusted for demographics, alpha fetoprotein level, comorbidity, MELD score, and viral hepatitis – receipt of curative therapy (HR 0.35, 95% CI: 0.28-0.44), palliative therapy (HR 0.42, 95% CI: 0.38-0.46), and tumor board discussion (HR 0.85, 95% CI: 0.80-0.92) were independently associated with improved survival.

**Conclusion:** In a large North American cohort, HCC mortality was very high and a minority of patients with early stage HCC received curative therapy. Discussion at a tumor board was associated with better rates of treatment receipt and overall survival.


**P-076** HEPATOCELLULAR CARCINOMA SURVEILLANCE IS ASSOCIATED WITH EARLY TUMOR DETECTION AND IMPROVED SURVIVAL IN THE UNITED STATES

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**Introduction:** Hepatocellular carcinoma (HCC) surveillance is recommended in patients with cirrhosis but further data evaluating its effectiveness in “real world” clinical practice are needed. Two systematic reviews highlighted that most current studies are single-institution and do not account for underlying liver dysfunction, patient performance status, or lead time bias. The aim of our study was to characterize the association between HCC surveillance and early tumor detection, curative treatment receipt, and overall survival in a multi-center cohort of patients with cirrhosis in the United States.

**Methods:** We identified patients diagnosed with HCC between June 2012 and May 2013 at four health systems in the United States. Each study site was associated with an academic medical center and included two tertiary care centers and two safety net health systems. Authors adjudicated HCC cases to confirm they met diagnostic criteria, based on AASLD criteria. Patients were categorized in the surveillance group if HCC was detected by imaging performed for surveillance purposes as determined by review of imaging orders, imaging reports, and associated clinical notes. Generalized linear models and multivariable Cox regression with frailty adjustment, adjusting for lead time bias, were used to compare surveillance and non-surveillance patients.
Results: We identified a total of 374 HCC patients who met inclusion criteria, ranging between 68 and 107 patients at each site. HCC was detected via surveillance in 42% of cases, ranging from 35% to 49% between study sites. Surveillance-detected patients had a significantly higher proportion of early stage tumors (Barcelona Clinic Liver Cancer (BCLC) stage O-A 63.1% vs. 36.4%, p<0.001), within Milan criteria 66.2% vs. 28.6%, p<0.001). Curative treatment rates were low overall, with only 20.3% of patients undergoing curative treatment; however, curative treatment receipt was significantly more likely among those detected by surveillance (30.6% vs. 13.0%, p=0.02). HCC surveillance was significantly associated with improved survival (HR 0.41, 95%CI 0.36-0.65) after adjusting for patient demographics, Child Pugh class, and performance status. Median survival of surveillance patients was 14.6 months, compared to 6.0 months for non-surveillance patients, with the difference remaining significant after adjusting for lead-time bias (HR 0.59, 95%CI 0.37-0.93). When stratified by BCLC tumor stage, surveillance was significantly associated with improved survival in BCLC stage A (p=0.05) and BCLC stages B-C (p=0.02) but not BCLC stage D (p=0.64) in multivariate analysis.

Conclusion: HCC surveillance is significantly associated with increased early tumor detection and improved overall survival after adjustment for known confounders and accounting for lead-time bias; however, a minority of HCC in clinical practice are detected by surveillance. Interventions to increase HCC surveillance use in patients with cirrhosis may help curb HCC mortality rates in the United States.

Disclosure of Interest: None Declared

P-077 A PANEL OF THREE MARKERS (H4K20ME2, H4K16AC AND PIVKA-II) FOR PREDICTION OF MICROVASCULAR INVASION IN HEPATOCELLULAR CARCINOMA.
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Introduction: Microvascular invasion (mVI), only assessable on microscopic examination of the surgical specimen, is a poor prognostic marker of hepatocellular carcinoma (HCC), associated with post-operative recurrence. There are currently no validated predictive tissue biomarkers of mVI. We previously showed, by immunohistochemistry, that high expression of PIVKA-II (Prothrombin Induced Vitamin K Absence-II) and two modified forms of histone H4, namely H4K20me2 (Histone H4 dimethylated on K20) and H4K16ac (histone H4 acetylated on K16), was significantly associated with the presence of mVI in a series of HCC surgical specimens (1,2).

This study aimed to assess (1) the concordance of H4K20me2, H4K16ac and PIVKA-II immunostainings between surgical and biopsy specimens of HCC, and (2) the performance of this panel of prediction for mVI in a series of HCC biopsy samples.

Methods: This retrospective study included a cohort of 64 formalin fixed and paraffin embedded (FFPE) HCC surgical specimens (mVI+, n=33; mVI-, n=31), H4K20me2, H4K16ac and PIVKA-II immunostainings were performed on consecutive slides for each case, and the percentage of immunoreactive tumor cells was semi-quantitatively assessed, blinded to the clinico-pathological data. Optimal cut-off values for mVI prediction for each marker were determined in surgical specimens using ROC curves, and then applied on “virtual biopsies” performed on digitized slides of these specimens, and in an independent validation cohort of 52 FFPE HCC biopsy samples (mVI+, n=31; mVI-, n=21) (“routine biopsies”). Concordance of immunostainings between the surgical specimens and the virtual biopsies was assessed using the Spearman’s rank correlation test (ρ).

Results: Concordance of immunostainings between the surgical specimens and the virtual biopsies was high (H4K20me2, ρ = 0.82; H4K16ac, ρ = 0.83; PIVKA-II, ρ = 0.79; p<0.001), H4K16ac had the best performance for mVI prediction in both virtual and routine biopsies, with a sensitivity (Se) 94%, specificity (Sp) 96%, positive predictive value (PPV) and negative predictive value (NPV) of 45%, 87%, 79% and 60% in virtual biopsies and 58%, 52%, 64% and 46% in routine biopsies, respectively. When combined with PIVKA-II immunostaining, performance of the panel reached a Se, Sp, PPV and NPV of 21%, 87%, 67% and 54% in virtual biopsies and 35%, 81%, 73% and 46% in routine biopsies, respectively.

Conclusion: These results show that the concordance of H4K20me2, H4K16ac and PIVKA-II immunostainings between surgical and biopsy specimens is high, and this panel is performant for predicting mVI in HCC biopsy samples. The use of these markers could help in the management of patients with HCC by identifying those at high risk of recurrence.

Disclosure of Interest: None Declared

P-078 OUTCOME OF PATIENTS LISTED FOR LIVER TRANSPLANTATION WITH HEPATOCELLULAR CARCINOMA BEYOND MILAN AND UCSF CRITERIA
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Introduction: Liver transplantation (LT) eligibility for hepatocellular carcinoma (HCC) is typically based on the size and number of HCC lesions. Most liver transplant centers follow either the Milan or UCSF criteria for transplantation of patients with HCC. More liberal criteria have been proposed and adopted by some centers. At the University of Toronto we have adopted the Extended Toronto Criteria (ETC): no limit in size/number of HCC, no cancer-related symptoms, no vascular invasion or extrahepatic disease and no poorly differentiated tumors. This study describes our experience with patients listed for LT beyond Milan and UCSF criteria but within the ETC.

Methods: All patients with HCCs beyond Milan and UCSF but within the ETC listed for LT were included in this study. Data were retrospectively extracted from our prospectively collected electronic transplant database. Univariate and multivariate analysis was performed to identify risk factors of death. Response/progression of HCC was assessed using modified RECIST criteria. Outcomes were calculated both from the time of listing and from the time of LT.

Results: Ninety-six patients were listed for LT beyond Milan and UCSF criteria, but within the ETC between January 1999 and August 2014. Median follow-up was 27 months (IQR 12-57). On pre-operative imaging, the median size of the largest tumor was 3.3cm (IQR 1.5–5.9) and the median number of lesions was 5 (IQR 3–10). Sixty-two (65%) received bridging therapy on the waiting list. Bridging therapy led to a significant reduction in tumor burden (p<0.001). The majority of those listed underwent LT (n=69, 72%), both tumor progression on waiting list (HR 4.973 [1.599 - 15.464], p=0.006) and peak AFP >400 ng/ml (HR 4.604 [1.660 – 12.788], p=0.003) were independently associated with waiting list dropout. HCC recurrence rate post-LT was 35% (n=24); Time spent on waiting list was not associated with HCC recurrence. The 1-, 3- and 5-year actuarial survival was 76%, 56% and 47% from listing (intention-to-treat) and 91%, 71% and 66% from LT.

Conclusion: The post-transplant survival of patients with unresected tumor burden is comparable to those within well-established criteria such as Milan and UCSF.

Disclosure of Interest: None Declared

P-079 INVESTIGATING THE SELECTIVE SUBCELLULAR ANTICANCER EFFECTS OF LOW-DENSITY LIPOPROTEIN-DOCOSAHEXAENOIC ACID NANOPARTICLES IN HCC CELLS
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Introduction: Recent studies have shown that the hepatic arterial infusion of low-density lipoproteins reconstituted with the natural omega 3 fatty acid docosahexaenoic acid (LDL-DHA) is able to selectively kill rat hepatoma cells and retard the growth of liver tumors in rats without injury to the surrounding liver. The hallmark feature of LDL-DHA nanoparticle anticancer effects is a global disruption of redox regulatory pathways within cancer cells which ultimately induces cell death. To date, little is known about the subcellular events which transpire following LDL-DHA treatment. Herein, we investigated the differing subcellular responses of normal and malignant liver cells to LDL-DHA nanoparticle treatment.

Methods: In the present study the murine noncancer and cancer liver cells, TIB-73 and TIB-75 respectively, were treated with LDL-DHA nanoparticles and investigated utilizing a variety of chemical and viability assays, confocal microscopy and flow cytometry.

Results: Our studies first showed that basal levels of oxidative stress and iron are significantly higher in the malignant TIB-75 cells compared to the normal TIB-73 cells. In particular, the lysosomes within cancer cells were found to contain high concentrations of reactive oxygen species (ROS). Following LDL receptor mediated uptake, the LDL-DHA nanoparticles are deposited in lysosomes. Within the malignant TIB-75 cells, DHA is rapidly oxidized inducing global and lysosomal lipid peroxidation along with increased lysosomal permeability. This leakage of lysosomal contents and lipid peroxidation products in the cytosol triggers subsequent mitochondrial depolarization and ROS generation. In addition, nuclear injury and DNA damage were also observed in the TIB 75 cells. The accumulation of subcellular insults and dysfunctions induced by the LDL-DHA nanoparticles ultimately ushers the cancer cell’s death. Interestingly, albumin mediated delivery of DHA was unable to evoke cytotoxicity in TIB-75 cells. These findings suggest that the LDL mediated transport of DHA plays an important role in potentiating the anticancer activity of this lipid. The cascade of LDL-DHA mediated lipid peroxidation and organelle damage was partially reversed by the administration of the antioxidant, ...
Disclosure of Interest: None Declared


Disclosure of Interest: None Declared

P-080 WHOLE-GENOME SEQUENCING OF TWO LIVER TUMORS FROM ONE PATIENT

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Introduction: We sequenced two liver tumors from one patient; one was combined hepatocellular-cholangiocarcinoma (CHCCC) and the other was well differentiated hepatocellular carcinoma (HCC), after alignment to human reference genome and removal of duplications, three genomes were compared with each other.

Results: We obtained nucleotide sequences covering 106.0 Gb of CHCCC genome (37.1 x coverage), 102.6 Gb of HCC genome (35.9 x coverage), and 106.6 Gb (37.3 x coverage) of NCL genome. The sequenced reads covered 99.5% on all three genomes. Comparison of the HCC and NCL genomes showed 13,544 somatic single nucleotide variants (SNV), 3,789 small insertions and deletions, and 57 structural variants in CHCCC genome. Distinct SNVs were composed of 2.2% on exon, 37.3% on intron, and 60.5% on intergenic regions. Comparison of the CHCCC and NCL genomes showed 3,675 somatic single nucleotide variants (SNV), 3,491 small insertions and deletions, and 37.3% on exon, 37.3% on intron, and 60.5% on intergenic regions. Comparison of the CHCCC and NCL genomes showed 3,675 somatic single nucleotide variants (SNV), 3,491 small insertions and deletions, and 37.3% on exon, 37.3% on intron, and 60.5% on intergenic regions.

Conclusion: The prevalence of somatic SNVs in CHCCC is much more than HCC when compared with NCL. And that indicates more complex process were involved in CHCCC. Further researches will be needed to understand the mechanisms involved in CHCCC.

Disclosure of Interest: None Declared

P-081 FINAL RESULTS OF A PHASE 2 STUDY OF GALUNISERTIB, A TRANSFORMING GROWTH FACTOR-BETA (TGF-ß) RECEPTOR 1 KINASE INHIBITOR, IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: We report the final results of a phase 2 study investigating galunisertib in patients with HCC.

Methods: Eligible patients with HCC included: those who had progressed on or were ineligible to previous treatments; patients with advanced hepatic cancer with measurable disease; absence of previous treatment with TGF-ß receptor inhibitors; and patients with a life expectancy of 9 months or more. Adverse events were recorded and graded according to the common terminology criteria for adverse events (version 4.0). The primary endpoint was the Median Time to Progression (MTP). Secondary endpoints included overall survival (OS) and safety (CTCAE, v. 4.0). Biopsies were assessed in the tumor tissue and included IHC analysis of markers including E-cadherin, AFM, pRAS, pMAPK, CX41 and TGFBI. Transcriptome expression profiling of FFPE tumor tissue was performed by Almac using the Almac XcelTM Array.

Results: 149 patients were enrolled (109 in Part A and 40 in Part B). 85% of patients were male; median age 65 years; PS = 01, 56% HCV, 44% alcoholic cirrhosis; 86%/14% etiology: hepatitis C 24%, hepatitis B 20%, alcohol 20%; multiple 9.4%. Overall, 83% of patients had received prior sorafenib. 11 patients discontinued treatment due to adverse events (AEs); 8 were considered related to study treatment. Grade 3/4 possibly treatment-related AEs were observed in 26 (17%) patients. Of these AEs, neutrophil count decrease was observed in 4 patients; anemia, hypoglycemia, decreased bilirubin, fatigue, embolism in 2 patients each. All other AEs occurred in just 1 patient. TTP based on RECIST v1.1 and OS are summarised as median in weeks (90% confidence interval [CI]): TTP was 11.9 (6.3, 12.6) in part A; 18.0 (10.0, 24.0) in part B. Median OS was 31.4 (22.9, 40.6) in part A and 73.0 (45.4, 107) in part B. The median OS estimated for the overall population was estimated as 40.4 (31.1, 52.4). Patients with TGF-ß1 reduction of >20% had approximately 3 fold OS improvement. The most significant HCC biomarker was E-Cadherin. Patients with high tumor tissue E-cadherin expression had worse outcome [HR 2.76; 95% CI: 1.37-5.43; P = 0.004, adjusted for number of markers tested]. Transcriptome expression profiling was performed in samples from 16 patients; unsupervised clustering identified a cluster of samples enriched with responsive patients.

Conclusion: Galunisertib is well tolerated in HCC patients. HCC patients with TGF-ß1 reduction showed improved OS compared to patients without TGF-ß1 reduction.

Disclosure of Interest: None Declared

P-082 PROGNOSTIC SCORE OF SURVIVAL PREDICTION IN PATIENTS UNDER SORAFENIB TREATMENT: USEFULNESS OF CARBONIC ANHYDRASE IX BASELINE AND BASELINE AND EVOLUTIVE ANGIOPOTYETIN 2

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Introduction: The radiologic pattern of progression and early dermatological adverse events are predictors of overall survival in hepatocellular carcinoma patients under sorafenib. However, there is no plasma biomarker available to predict outcome in that population. Carbonic anhydrase IX is a crucial cell pH regulator that is considered as an asset in cancer aggressiveness but it has not been evaluated in hepatocellular carcinoma. Aim: To develop a prognostic score of survival including plasmatic biomarkers to improve the overall survival prediction based on the already known prognostic factors.

Methods: 89 hepatocellular carcinoma patients under sorafenib were enrolled prospectively in this study (54% HCV, 82% PS-0, 92% Child-Pugh A/B 86%/14%; 8 months; respectively). Baseline performance status and the presence of metastasis have the best AUC (0.78) to predict survival at 3 months. Clinical/biochemical evaluation was performed monthly. Tumor progression was assessed at month 1 and every 2 months thereafter. The treatment was maintained until symptomatic progression, toxicity or inclusion in a second line trial. Two statistical analyses were done: a) based on baseline characteristics and b) based on baseline characteristics and evolutionary events (time-dependent analysis).

Results: The median treatment duration, follow-up and overall survival was 6.7 (3.2-52.8), 10.6 (6.4-68.9) and 10.8 (9.6-12.9) months, respectively. Baseline performance status and the presence of metastasis have the best AUC (0.806) to predict survival at 60 days. However, the score based on baseline BCLC, performance status and ANGPT2 value, pattern of progression, carbonic anhydrase IX and/or ANGPT2 value at month 1 and early dermatologic events presents the best AUC to predict survival at 6 (0.969), 12 (0.979) and 18 (0.932) months respectively.

Conclusion: Baseline levels of ANGPT2 and carbonic anhydrase IX and/or ANGPT2 as well as BCLC, performance status, pattern of progression and the development of early dermatologic adverse events at month 1 are predictors of overall survival in hepatocellular carcinoma. This score is a useful tool in clinical practice and if it is externally validated, it will improve the accuracy prediction of overall survival and help to stratify patients at inclusion in second line trials.

Purpose: The aim of this study was to assess if preoperative tumors with high AFP required wider margins than tumors with low AFP.

Methods: Between April 2012 and January 2016, all patients of a single center who underwent an hepatectomy for HCC were included in a prospective database. Patients who underwent a first hepatectomy without macroscopic residual disease (R2) were analysed. High AFP rate was defined as > 100ng/ml. Preoperative prognostic factors for time to recurrence were analyzed in univariate and multivariate analysis. Pre-, intraoperative and pathological features of patients with low or high AFP rate were compared. The impact of surgical margins (≥ 1 cm), on time to recurrence (TTR), disease-free survival (DFS) and overall survival (OS) was studied.

Results: Curative hepatectomy (36% major – 64% minor) was performed in 148 patients (119M/29F – Mean Age : 63±13). Preoperative high AFP rate (> 100 ng/ml) was retrieved in 41 patients. Postoperative 90-days mortality was 2%. Tumor were unique in 82% of the patients with a median diameter of 4 cm (0.7-18). Underlying liver parenchyma was classified F3-F4 in 109 (74%) patients and F0-F2 in 39 (26%) patients. Mean surgical margin was 0.7cm ± 1.1 and 41 (29%) had a resection margin > 1 cm. With a mean follow-up of 17 months, 1 year and 3 years OS were 88%, 81% and DFS were 70% and 62%. One year and 3 years recurrence were 24% and 31%. Among 46 patients with recurrence, 10 were treated curatively (5 liver transplantations – 5 repeat hepatectomies). In multivariate analysis, preoperative prognostic factors for time to recurrence were AFP > 100ng/ml (HR=3.319 ; IC95% [1.717-5.737] ; p<0.001) and number of tumors (HR=2.1 ; IC95% [1.383-3.190] ; p=0.001). The comparison of low and high AFP patient groups were AFP > 100ng/ml (HR=3.319 ; IC95% [1.717-5.737] ; p<0.001) and number of tumors.

Conclusions: Preoperative AFP >100 ng/ml was independently associated with worse time to recurrence. Surgical margin was highly mandatory in such patients to decrease the risk of recurrence.


Disclosure of Interest: None Declared

P-084 COMPARISON OF HEPATIC RESECTION AND TRANSARTERIAL CHEMOMOBILIZATION FOR INTERMEDIATE HEPATOCELLULAR CARCINOMA WITH PORTAL HYPERTENSION: A PROPENSITY SCORE ANALYSIS

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Introduction: The most intensive debate about BCLC staging system revolves around its simplicity of recommending only TACE for intermediate HCC, although it includes an extremely diverse set of patients[2]. The optimal treatment for intermediate hepatocellular carcinoma (HCC) in cirrhotic patients with portal hypertension (PHT) is still controversial[3-5]. The objective of this study is to assess the therapeutic value of Hepatic resection (HR) by comparing it with TACE for treating intermediate HCC patients with PHT.

Methods: A series of 379 intermediate HCC with PHT undergoing HR or TACE were retrospectively analyzed. The short-term outcome and long-term survival were compared. In current study we classified BCLC-B tumors into two subtypes: BCLC-B1: with a single nodule larger than 5 cm; and others were classified as BCLC-B2. Subgroup analysis by degree of PHT and subtypes of BCLC-B were conducted. Independent prognostic predictors were also determined by the Cox proportional hazards. To overcome selection bias, propensity score analysis were conducted.

Results: Postoperative complications and 30-day mortality were similar between groups. And HR group showed significantly higher overall survival rates (1, 2, 3, and 5 years were 81.7%, 69.3%, 52.1%, and 23.9% vs 69.7%, 54.3%, 27.2%, and 5.4%, P<0.001) in the whole study population (Figure 1). Similar results were observed in the propensity score analysis (Figure 1). Subgroup analysis demonstrated that in patients with BCLC-B1 tumors, overall survival in HR group was better than TACE group while no significant difference in BCLC-B2. And overall survival of patients receiving HR was significant better than TACE group both in severe and mild PHT. Three independent prognostic factors were associated with worse overall survival: BCLC-B2 and TACE before propensity matching, while AFP=400ng/ml, BCLC-B2 and TACE were identified as independent prognostic factors after propensity matching.

Conclusion: HR appears to be as safe as TACE for intermediate HCC patients with PHT, and it provides better long-term survival. This is especially true for patients who have single nodule.


Disclosure of Interest: None Declared
Introduction: Non alcoholic steatohepatitis (NASH) is a growing health problem in western countries, strongly related with the development of cirrhosis and hepatocarcinoma (HCC). Both insulin resistance and associated inflammatory phenomena could likely play a pathogenic role linking NASH and carcinogenesis, although the ultimate mechanism by which NASH contributes to the development of HCC remains unclear. Armcx1-6/Armc10 genes encode for a family of proteins that regulate mitochondrial biology and Wnt pathway. A deficient mouse for Armcx1 has shown a marked glucose phenotype. insulin resistance and hepatomegaly with hepatic steatosis. Moreover, dynamic changes in mRNA expression of ARMCX1/ARMC10 genes have been observed in wild type mice according to administered type of diet. Deregelation of the Armcx1-6/Armc10 genes could participate in HCC development, therefore analyzing their gene and protein expression in human HCC and NASH has a major interest.

Methods: Gene and protein expression of ARMCX3[α1], ARMC10 y CTNNB1 (B-Catenin) were analyzed in 9 HCC human cell lines (Hep3B, HepG2, HuH7, PLC5, SNU387,398,449 and 182) by qPCR and western blot and in human tissue. First, an exploratory set of fresh frozen tissue (FF) samples of healthy liver(=13), cirrhosis(=11), HCC(=11) from the tissue bank and NASH(=9) collected prospectively from patients undergoing bariatric surgery and then, a larger FFPE cohort: Liver (n=9), NASH (n=16), Cirrhosis (n=50) and HCC (n=53).

Results: ARMCX3 showed lower gene and protein expression in SNU398 and 449 compared to normal liver, while 6 HCC cell lines didn’t show any variation. ARMC10 is under-expressed in HCC and NASH, with an increase in cirrhosis and FFPE tissue. Gene expression of ARMC10 was significantly increased in the exploratory cohort of HCC (3.9±0.59) and NASH (4.15±0.37) FF tissue compared to healthy liver (0.9±0.18) and cirrhosis (2.4±0.67). This trend was also observed in the FFPE cohort. WB analysis showed a non-significant increase in NASH compared to healthy liver in ARMC10 protein expression. As expected, CTNNB1 (B-Catenin), mRNA and protein levels, were significantly over-expressed in HCC compared to healthy liver and cirrhosis. Overexpression of CTNNB1 was associated to overexpression of ARMC10 in HCC samples.

Conclusion: ARMC10 is over-expressed in NASH and HCC and is associated to overexpression of CTNNB1 in HCC. Deregulation of ARMC10 could have an important role in NASH and HCC development through mitochondrial function alterations. Functional studies are needed to elucidate the potential mechanistic relation between ARMC10 and B-Catenin and their implication in NASH and HCC.

Disclosure of Interest: None Declared

P-086 PREVENTION OF POST HEPATECTOMY LIVER FAILURE BY DIRECT FUNCTIONAL MEASUREMENT OF FUTURE LIVER REMNANT – A NOVEL INTRAOPERATIVE ICG ASSESSMENT

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Introduction: Liver failure after major hepatectomy ranged from even 4-8% in high volume centers despite careful preoperative liver function evaluation. A better functional assessment of future liver remnant is needed.

Methods: This prospective single-center study aims to evaluate the safe limited of ICG retention at 15 minutes of the future liver remnant in order to prevent post-hepatectomy liver failure. The study commenced in January 2010. Patients undergoing major hepatectomy for suspected malignancy were included. All patients were evaluated as suitable candidate for major hepatectomy by the surgical board.

0.5mg/kg of ICG was injected during laparotomy. The ICG retention rate of the future liver remnant was measured by LI-COR pulse densitometry after the ipsilateral inflow of hemi-liver with tumour was temporarily clamped. The surgeon is blinded from ICG measurement.

Results: 98 patients with 78 male and 20 females were included. 74 patients had HCC and 24 patients had other tumours. 71 Patients had Right hepatectomy, 18 patients had left hepatectomy, 6 patients and 3 patients had right trisectionectomy and left trisectionectomy respectively, 12 patients had ALPPS procedures. The median operation time was 351 minutes. The median blood loss was 800ml. 4 patients developed liver failure after hepatectomy. 2 patients end up in mortality and 1 patient received rescue liver transplant. All of them had intraoperative ICG15 > 50%. The risk of liver failure, hospital mortality and postoperative morbidity increased from 0% to 100% (p<0.001), 1.1% to 50% (P=0.001) and from 20.2% to 100% (P=0.002) respectively if the intraoperative ICG15 is greater than 50%.

Image:

Conclusion: Intraoperative ICG measurement is an essential additional test during laparotomy. A change of surgical plan can prevent liver failure if the ICG15 is >50%.

Disclosure of Interest: None Declared

P-087 THE PREDICTING FACTORS FOR MORTALITY AND RECURRENCE IN TAIWANESE PATIENTS WITH HEPATOCELLULAR CARCINOMA AFTER LIVER RESECTION

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Introduction: Clinical factors such as liver functions and tumor characteristics have been documented to be associated with all-cause mortality or the recurrence rate after resection of hepatocellular carcinoma (HCC), which is the first-line treatment option for patients with early tumors. Death occurring prior to HCC recurrence as informative censoring often leads to overestimation of the recurrence probability. The present study aimed to explore prognostic risk factors for mortality and recurrence rate when considering the competing risk in Taiwan where chronic hepatitis B (CHB) and C (CHC) are endemic.

Methods: Total 477 patients with a diagnosis of liver cancer were consecutively examined for eligibility from a medical center in Taiwan. A patient cohort of the hospital-based follow-up study was designed to collect serological markers to further assess liver functions. During operations, liver histopathology and tumor characteristics were measured. We modified the Kaplan-Meier method according to the competing death for comparing recurrence stratified by risk factors and used multivariate Cox proportional hazard regression to adjust for significant risk factors.

Results: A cutoff of 5 cm in diameter of the largest tumor size was the best cutoff for predicting mortality and recurrence rate in Taiwanese patients. In addition to advanced fibrosis, tumor size ≥ 5 cm was significantly associated with higher mortality vs. tumors < 5 cm within the 5-year period (43.3% vs. 13.2%, respectively, P<0.0001). Patients with tumor sizes ≥5 cm also easily progressed to early recurrence within 2 years when precisely accounting for death as a competing risk event (20.1% vs. 10.1%, P<0.01). Among patients with tumor size>5 cm, we identified higher alpha-fetoprotein (AFP) levels play an important role in further predicting higher mortality. 4.4±5-fold and a 2.2-fold higher mortality in patients with sizes 5 cm/ AFP=20 ng/mL and with sizes 5 cm/ AFP>20 ng/mL, respectively, were found when compared to those patients with small tumors.

Conclusion: A tumor size>5 cm might be a good predicting factor for mortality and early recurrence when considering death as a competing risk. In patients with tumor size >5 cm, higher AFP levels were associated with mortality indicating the important value of AFP follow-up in these patients.

Disclosure of Interest: None Declared
P-088 SYSTEMIC IMMUNE-INFLAMMATION INDEX PREDICTS OUTCOME OF PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH SORAFENIB

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Introduction: We evaluated a systemic immune-inflammation index (SII) based on lymphocyte, neutrophil and platelet counts and explored its prognostic value in patients with advanced hepatocellular carcinoma treated with sorafenib. Neutrophils promote the secretion of circulating growth factors such as VEGF and proteases, while lymphocytes play a crucial role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration, thereby dictating the host’s immune response to malignancy. Several inflammation and immune-based prognostic scores have been developed to predict survival and recurrence, e.g. lymphocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio.

Methods: Ninety-seven patients with advanced hepatocellular carcinoma (HCC) receiving sorafenib were available for our analysis. Lymphocyte, neutrophil and platelet counts were measured before the beginning of treatment. Prediction accuracy was evaluated by receiver operating characteristic analysis (ROC).

Results: An optimal cutoff of 360 for the SII stratified patients into high (≥360) or low SII (<360) groups in the training cohort. Univariate and multivariate analyses revealed that SII was an independent predictor of overall survival and recurrence-free survival, and a prognostic marker for advanced HCC patients treated with sorafenib. Patients with SII < 360 had a better outcome than those with SII > 360, median PFS 3.9 months (95%CI 2.8-6.2) vs. 2.6 months (95%CI 1.8-3.3, p=0.026) and median OS of 13.9 months (95%CI 5.7-22.8) vs. 5.6 months (95%CI 3.2-10.4, p=0.024), respectively.

Conclusion: In our study, the SII was a powerful prognostic indicator of poor outcome in patients with advanced HCC treated with sorafenib. The fact that it is calculated from the results of a routine blood test makes it a potentially useful strategy to assess prognosis in patients with advanced HCC.

Disclosure of Interest: None Declared

P-089 PHENOTYPE PROFILING OF CIRCULATING TUMOR CELLS AS A PROGNOSTIC BIOMARKER IN HEPATOCELLULAR CARCINOMA: IMPLICATIONS FOR TREATMENT SELECTION

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Introduction: The current hepatocellular carcinoma (HCC) clinicopathological staging systems and serum biomarkers are poor discriminators of outcome for patients amenable to surgical resection and liver transplantation (LT), where postoperative recurrence remains a significant challenge. Circulating tumor cells (CTCs) have been implicated as the main source of recurrence and systemic metastasis. Existing CTC technologies mainly rely on epithelial cell adhesion molecule (EpCAM) based capture of CTCs, resulting in inefficient capture of HCC CTCs which have low EpCAM expression. We sought to develop a novel, blood-based assay capable of detecting various HCC CTC phenotypes that may represent biological alterations in the underlying tumor that predispose patients to more aggressive disease. Longitudinal follow-up with evaluation of cancer-specific outcomes is necessary to establish whether CTCs may improve current clinical staging systems, and guide selection of candidates for liver transplantation.

Methods: We assessed seven single nucleotide polymorphisms (SNPs) of the AXIN1, AXIN2, CTNNB1, and WNT2 genes in 245 patients with hepatitis B virus (HBV)-associated HCC.

Results: SNPs in AXIN1 rs214252 C allele showed longer survival than those with the TT genotype (p=0.001). AXIN1 CTCTNBB1 rs3864004 A allele was associated with a decreased risk of HCC development (P= 0.020). In the present study, we determined whether genetic variation in the Wnt/β-catenin signaling pathway is associated with the development and/or progression of HCC and the survival of patients with hepatitis B virus (HBV)-associated HCC.

Conclusion: CTCs are a promising serum biomarker in hepatocellular carcinoma, with excellent discrimination of non-HCC and HCC patients, as well as early and advanced stage patients. Vimentin(+)-mesenchymal-type CTCs are almost exclusively found in clinically advanced stage IV patients, and may represent biological alterations in the underlying tumor that predispose patients to more aggressive disease. Longitudinal follow-up with evaluation of cancer-specific outcomes is necessary to establish whether CTCs may improve current clinical staging systems, and guide selection of candidates for liver transplantation.

Disclosure of Interest: None Declared

P-090 GENETIC POLYMORPHISMS IN THE WNT/B-CATENIN PATHWAY GENES AS PREDICTORS OF TUMOR DEVELOPMENT AND SURVIVAL IN PATIENTS WITH HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA

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Introduction: Wnt/b-catenin signaling has a pivotal role in the pathogenesis of hepatocellular carcinoma (HCC). The present study aimed to determine whether genetic variation in the Wnt/b-catenin signaling pathway is associated with the development of HCC and the survival of patients with hepatitis B virus (HBV)-associated HCC.

Methods: We prospectively evaluated CTC enumeration (per 4mL) and phenotype in 59 patients (41-HCC, 8-cirrhosis, 10-healthy controls), and correlated CTC number and phenotype with clinicopathological staging data. CTCs were defined as DAPI+/Pan-CK+/CD45-. A subpopulation of mesenchymal-type Vimentin(+) CTCs were defined as DAPI+/Pan-CK+/CD45-/Vimentin+.

Results: Multimarker CTC capture resulted in the detection of significantly greater number of CTCs than EpCAM alone for both cell line and patient samples (p<0.05). CTCs were detected in all HCC patients (Mean=7.0, range=1-27), correlated linearly with AJCC T stage, and accurately discriminated HCC and non-HCC patients (≥2 CTCs, sensitivity=97.9%, specificity=83.3%, AUROC=0.957, p<0.001). LT eligible early-stage I-II and LT ineligible advanced stage (III-IV) HCC patients (≥8 CTCs, sensitivity=74%, specificity=96%, AUROC=0.892, p<0.001; Fig). Vimentin(+) CTCs were detected nearly exclusively in advanced stage (IV) patients (Mean = 4.6, range = 0-14), with excellent discrimination among early and advanced stage patients (AUROC = 0.941, p<0.001; Fig). In patients with serial CTC analysis, CTC enumeration demonstrated utility for disease monitoring after both surgical resection (CTC count down to 0 in stage 3A) and thermal ablation (CTC count down to 2 in stage 1). In select patient samples, CTC enumeration proved to be a better indicator of true disease stage than what was clinically apparent at blood draw, predicting the development of metastases (e.g. CTC count of 27 much higher than expected for a radiologically staged 3a patient, who developed metastases 8 weeks following enumeration), and correctly predicting clinical overstaging (e.g. CTC count of 4 much lower than expected for radiologically staged 3b disease, with subsequent surgical pathology revealing bland thrombus and T1 disease).

Conclusion: CTCs are a promising serum biomarker in hepatocellular carcinoma, with excellent discrimination of non-HCC and HCC patients, as well as early and advanced stage patients. Vimentin(+) mesenchymal-type CTCs are almost exclusively found in clinically advanced stage IV patients, and may represent biological alterations in the underlying tumor that predispose patients to more aggressive disease. Longitudinal follow-up with evaluation of cancer-specific outcomes is necessary to establish whether CTCs may improve current clinical staging systems, and guide selection of candidates for liver transplantation.

Disclosure of Interest: None Declared
Conclusion: Although activity measurements reveal that basal kinase activity is similar in FL-HCCs and normal liver, our analyses demonstrate that the magnitude of the PKA activation response is higher in tumor samples. A potential explanation is that the neurotransin pathway also is upregulated in FL-HCCs, and could serve as an ongoing source of cAMP in these tumors. Neurotensin seems to act as a co-mitogen with EGF to increase cell proliferation in hepatocytes. In addition to PKA activation in FL-HCC, and could serve as an ongoing source of cAMP in these tumors. Neurotensin seems to act as a co-mitogen with EGF to increase cell proliferation in hepatocytes.
Introduction: Targeting co-inhibitory pathways has been shown to be a promising novel therapeutic approach for several types of cancer, but so far not in colorectal cancer (CRC). This lack of success is probably related to the low levels of co-inhibitory receptors expression on tumor-infiltrating lymphocytes (TIL) in the majority of primary CRC tissues. Liver metastasis (LM) is a leading cause of CRC-related mortality. LM are present in 20-25% of patients at diagnosis and develop in another 10-20% of patients during the course of the disease.

Methods: Therefore, our aim was to determine whether co-inhibitory pathways participate in intratumoral suppression of T cell responses in LM from CRC. For this purpose, we used paired samples of leukocytes freshly isolated from resected metastatic liver tumors, tumor-free liver tissues (TFL) and peripheral blood of patients with LM-CRC. Expression of co-inhibitory receptors on T cells was then measured by flow cytometry.

Results: We found that expression of PD-1, TIM-3 and LAG-3 on CD8+ cytotoxic T cells, and expression of PD-1, TIM-3 and CTLA-4 on CD4+ Foxp3- T helper cells were significantly higher in tumor than in TFL or in the blood. In contrast, no up-regulation of BTLA in TIL was observed. In addition, their ligands PD-L1, Galectin-9, MHC-II, CD80 and CD86 were expressed on dendritic cells, monocytes and B cells in the tumor. Compared to the cells without expression, CD68+ and CD4+Foxp3- TIL expressing higher levels of HLA-DR and CD69, indicating a more activated status. However, they did not show increased expression of granzyme B or increased cytotoxic production upon polyclonal stimulation, suggesting restricted functionality. Blocking PD-L1 or LAG-3 with neutralizing antibodies enhanced ex vivo proliferation and effector cytotoxic production of CD8+ and CD4+ TIL to polyclonal stimuli.

Conclusion: PD-1, TIM-3, LAG-3 and CTLA-4 are up-regulated on tumor-infiltrating T cells in liver metastasis from colorectal cancer, and blocking PD-L1 or LAG-3 can enhance the functionality of tumor-infiltrating T cells. Therefore, these two co-inhibitory pathways may be promising immunotherapeutic targets for the most prevalent type of secondary liver cancer.

Disclosure of Interest: None Declared

Conclusion: The findings in the present study suggest that evaluation of the ALBI grade before and after HAIC treatment may be useful in predicting the prognosis of patients treated with HAIC.

Disclosure of Interest: None Declared

Introduction: Locally advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombosis is known to have a poor oncologic outcome. While the current standard of practice recommends only palliative treatments, many attempts with different modalities to increase survival have been undertaken. Primary goal of this study was to evaluate the oncologic outcome of surgical resection after down-staging with localized concurrent chemoradiotherapy (CCRT) followed by hepatic arterial infusion chemotherapy (HAIC) in locally advanced HCC with portal vein thrombosis.

Methods: From 2005 to 2014, 354 patients with locally advanced HCC underwent localized CCRT followed by HAIC. Among them, 149 patients with portal vein tumor thrombosis were analyzed. In order for an intention-to-treat analysis, exclusion criteria included total bilirubin >2mg/dL, platelet count <100000, and ICG R15>20%. During the same study period, eighteen patients with portal vein tumor thrombosis underwent surgical resection as the first treatment modality. Clinicopathologic characteristics and oncologic outcomes between the groups were compared.

Results: With 51 patients in the exclusion criteria, 98 patients were finally analyzed in localized CCRT group. Among the 98 patients, 26 patients (26.5%) finally underwent curative resection. Clinicopathologic characteristic showed more frequent tumor thrombosis in the first order (81.6% vs. 22.2%, p<0.001) and bigger tumor size (8.0cm vs. 5.9cm, p=0.003) in localized CCRT group compared to the operation first group. Overall survival between the localized CCRT group and the operation first group, however, did not have a significant difference (median 13 months (95% CI: 10.10-15.99) vs. median 15 months (95% CI: 10.84-18.16), p=0.323). Further comparison of overall survival between the resection after localized CCRT group and the operation first group have shown significant difference (median 62 months (95% CI: 22.99-101.01) vs. median 15 months (95% CI: 10.84-19.16), p<0.006). Disease-free survival between these groups also revealed significant difference (median 32 months (95% CI: 3.47-60.54) vs. 3 months (95% CI: 2.03-3.97), p=0.000).

Conclusion: In HCC with portal vein thrombosis, patients who received resection after CCRT showed better overall and disease-free survival compared to those who received operation first. Localized CCRT can be a tool in identifying optimal surgical candidates in HCC with portal vein tumor thrombosis.

Disclosure of Interest: None Declared

Introduction: A new evidence-based model, the albumin-bilirubin (ALBI) grade, has been recently proposed for assessing the liver function in patients with hepatocellular carcinoma (HCC). In Japan, hepatic arterial infusion chemotherapy (HAIC) is applied to patients with TACE-resistant unresectable advanced HCC. The primary strategy of HAC in our hospital is a combination of low-dose cisplatin (CDDP) and continuous infusion of 5-fluorouracil (5-FU) regimen or an injection of CDDP suspended in lipiodol followed by a continuous infusion of 5-fluorouracil using a balloon pump (New FP regimen). We retrospectively evaluated the usefulness of the ALBI grade in predicting the survival following HAIC.

Methods: From June 2003 to July 2015, 204 patients treated with HAIC for HCC at Yamaguchi General Hospital were enrolled in the present study (mean age, 69.4 years; Child-Pugh class B/C: 104/76/24 cases; Stage 3A/3B/4B: 79/103/22 cases; mean tumor size 69.2 mm; Low-dose FP/New FP regimen, 100/104 cases). We calculated the ALBI grade from the albumin and bilirubin values of the 204 patients and then compared the ALBI grades pre-HAIC and after one month of HAIC post-HAIC. In addition, we compared the ALBI grades for two different regimens (Low-dose FP and New FP). Cumulative survival analysis (OS) was estimated using Kaplan–Meier survival curves, and the OS rates for each ALBI grade were compared using a log-rank test.

Results: The number of ALBI grade 1/2/3 in pre-HAIC was 69/143/12, respectively. The median survival time (MS) was 12 months. The MST of patients with ALBI grade 1/2/3 in pre-HAIC was 21/10/8 months, respectively (p<0.001). In contrast, patients received Low-dose FP, the MST of patients with ALBI grade 1/2/3 in pre-HAIC was 24/10/9 months, respectively (p=0.004). The MST of patients with ALBI grade 1/2/3 in post-HAIC was 21/11/9 months, respectively (p<0.001). In contrast, patients received New FP, the MST of patients with ALBI grade 1/2/3 in pre-HAIC was 18/10/6 months, respectively (p=0.243). The MST of patients with ALBI grade 1/2/3 in post-HAIC was 27/10/4 months, respectively (p<0.001). The number of patients who recovered to ALBI grade 1 after HAIC was 13 in New FP group and 2 in Low-dose FP group.

Conclusion: A significant response rate regarding symptoms was observed in patients undergoing RT for LN metastasis from HCC. The prognostic grouping can be effectively used for the prediction of survival for these patients.

Disclosure of Interest: None Declared

Conclusion: P-096 RADIOTHERAPY FOR SYMPTOMATIC LYMPH NODE METASTASIS FROM HEPATOCELLULAR CARCINOMA

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Introduction: Lymph node (LN) metastasis from hepatocellular carcinoma (HCC) is known as a poor prognostic indicator for survival while being uncommon. With the improvement of diagnostic imaging and survival in advanced HCC patients, however, the incidence is more likely to increase. The purpose of this study is to evaluate the treatment outcomes of external beam radiotherapy (RT) for symptomatic LN metastasis from HCC.

Methods: Between 2004 and 2015, 51 HCC patients underwent RT for symptomatic LN metastasis. The most common symptom was pain which was present in 72.5%. The mean age, biologically effective RT dose, and follow up period were 58 years, 50 Gy(10), and 3.6 months, respectively.

Results: Regarding symptoms, a response rate of 80.9% was observed. Among the 47 patients available for post-RT symptom evaluation, 38 showed either a complete remission of symptoms or a significant improvement, and only 9 showed no change in symptoms. The median survival (MS) was 3.8 months. On multivariate analysis of pre-RT factors, Child-Pugh class B-C (HR, 3.70), non-radial distant metastasis (HR, 2.14), and uncontrolled intrahepatic disease (HR, 1.88) were significantly poor prognostic indicator for survival (all p<0.05). Prognostic grouping into 3 groups by the number of risk factors also had a significant value for survival, with patients having 0, 1, and 2 risk factors demonstrating MS of 6.1, 3.9, and 2.2 months, respectively (p<0.001).

Conclusion: A significant response rate regarding symptoms was observed in patients undergoing RT for LN metastasis from HCC. The prognostic grouping can be effectively used for the prediction of survival for these patients.

Disclosure of Interest: None Declared
Introduction: SerpinB3 is a member of the serine-protease inhibitors and protects cells from oxidative stress conditions, but in chronic liver damage this serpin may lead to hepatocellular carcinoma through different strategies, including inhibition of apoptosis, induction of epithelial to mesenchymal transition and decrease of desmosomal junctions, cell proliferation and invasiveness. In the liver SerpinB3 is undetectable in normal hepatocytes, but its expression progressively increases in chronic liver diseases, dysplastic nodules and hepatocellular carcinoma. In the present study we have investigated the mechanisms of action of SerpinB3 in different HCC models.

Methods: The activity of SerpinB3 has been investigated by taking advantage of morphological, molecular and cell biology techniques in the following experimental models: i) hepatic cells stably transfected to overexpress SerpinB3; ii) transgenic mice overexpressing SerpinB3 in the liver; iii) HCC patients with cirrhosis of different etiology.

Results: SerpinB3 expression in liver tumor has been correlated with liver regeneration activity, and increased proliferation. This was documented in hepatoma cell lines over-expressing SerpinB3 and in a mouse model transgenic for this serpin. SerpinB3 is highly expressed in the hepatic stem/progenitor cell compartment of both fetal and adult livers. After its induction by HIF-2alpha in an hypoxic environment, SerpinB3 was shown to be crucial for tumour invasiveness and metastasis, since it promotes epithelial-mesenchymal transition and TGF-beta production.

Second, the oncogene Myc was up-regulated by SerpinB3 through calpain and Hippo-dependent molecular mechanisms in hepatoma cells overexpressing SerpinB3, in transgenic mice, and also in human hepatocellular carcinomas. We have demonstrated that liver tumors with high SerpinB3 tissue expression exhibit also higher levels of beta-catenin and these features are associated with early recurrence after surgical resection.

Conclusion: The presented data provide evidence that SerpinB3 plays a relevant role in hepatocarcinogenesis through the activation of molecular pathways already recognized involved in liver cancer. This molecule might therefore be considered a novel molecular target in the prevention and control of liver carcinogenesis.

Disclosure of Interest: None Declared

P-100 CXCCL1 EXERTS ONCOGENE FUNCTIONS IN HEPATOCELLULAR CARCINOMA AND REGULATED BY MICRORNA-200A

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Introduction: In most situation, Chronic liver inflammation caused by viral hepatitis was the major risk for HCC1. In most situation, Cumulative evidence suggests that the interaction between Hepatocellular carcinoma cells and the surrounding tumor microenvironment has acted as a pivotal factor in progression of HCC. CXCCL1 (chemokine C-X-C motif ligand 1), a member of CXC family, which takes positive effects in neoplastic transformation, tumorigenesis, and angiogenesis in breast, lung, prostate, colorectal, bladder, prostate cancers and melanoma by binding CXCR2 specifically2. Nonparenchymal liver cells, including hepatic stellate cells, hepatic dendritic cells, neutrophils, monocytes, Kuffer cells could secrete CXCCL1 and other chemokines to attract inflammation cells and target liver cancer cells3,4. Although the functions of chemokines in tumors have been explored extensively recently, the function of CXCCL1 in HCC still not fully clarified.

Methods: The expression of CXCCL1 was investigated in paraffin sections, frozen tissues and serum from human HCC. The value of CXCCL1 expression in predicting prognosis in patients with HCC was explored. The effects of CXCCL1 on the progression of HCC was evaluated in vivo and in vitro. Cellular respiration function, Autophagic flux analysis were used to explore the possible mechanisms. One microRNA candidate that negatively regulate the expression of CXCCL1 was identified by biological information analysis and 3′-UTR lucerase reporter assay. The relationship between expression of microRNA and CXCCL1 was analyzed in HCC tissues. The cell function and rescue assays were all performed to validate the effects.

Results: High CXCCL1 expression predicted recurrence in HCC patients and promoted tumor progression in vivo and vitro. Mitochondrial metabolism and epithelial-mesenchymal transition were involved with and regulated in this process. Furthermore, CXCCL1 was identified as an direct target which was negatively regulated by miR-200a (miR-200a-200c). MiR-200a was inversely correlated with the levels of CXCCL1 expression in HCC tissues.

Conclusion: In conclusion, Our findings revealed that CXCCL1 could act an oncogenic role in HCC progression through activating mitochondrial metabolism, EMT pathways. MiR-200a could play an anti-tumor role in HCC progression partly by targeting CXCCL1 expression. These findings may provide an opportunity for therapy HCC by miR-200a/ CXCCL1 pathway.


Disclosure of Interest: None Declared
Acute Kidney Injury Following Liver Resection for Hepatocellular Carcinoma: Incidence, Risk Factors and Prognostic Value

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Introduction: Acute kidney injury following liver resection remains understudied in terms of diagnosis, severity, recovery and prognosis. The aim of this study was to assess the risk factors and prognostic value of acute kidney injury on short- and long-term outcomes following hepatectomy for hepatocellular carcinoma.

Methods: This is a retrospective analysis of a single-center cohort of 457 consecutive patients who underwent hepatectomy for hepatocellular carcinoma. The Kidney Disease Improving Global Outcomes criteria were used for Acute Kidney injury diagnosis. The incidence, risk factors, and prognostic value of acute kidney injury were investigated.

Results: Acute kidney injury occurred in 67 patients (15%). The mortality and major morbidity rates were significantly higher in patients with Acute kidney injury (37% and 69%) than in those without (6% and 22%; p < 0.001). Renal recovery was complete in 35 (52%), partial in 25 (37%), and absent in 7 (11%) patients. Advanced age, an increased Model for End-Stage Liver Disease score, major hepatectomy and prolonged duration of operation were identified as independent predictors of Acute Kidney injury. Acute kidney injury was identified as the strongest independent predictor of postoperative mortality but did not impact survival.

Conclusion: Acute Kidney injury is a common complication after hepatectomy for hepatocellular carcinoma. Although its development is associated with poor short-term outcomes, it does not appear to be predictive of impaired long-term survival.

Disclosure of Interest: None Declared

P-103 Neutrophil-to-Lymphocyte Ratio Change Predicts Survival of Patients with Hepatocellular Carcinoma Undergoing Trans-Arterial Chemoembolization

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Introduction: An elevated neutrophil-to-lymphocyte ratio (NLR) detected before initiation of treatment has been found to be a prognostic factor for hepatocellular carcinoma (HCC) patients after different treatment modalities (reference). However, the change in NLR after therapy has not been studied in patients undergoing trans-arterial chemo-embolization (TACE).

Methods: One hundred and three consecutive patients with intermediate stage (BCLC B) HCC treated with TACE were prospectively evaluated. The NLR was recorded within 3 days before and 1 month and 6 months after TACE. Baseline characteristics including Child-Turcotte-Pugh (CTP), BCLC, performance-status (PS) and therapeutic response were correlated to pre/post procedure NLR change.

Results: The mean age was 58.6 ±8.4, 84.5% were male, 85.7% had multiple focal lesions. The mean AFP level was 664 ng/ml. The overall response rate was 68% and 24% after 1 and 6 months respectively. One month after TACE, post procedure NLR decreased in 39 patients and increased in 64 patients compared to pre-procedure NLR level. No significant differences were identified between responders and non-responders regarding the baseline clinic-pathologic features. Elevated post/pre-procedure NLR was found in 48.5% of responders and 77.1% of non-responders, while decreased post/pre-procedure NLR was found in 51.5% of responders and 22.9% of non-responders (p=0.01, OR: 3.58 (2.42-9.99)).

Conclusion: The post/pre-procedure NLR change may be an indicator for therapeutic response in patients with intermediate stage HCC undergoing TACE.

Disclosure of Interest: Reham Hamed (Grant/research support: 1), Asmaa Gomaa* (Grant/research support: 1), Naglaa AlAmi (Grant/research support: 1), Anwar Aboel Akm (Grant/research support: 1), Ashraf AlJaky (Grant/research support: 1), Eman Rewishta (Grant/research support: 1), Imam Waked (Grant/research support: 1).


Disclosure of Interest: None Declared

P-104 New Scoring System Based on Preoperative Tumor Factors for Single Resectable Hepatocellular Carcinoma with the Maximum Tumor Size SCM or Less

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Introduction: In this study, we established a new scoring system using preoperative tumor factors, which can predict postoperative prognosis and offer optimal surgical extent of resection.

Methods: We set inclusion criteria of this study as the following: solitary tumor ≤ 5cm, no preoperative treatments. Child-Pugh score A. Total of 265 HCC patients who underwent hepatectomy from 2000 to 2012 was used to identify preoperative factors which can be useful to construct new scoring system. Using selected preoperative factors which compose new scoring system for HCC patient, specifically tumor size, DCP level and gross pattern, all patients were classified into high risk group and low-risk group and analyzed if this classification is useful for prediction of prognosis and choosing surgical treatment for HCC patient.

Results: The independent poor prognostic factors for recurrence-free survival were the presence of MRI, tumor size and major liver resection. The independent predictive factors for MRI were high DCP level and non-boundary growth pattern. Using three preoperative tumor variables including tumor size, DCP level and growth pattern, patients were divided into low risk group and high risk group. The recurrence-free survival and overall survival rate of high risk group was significantly lower than that of low risk group (p<0.01). Major hepatectomy showed significant higher recurrence-free survival rates compared to minor resection in high risk group (p<0.01). However, in low risk group, the extent of resection did not show significant difference in recurrence-free survival (p=0.12).

Conclusion: Our new scoring system using preoperative tumor factors could predict postoperative recurrence and overall survival. This scoring system might help us to select the optimal extent of resection prior to surgery in well selected HCC patients.

Disclosure of Interest: None Declared

P-105 Single Hepatocellular Carcinoma: Liver Imaging Reporting and Data System (LI-RADS) Categorization and Prognosis After Curative Resection or Radiofrequency Ablation

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Introduction: To examine the relationship between LI-RADS (Liver Imaging Reporting And Data System) categorization and prognosis after curative resection or radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC).

Methods: This retrospective study was approved by the institutional review board, and the requirement to obtain written informed consent was waived. A total of 260 at-risk patients underwent curative hepatic resection or RFA for single HCC after gadolinium-acid-enhanced magnetic resonance imaging (MRI) from January 2008 to December 2010 at a single institution. Two radiologists reviewed MRI images and categorized all hepatic lesions based on the LI-RADS diagnostic algorithm (v2014) by consensus. Disease-free survival was compared according to the LI-RADS categories using the Kaplan-Meier method with log-rank testing.

Results: Of 260 HCCs, 2 (0.8%), 60 (23.1%), 189 (72.7%), and 9 (3.5%) were preoperatively categorized as LR-3, LR-4, LR-5, and LR-M, respectively. Patients with HCCs categorized as LR-M showed significantly worse disease-free survival than those categorized as LR-3, LR-4, or LR-5. Median disease-free survival was 2,202 days and 140 days for LR-3/4/5 and LR-M, respectively (P<0.001). No difference was found in disease-free survival among patients categorized as LR-3, LR-4, and LR-5. However, in a subgroup analysis of patients undergoing RFA, patients with LR-4 HCCs showed significantly better prognosis than those with LR-5 HCCs (P=0.024).

Conclusion: Patients with HCCs preoperatively categorized as LR-M may have worse prognosis after curative resection or ablation than ordinary HCCs.

Disclosure of Interest: None Declared


Disclosure of Interest: None Declared
Posters

P-106 PREVALENCE OF LARGE ESOPHAGEAL VARICES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A LARGE COHORT STUDY

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Introduction: Hepatocellular carcinoma (HCC) and esophageal varices (EVs) are two important complications of cirrhosis. According to the Baranco recommendation, surveillance endoscopy for EVs is suggested in all patients with cirrhosis. In patients with HCC, the presence of EVs indicates poor outcome, however, not all HCC patients have advanced liver fibrosis and the incidence of EVs in these group is not well investigated. This phenomenon is especially important in hepatitis B prevalent area, which can cause HCC without accompanying cirrhotic change. Therefore, we aimed to explore the prevalence and predictors of large EVs (LEVs) in HCC patients and stratify them by viral etiologies and Child-Pugh grade.

Methods: This is a single center cohort study in Taiwan. From October 2007 to April 2014, all treatment-naive HCC patients in Taipei Veterans General Hospital were registered in a task-intensive management program, and their clinical data were collected prospectively. From this data base, the HCC patients who had received surveillance or treatment upper gastrointestinal endoscopy (EGD) within 3 months of HCC diagnosis were included into the EGD cohort and HCC patients who didn’t receive endoscopy within 3 months of HCC diagnosis were assigned into the non-EGD cohort. We used EGD cohort to analysis the prevalence and predictors of LEVs and build risk score. Non-EGD group was used to be a validation group and compare the nature EV bleeding risk in different group divided by risk score.

Results: A total of 3030 patients with first diagnosed HCC were registered during the study period. After excluding 100 patients with previous treatment for EV and 407 patients with missing data, 1283 patients were included into EGD cohort and 1240 patients were included into non-EGD cohort, respectively. For the EGD cohort, the prevalence rates of EVs/size EVs were 45.4/27.7%, respectively. Low hemoglobin and albumin levels, lower platelet count, high serum bilirubin levels, and presence of portal vein thrombosis were the independent predictors of LEVs by multivariate analysis. Of note, among patients with well-preserved liver function and with Child-Pugh grade A, the incidences of LEVs were different between HBV- and HCV-related HCC patients (14.4 vs 23.6%, p = 0.003, respectively). By multivariate analysis, the predictors of LEVs in patients with HBV-related HCC and Child-Pugh grade A were platelet count <150000/mm³, serum bilirubin >0.8 mg/dL, and albumin <3.5 g/dL. One point is given if presence of any above predictions to build a risk score (range 0-3). To validate this score, in the non-EGD cohort, patients with HBV-related HCC and with Child-Pugh grade A were divided by risk score into low risk group (0-1) and high risk group (2-3). During the follow-up period, the risk of EV bleeding in low risk group was significantly lower than that in the high risk group (p=0.02) and was similar to patients without LEVs in EGD cohort (p=0.26).

Conclusion: It is difficult to determine if coexistence of cirrhosis in HBV-HCC patients with preserved liver function on clinical. We found these patients with low risk score ≤1 (around one of four treatment-naive HCC patients in Taiwan) had low EV bleeding risk similar to patients without LEVs by endoscopy and surveillance endoscopy may be saved in this group except patients with gastrointestinal symptoms.

Disclosure of Interest: None Declared

P-107 PATIENTS OVER 80 YEARS OLD WITH HEPATOCELLULAR CARCINOMA (HCC) HAVE AN EQUALLY GOOD RESPONSE AND OVERALL SURVIVAL WHEN TREATED WITH Loco-REGIONAL THERAPY

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Introduction: The incidence of hepatocellular carcinoma is increasing in several developed countries. It is known that increasing age is a poor prognostic factor for HCC owing to co-morbidities and or late diagnosis. Given the increase in non- alcoholic liver disease (NASH) related cirrhosis which is linked to metabolic diseases, the number of older patients with HCC is likely to rise in these populations. Our study evaluates the impact of age on response to treatment for HCC and overall survival.

Methods: A retrospective study of consecutive patients diagnosed with HCC in the Liverpool region, UK. All patients confirmed to have HCC during the period 2009 to 2014 were followed up till last encounter, lest to follow up or death. Age, gender, aetiology of liver disease, Barcelona Clinic for Liver Cancer (BCLC) stage and treatment given were all recorded. The subjects were grouped into those below 80yrs and those ≥80yrs of age. Patient survival was compared between groups using Kaplan Meier curves. P values of less than 0.05 defined statistical significance.

Results: 671 patients with HCC were diagnosed during the study period. 569 (84.8%) were below 80yrs of age at diagnosis with no difference in gender split between groups (older: 77.5% male, younger 76.1% male). Unsurprisingly, overall survival was better in the younger group compared to the older group (median 15 months vs. 7 months, p=0.0007). This was associated with significantly more patients with advanced disease (BCLC D) than early stage disease (BCLC 0 and A) in the older age group (p=0.0008). Of those with intermediate stage disease (BCLC B), there were similar proportions of patients (older 19.6% vs. 16.3%) with no difference in median survival (older: 23 months, vs. 21 months, p=0.47). For all patients treated with loco-regional therapy, there was no difference in survival between the groups (older: 33 vs. 31 months, p=0.72).

Conclusion: Whilst older patients with HCC fare worse overall, we feel that this is likely to be due to higher proportions with more advanced disease, significant co-morbidities and poorer performance status. Our study confirms however, that older patients with intermediate stage HCC or those who are deemed fit for loco-regional treatments have equally good outcomes to younger patients. Those over 80 who are otherwise fit for treatment should therefore be offered active treatment for their tumours.

Disclosure of Interest: None Declared

P-108 RISK FACTORS FOR EARLY MORTALITY AFTER HEPATECTOMY FOR HEPATOCELLULAR CARCINOMA

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Introduction: Despite advances in surgical technique and medical care, liver resection for hepatocellular carcinoma (HCC) remains a high-risk major operation, especially in patients with co-existing underlying liver diseases. Previous studies had shown clinical risks factors for perioperative morbidity and mortality after liver resection; nevertheless, none had tried to indicate potential risk factors influencing early (6-month) mortality after hepatectomy. The present study evaluated the risk factors for early mortality after hepatectomy. A scoring system was also developed to predict the risk of early mortality after the operation.

Methods: We retrospectively reviewed records of patients undergoing liver resection for primary HCC at our hospital between 1993 and 2015. Patient demographics, laboratory data, treatment, pathologic characteristics, and survival outcome were collected. Statistical analyses were conducted between patients with and without early mortality. Student t test, Chi-square test, and logistic regression analysis were employed for univariate and multivariate analyses, respectively. Survival was analyzed and compared by the Kaplan-Meier method and the log-rank test. A point score (Risk Assessment for early Mortality (RAM) score) for hepatectomy was developed based on multivariate analyses.

Results: A total of 3,383 patients with HCC underwent surgery during this study period. Three hundred and eighty-three patients (11.3%) expired within 6 months after the operation. The mean survival length of this group of patients was 81 days (range 0 – 179 days). Logistic regression analyses identified that operative duration longer than 270 minutes and blood loss greater than 800cc were significant predictors of major surgical complications (p = 0.013 and 0.002, respectively). On the other hand, diabetes mellitus, albumin ≤ 3.5 g/dL, α-fetoprotein > 200 mg/mL, major surgical procedure, blood loss > 800cc, and major surgical complications were independent risk factors for early mortality after hepatectomy (p = 0.019, <0.001, <0.001, 0.006, 0.018, and <0.001, respectively). RAM score identified three subgroups of patients with distinct 6-month mortality rate, with Class I (score 0) having highest risk of early mortality after liver resection.

Conclusion: Our study demonstrated that meticulous surgical techniques to minimize blood loss and avoid prolonged operative time may help decrease the occurrence of major surgical complications. In addition to major surgical complications, we should be aware that diabetes mellitus, hypoalbuminemia, high α-fetoprotein, massive blood loss, and major surgical procedure are independently associated with early mortality for patients undergoing liver resection. Further study is warranted to validate the utility of RAM score as a bedside scoring system to predict postoperative outcome.

Disclosure of Interest: None Declared

P-109 STRATIFICATION OF BARCELONA CLINIC LIVER CANCER STAGE C HEPATOCELLULAR CARCINOMA BY VASCULAR INVASION AND METASTASIS

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P-111 CHARACTERISTICS OF PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH SORAFENIB WHO ACHieved LONG-TERM SURVIVAL OF >3 YEARS

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Introduction: Sorafenib is recognized as a standard therapy for advanced hepatocellular carcinoma (HCC). However, the SHARP study, a large-scale, phase III clinical trial, reported that the median overall survival (OS) was 10.7 months and that it was difficult to achieve a long-term survival. We previously reported the continued sorafenib treatment after radiologic confirmation of disease progression or administration of the following treatment to sorafenib may improve the survival in patients with advanced HCC, however characteristics of long-term survivors treated with sorafenib remains obscure. Clarification of the characteristics of long-term survivors treated with sorafenib for advanced HCC can ameliorate the treatment strategies for advanced HCC. This study aimed to identify the characteristics of patients with advanced HCC treated with sorafenib who survived for >3 years.

Methods: Characteristics of 99 patients with advanced-stage HCC who received sorafenib therapy between July 2009 and May 2015 in our department were retrospectively reviewed. Of 99, 18 patients who achieved long-term survival of >3 years from the initiation of sorafenib administration (group L) were compared with 81 short-term survivors who died within 1 year from the initiation of sorafenib administration (group S). Clinical characteristics, OS, progression-free survival (PFS), and period of sorafenib administration were assessed.

Results: Patients in group L tended to be older with advanced tumor stages and better liver function than those in group S. Two patients in group L and 10 patients in group S discontinued sorafenib within 1 month from its initiation. Response and disease-control rates of group L were superior to those of group S (25.0% vs. 9.3% vs. 0% and 39.2%, respectively, p < 0.001). The median PFS of group L was superior to that of group S (5.4 vs. 22 months, respectively). Furthermore, the median period of sorafenib administration of group L was superior to that of group S (5.5 vs. 2.3 months, respectively, p < 0.001). Multivariate analysis revealed that independent prognostic factors for long-term survival were hazard ratio (95% confidence interval) were survival (0.38, 0.15-0.87), and administration of the following treatment to sorafenib (0.50, 0.25-0.97).

Conclusion: Characteristics of long-term survivors over 3 years may be good liver function, prolonged period of stable disease, continued sorafenib treatment after radiologic disease progression, and administration of the following treatment to sorafenib.

Disclosure of Interest: None Declared

P-110 ADJUVANT IMMUNOTHERAPY WITH AUTOLOGOUS CYTOKINE-INDUCED KILLER CELLS FOR HEPATOCELLULAR CARCINOMA PATIENTS AFTER CURATIVE RESECTION, A SYSTEMATIC REVIEW

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Introduction: Cytokine-induced killer (CIK) cells have been used as an adjuvant treatment for hepatocellular carcinoma with curative treatment. However, the outcomes remain controversial. We conducted this meta-analysis to assess the safety and efficacy of cytokine-induced killer cells.

Methods: Randomized controlled trials on cytokine-induced killer cells based adjuvant treatment for hepatocellular carcinoma with curative treatment were identified by electronic searches. Methodological quality of trials was assessed by Jadad score. A meta-analysis was carried out to examine disease-free survival, overall survival, and adverse effect.

Results: Six Randomized controlled trials with 844 patients were included according to the inclusion criteria and five of them were considered as high quality with the score more than 4. Our meta-analysis showed that cytokine-induced killer cells adjuvant treatment can not only improve the 1-year (RR = 1.23, 95%CI: 1.13-1.34, P < 0.001, I²=50%), 2-year (RR = 1.37, 95%CI: 1.18-1.59, P < 0.001, I²=34%) and 3-year (RR = 1.35, 95%CI: 1.10-1.65, P = 0.004, I²=7%) disease-free survival, but also improve the 1-year (RR = 1.05, 95%CI: 1.03-1.13, P = 0.001, I²=0%), 2-year (RR = 1.14, 95%CI: 1.06-1.23, P < 0.001, I²=0%) and 3-year (RR = 1.15, 95%CI: 1.03-1.29, P = 0.02, I²=0%) overall survival. However, it failed to affect the 4-year and 5-year disease-free survival and overall survival (P > 0.05). At the same time, cytokine-induced killer cells treatment was proved to be a safe strategy with the comparable adverse events comparing to the control group (RR = 1.24, 95%CI: 0.76-2.03, P = 0.39, I²=47%).

Conclusion: This review provides the best available evidence that adjuvant cytokine-induced killer cells treatment can safely be used to improve the early disease-free survival and survival not the late disease-free survival and survival.

Disclosure of Interest: None Declared

Methods: A total of 234 patients diagnosed with BCLC C HCC between 2005 and 2015 were identified in a prospectively maintained HCC database. Patients were stratified into three groups based on tumor characteristics: 1) vascular invasion alone, 2) metastasis alone, and 3) vascular invasion and metastasis. Overall survival was compared using a Cox proportional hazards regression model. A subgroup analysis compared overall survival based on extent of vascular invasion and site of metastasis.

Results: The cohort comprised 123 (53%) patients with vascular invasion alone, 34 (15%) with metastasis alone, and 77 (33%) with both vascular invasion and metastasis. Median survival was 5.7, 3.9, and 3.0 months, respectively. Patients with vascular invasion or metastasis alone had significantly better overall survival compared to those with vascular invasion and metastasis (adjusted hazard ratio (HR), 0.68 (95% CI: 0.49 – 0.94) and 0.61 (95% CI: 0.39 – 0.96), respectively. Compared to tumoral invasion of branch portal veins, involvement of the main portal vein was associated with worse outcomes (HR, 2.13; 95% CI: 1.29 – 3.49). Overall survival did not differ by the site of metastasis.

Image: [Image]

Conclusion: Stratification of patients with BCLC C HCC by vascular invasion and presence of metastasis further discriminates patient prognosis.

Disclosure of Interest: None Declared
Introduction: Hepatocellular carcinoma (HCC) is a major health problem with high mortality rates, especially in patients with hepatitis B virus (HBV) infection. Telomerase function is one of common mechanisms affecting genome stability and cancer development. Recent studies demonstrated that genetic polymorphisms of telomerase associated genes such as telomerase associated protein 1 (TEP1) rs1742330 and PIN2/TERF1-interacting telomerase inhibitor 1 (PINX 1) rs1469557 may be associated with risk of HCC and other cancers.

Methods: In this study, 325 patients with HCC and 539 non-HCC groups [193 healthy controls, 80 patients with HBV-related liver cirrhosis (LC) and 266 patients with HBV-related chronic hepatitis (CH)] were enrolled to explore genetic polymorphisms of both SNPs using the allelic discrimination method based on MGB probe TaqMan real time PCR.

Results: We demonstrated that all genotypes of both genes were in Hardy-Weinberg equilibrium (P>0.05). Moreover, there was no significant association between rs1742330 genotypes and HCC risk, HCC progression and overall survival (P>0.05). Interestingly, we observed positive association of rs1469557 with risk of HCC when compared with the LC group under dominant CC versus CT+TT, OR=1.89, 95% CI: 1.46–3.40, P=0.003 and allelic C versus T alleles, OR=1.74, 95% CI: 1.04–2.94, P=0.033 models, respectively. Moreover, overall survival of HCC patients with CC genotype of rs1469557 was significantly higher than non-CC genotype (log-rank P=0.015).

Conclusion: These findings suggest that PINX1 rs1469557 but not TEP1 rs1469557 might play a role in HCC progression in Thai patients with LC and be used as the prognosis marker to predict overall survival in HCC patients.

Disclosure of Interest: None Declared

P-115 ASSOCIATION OF MICRORNA MACHINERY GENES WITH HEPATOCELLULAR CARCINOMA IN A KOREAN POPULATION

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Introduction: Single-nucleotide polymorphisms (SNPs) in microRNA machinery genes might affect microRNA processing and subsequently impact tumorigenesis. The aim of this study was to investigate the associations between SNPs in microRNA machinery genes and hepatocellular carcinoma (HCC) in a Korean population.

Methods: Genotyping of six SNPs in microRNA machinery genes was performed using blood samples from 147 patients with HCC and 209 healthy control subjects.

Results: None of the six SNPs in microRNA machinery genes were significantly associated with HCC development. However, among the models for six polymorphic loci—DICER (rs1742330 and rs13078), DRD2A (rs10719 and rs617424), RAN (rs14035) and XRPS (rs11077)—one allele combination (A-A-C-C-C-C) showed synergistic effects in terms of an increased risk of HCC development (odds ratio=8.881, 95% confidence interval [CI]=1.889–41.750; P=0.002). Multivariate Cox proportional hazard regression analysis showed a significant survival benefit for HCC development (odds ratio=8.881, 95% CI=1.889–41.750; P=0.002).

Conclusion: The results of this study revealed that XRPS rs11077 and XRPS C/T genotype combination could be a potential risk factor for HCC in a Korean population.

Disclosure of Interest: None Declared

P-116 USE OF RADIOFREQUENCY ABLATION AND STEREOTACTIC BODY RADIOTHERAPY FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA: AN ANALYSIS OF THE SEER-MEDICARE DATABASE

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Introduction: Hepatocellular carcinoma (HCC) is an increasingly common and highly morbid malignancy worldwide, including the US. For early stage patients ablative strategies are important and potentially curative treatment options. Stereotactic body radiotherapy (SBRT) has emerged as a promising non-surgical ablative therapy, although it is technically demanding and its comparison with radiofrequency ablation (RFA) remains confined to a single institution retrospective review. We queried the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to assess RFA and SBRT use in the US.

Methods: We identified patients greater than 65 years old who were diagnosed from 2004-11 with stage 1 or 2 HCC and treated with RFA or SBRT. Survival analysis was conducted using Kaplan-Meier curves and log rank test. Factors associated with overall survival (OS) and early (≤90 day) hospital admission post-treatment were identified using propensity score (PS) adjusted multivariate analysis.

Results: 825 patients were identified, 747 treated with RFA and 78 SBRT. 22 pts received both treatments and were excluded from this analysis. The mean Charlson comorbidity index was 8.0. The mean Charlson comorbidity index was 8.0. Life expectancy was worse for patients treated with SBRT compared to RFA. The estimated 5-year survival rate was 34.7% in the RFA arm and 15.2% in the SBRT arm (P=0.002). In a multivariate model adjusting for age, gender, race, comorbidity, tumor stage, treatment modality, and treatment year, the hazard ratio for death was 2.43 (95% CI: 1.42-4.12, P=0.001) for SBRT compared to RFA.

Disclosure of Interest: None Declared
P-118 THE ONSET OF ASCITES IMPAIRS THE SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH DEB-TACE.

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Introduction: Survival of patients with intermediate stage HCC is heterogeneous (median 16-48 months) and it is influenced by baseline characteristics and effectiveness of chemoreosumbolization (TACE). It has been reported that ascites is a marker of poor prognosis in BCLC-B patients. Conventional TACE (cTACE) and TACE with DC-Beads (DEB-TACE) allow the same survival, although the last one is better tolerated and has fewer adverse effects. In most series some baseline characteristics and treatment response is independent prognostic factors of survival after TACE, but there is not enough information about post-procedure complications and their influence on patient survival.

Aim: To analyze the influence of complications of first DEB-TACE procedure on survival of patients.

Methods: Prospective monocentric cohort recruited from OCT 15th 2008 to OCT 2020, with follow-up until death or last visit at JAN 20th 2016. Baseline characteristics, response to treatment (mRECIST criteria, multiphase CT scan at 5 weeks) and complications until 60 days after DEB-TACE (scale CT-CAE v 3.0) were prospectively collected. Patients treated during the waiting list for liver transplant, those treated within trials and those treated after radioembolization or systemic therapy were excluded. Statistical analysis was made using SPSS 20.0.

Results: 216 compensated cirrhotic patients were included: male 70.5 years, 83% males, 45% alcohol and 36% hepatitis C. Child-Pugh class A 93%, BCLC-A 41% and BCLC-B 59%. Median AFP 12.8 ng/mL. Median tumor diameter 35 mm. Objective response 72%(complete 27%, partial 45%). Most common complications were radiotherm in 2, liver abscess in 4, cholecystitis in 1 and ascites in 20% of cases. DEB-TACE mortality was 8.5%. Median survival was 29 months (95% CI 27.3-31). Baseline BCLC stage (median 148 (95% CI 136-160) p 0.008), objective response (median 150 (1.049-2.292) p 0.028), postTACE AFP value (median 0.575 (0.384-0.862) p 0.007) and onset of ascites (median 148 (1.070-1.685) p 0.002) were independently associated with survival. The onset of ascites was not related to different baseline BCLC stage (p 0.859), AFP (p 0.499), Creatinine (p 0.676), Hemoglobin (p 0.416), Sodium (p 0.121), Albumin (p 0.406), Alkaline Phosphatase (p 0.085), Platelets (p 0.638) or objective response to first DEB-TACE (p 0.638). By contrast baseline bilirubin levels (p 0.002), presence of esophageal varices (p 0.018) and prior use of diuretics (p 0.001) were between those that developed ascites or not.

Conclusion: In our series of compensated cirrhotic patients, development of complications after DEB-TACE is rare, but the appearance of ascites is significantly and independently associated with decreased survival (18 vs 30 months). Onset of ascites is related to same degree of basal hepatic dysfunction (compensated pre-TACE ascites, esophageal varices, slightly elevated bilirubin). It is necessary to define criteria for predicting which patients will decompensate, in order to optimize or change treatment.


Disclosure of Interest: None Declared.

P-119 HEPATOCELLULAR CARCINOMA TUMOR RESPONSE AFTER HEPATITIS C TREATMENT.

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Introduction: Hepatocellular carcinoma (HCC) remains a fatal disease with low rates of tumor response to locoregional therapy. Sorafenib prolongs overall survival in patients with advanced disease, however the benefit is very limited. We previously reported a case of complete regression of HCC after hepatitis C (HCV) treatment [1]. In patients with active HCV and HCC, little is known about the safety and efficacy of HCV directed therapy in combination with HCC directed therapy, particularly given the impressive results with ledipasvir/sofosbuvir in patients with active HCV without HCC.

Methods: We retrospectively studied adults with HCV-induced cirrhosis treated for HCC (with either locoregional therapy or sorafenib) with and without anti-HCV therapy. Primary outcome was HCC tumor response by modified RECIST with secondary outcome being safety of anti-HCV therapy. For statistical analysis, Fisher’s exact test was used to compare tumor response between patients treated with and without anti-HCV therapy (p value <0.05 was considered statistically significant).

Results: Twenty-eight patients were identified: Thirteen patients (10 male, 3 female) were treated for HCV while 15 patients (14 male, 1 female) did not receive anti-viral therapy (most often due to physician preference). Patient characteristics were similar between HCC/HCV and HCC treated groups with median MELD of 10 and 11, and average age of 61 and 62, respectively. HCV treatment led to an improved tumor response compared to the non-HCV treated group (p =0.01). Of the 13 HCV treated patients, 3 achieved complete response (CR); 2 partial response (PR); 4 had stable response (SD); and 4 had progressive disease (PD). Of the 15 non-HCV treated patients, 1 achieved CR; 1 SD and 13 with PD. The majority of both groups (27/28) underwent locoregional therapies (TACE or RFA), and 9 patients received sorafenib (1 HCV treated patient and 8 control patients). Median baseline AFP for the HCV treatment group was 13 ng/dL before vs. 5.6 ng/dL, after receiving most recent HCC treatment. Median baseline AFP for the control group was 25 ng/dL before vs. 67.8 ng/dL, after receiving most recent HCC treatment. Median total follow up from HCC diagnosis to most recent imaging was 19 months for both groups. Median follow up from HCV treatment to most recent imaging was 6 months for the HCV treated group. All patients treated for HCV completed therapy and achieved sustained virologic response without adverse effects leading to therapy discontinuation.

Image:

Conclusion: HCV targeted therapy, in combination with standard HCC treatment is safe and shows a promising tumor response that needs to be validated in prospective studies with larger sample sizes and perfectly matched cohorts. While this remains to be studied, a proposed mechanism for this observed response includes decreased cell turnover and inflammation leading to less HCC tumor progression.


Disclosure of Interest: None Declared.

P-120 THE EFFICACY OF SORAFENIB IN HEPATOCELLULAR CARCINOMA (HCC) SECONDARY TO NONALCOHOLIC STEATOHEPATITIS (NASH) IN ANIMAL MODEL: EVALUATION BY 18F-FDG PET IMAGING AND HISTOLGICAL ANALYSIS.

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Introduction: Nonalcoholic Steatohepatitis (NASH) has been associated with hepatocellular carcinoma (HCC). PET image provides physiologic information, monitors in vivo onset and progression of the HCC, monitors treatment response and identify metatadismic spread. The aim of this study is to create a pattern to use 18F-FDG PET on the experimental animal model of NASH-related HCC and to evaluate the efficacy of sorafenib for 3 weeks in this model.
Methods: NASH-related HCC was induced in 30 adult Sprague-Dawley male rats with 11 weeks old and mean weight of 300g, by the combination of high-fat diet deficient in choline (DHC) and diethylthiourea (DET) at a dose of 135 mL/kg in drinking water for 16 weeks. Then, rats were divided into two groups: control (n=10) using saline solution by daily gavage and sorafenib group (n=20), whose animals received sorafenib (5mg/kg/day) from 16th to 29th week after the induction.

The efficacy of sorafenib was assessed by 18F- FDG PET imaging in a small animal dedicated equipment (LabPET Triumph – Gamma camera) on the beginning of the 16th and 19th week, and far by histological analysis (Edmondson & Steiner’s and Kleiner classification) at the end of the protocol when the animals were sacrificed.

Results: The analysis of the PET images demonstrated increased 18F-FDG uptake in the lesions, suggesting high glycolytic metabolism rate in accordance with the degree of differentiation. 18 F-FDG PET obtained a sensitivity of 62.5% and specificity of 100% for HCC's diagnosis. It was also able to identify metastatic sites. Comparing the histological aspects and 18 F-FDG PET the Control group had 25 HCC nodules with the average number of them was 5.5 ± 0.7 and the sorafenib group had 23 HCC nodules with the average of 6.5 ± 3.5 of them per subject. On the control group, 46.3% of all nodules were dysplastic lesions (72.2% low grade dysplasia and 33.3% high grade dysplasia) and 53.7% were hepatocellular carcinomas (grade 1 – 22.7%, grade 2 – 22.7%, grade 3 -36.5% and grade 4 – 18.2%) with no vascular invasion. On the other hand, the sorafenib group had no dysplastic lesion. HCC was found on all of them and according to Edmondson Steiner classification: grade 4 was 1%, grade 2, 25%, grade 3 and 24% and grade 4. 4. The non-tumoral tissue showed control group NAS score=5 was present at 67.5% of them, while only in 42.8% in the sorafenib group suggesting that it can reduce also NAS. There was no difference between the groups on the grade of liver fibrosis.

Conclusion: 18F-FDG PET can be a tool to evaluate animal model of NASH-related HCC. The results show a reduction of the NAS score suggesting improvement of NASH by sorafenib, also a remarkable action on dysplastic lesion (low or high grade) as well early HCC in this animal model.


P-121 RADIATION SEGMENTECTOMY VS. TRANSARTERIAL CHEMOEMOBILIZATION COMBINED WITH MICROWAVE ABLATION FOR UNRESECTABLE SOLITARY HEPATOCELLULAR CARCINOMA ≤3 CM: ANALYSIS OF IMAGING RESPONSE AND PROGRESSION OUTCOMES.

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Results: The median (95% CI) follow-up time was 20.1 (18.1-22.5) months in the MWA group and 11.1 (8.4-13.8) months in the RS group (p < 0.001). There were 41 patients (RS: 11, TACE-MWA: 30) instances of progression occurring after an initial OR, of which 10 (24%) were classified as target progression (PE: 1, TACE-MWA: 9). The median (95% CI) overall OTP (months) was 11.1 (8.8-25.6) in the RS group and 12.1 (7.7-19.1) in the TACE-MWA group (p=1.0). Overall TTP was longer in patients with pre-treatment tumor size ≤ 2 cm (p=0.04).

Conclusion: Imaging response and progression outcomes of patients with solitary HCC ≤3 cm treated with RS were not significantly different compared to TACE-MWA. Tumor size ≤ 2 cm was predictive of a more favorable progression outcome. Longer follow up times will allow for a more robust progression analysis.

Disclosure of Interest: None Declared

P-122 PHOCUS: A PHASE 3 RANDOMIZED, OPEN-LABEL STUDY COMPARING THE ONCOLYTIC IMMUNOTHERAPY PEXA VEC FOLLOWED BY SORAFENIB (SOR) VS SOR IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) WITHOUT PRIOR SYSTEMIC THERAPY

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Introduction: Pexa-Vec (pegylated denisovanepox) is an oncolytic and immunotherapeutic vaccinia virus designed to selectively replicate in and destroy cancer cells. It causes direct oncolysis accompanied by tumor vascular disruption and anti-tumor immune mediated by expression of the transgene GM-CSF. Sorafenib, a multi-targeted tyrosine kinase inhibitor, is the standard of care for first-line systemic treatment of advanced HCC. Both preliminary preclinical and clinical data suggest complementary anti-tumor effects of a sequential combination of Pexa-Vec followed by sorafenib possibly by targeting the tumor vasculature via different mechanisms (Heo et al., Mol Ther 2011). A randomized phase II dose-finding study with Pexa-Vec intratumoral (i)T liver injections in first line advanced HCC patients showed an acceptable safety profile and a significant increase in overall survival (OS) in the highest dose group (10^9 pfu) (Heo et al., Nat Med 2013).

Methods: This global, randomized, open-label, phase III study will compare the efficacy and tolerability of Pexa-Vec followed by sorafenib versus sorafenib in advanced HCC patients. Eligible patients are Child-Pugh A, ECOG PS 0-1, BCL C/V, have at least one measurable and viable liver tumor (based on radiographic assessment) injectable under imaging guidance, have liver tumor mass ≤ 50% of the total liver volume, no evidence of the inferior vena cava, and had no prior systemic therapy for HCC. Six hundred patients will be randomized 1:1 to either Pexa-Vec IT injections administered every 2 weeks at a dose of 10^9 pfu (D1, W2, W4) followed by 400 mg BID sorafenib starting at W6 to or sorafenib-400 mg BID (from D1). Patients are allocated to treatment arm using minimization by center, HCC etiology, presence of extra-hepatic disease, vascular invasion, PS 0-1, AFP levels. The primary endpoint is OS (1-sided stratified log-rank test; α=0.05, 86% power, HR 0.83). Main secondary imaging endpoints are time to progression, progression-free survival, overall response rate and disease control rate (radiographic evaluation every 6 weeks). In addition, safety, biomarkers and quality of life will be evaluated.

Results: The clinical trial is ongoing with no results available at this time.

Conclusion: The Phase 3 PHOCUS trial is actively enrolling patients with the objective of assessing if the addition of an oncolytic vaccine, Pexa-Vec to the standard of care for advanced HCC, sorafenib, will improve outcomes, particularly overall survival.

P-123 PERFORMANCE OF THE ALBI SCORE AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED BY RADIOTHERMOABOLIZATION

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Introduction: The Albumin-Bilirubin (ALBI) scoring model offers an objective and discriminatory method of assessing liver function. In a large cohort of patients with hepatocellular carcinoma, ALBI grade predicts patient survival across stages. Our aim is to describe how ALBI discriminates prognosis in patients treated with radiotherapy using Yttrium-88 microspheres.

Methods: All consecutive patients with hepatocellular carcinoma treated by radioembolization from 2003 to 2012 were retrospectively analyzed. Patients not followed entirely in our center, those with a follow-up < 3 months, and those in which the ALBI grade could not be calculated were excluded. Although the analysis is retrospective, most variables were prospectively recorded. Survival was plotted from the day of treatment until death or last visit using Kaplan-Meier method and compared by log-rank test. Cox-regression analysis was used for multivariate analysis. C-statistic was used to compare the goodness of fit of logistic regression models.

Results: 122 patients analyzed had a mean age of 68 years and were predominantly males (82.8%), and cirrhotics (79.5%). Patients were in BCLC stages A (15.6%), B (60.8%) or C (33.6%); Child-Pugh class (A: 9.5% B: 13.9% C: 77.6); and ALBI grades (1: 77.6% 2: 22.1%). Median overall survival was 14.1 months (95%CI 11.7-17.2). Survival was not significantly different according to Child-Pugh class (A: 14.1 months [95%CI 10.8-17.3] vs. B: 10.8 months [95%CI 4.1-17.5]; p=0.42) but it was significantly different according to ALBI grade (grade 1: 15.8 months [95%CI 12.6-18.8] vs. grade 2: 10.8 months [95%CI 6.6-12.9]; p=0.016). Adjusted by BCLC stage, the prognostic ability was confirmed for ALBI grade (HR: 1.67 [95%CI 1.04-2.67]; p=0.033) and not for Child-Pugh class (HR: 1.29 [95%CI 0.73-2.38]; p=0.38). This is likely the result of patients with Child-Pugh score 6 surviving not differently from patients with Child-Pugh score 7 (p=0.87).

Conclusion: ALBI grade is a better predictor of survival than Child-Pugh class in patients with hepatocellular carcinoma treated by radioembolization.

Disclosure of Interest: J. Buades Mateu* None Declared, I. Barabar: None Declared, M. Iturria-arenague: None Declared, D. Martínez-Uribostondo: None Declared, M. De la Torre Alaez: None Declared, I. Bilbao Consulting of: received lecture and consulting fees from Sirtex Medical, B. Sangro Consulting of: received lecture and consulting fees from Sirtex Medical

P-124 RACIAL/ETHNIC DISPARITIES IN HEPATOCELLULAR CARCINOMA CARE DELIVERY

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Introduction: Hepatocellular carcinoma (HCC) has the highest mortality rates among racial/ethnic minorities and those of low socioeconomic status. Some studies hypothesize this difference is due to biologic differences in tumor behavior, while others have highlighted socio-demographic inequalities across the HCC care continuum as a potential etiology. The aim of our study was to compare HCC presentation and management between Caucasian and non-Caucasian patients in the United States.

Methods: We identified patients diagnosed with HCC between June 1, 2012 and May 31, 2013 at four centers in the United States. Demographic, laboratory, and clinical data were abstracted at each site using standardized forms. Wilcoxon rank-sum and Chi-square analysis was used to compare continuous and categorical variables, respectively, between Caucasian and non-Caucasian patients. HCC staging was determined by the Barcelona Clinic Liver Cancer (BCLC) system, with early stage defined as BCLC stage A. Curative treatments included liver transplant, resection, or local ablation. Survival was determined by Kaplan-Meier analysis and Cox regression was performed to identify associated factors. Statistical significance was defined as p<0.05.

Results: We identified 380 HCC patients, with median age 59.8 years and 75% male. Our cohort was racially diverse with 53% Caucasians, 20% Blacks, and 20% Hispanics. Caucasian patients were significantly younger (mean 63 ± 55, p<0.001) and less likely to have hepatitis C infection (52% vs. 62%, p=0.04) than non-Caucasians. Caucasians were more likely to have ascites (45% vs. 34%, p=0.03); however, there were no differences in hepatic encephalopathy (p=0.21) or Child-Pugh (p=0.13). Although Caucasians were more likely to receive Hepatology care prior to HCC diagnosis (51% vs. 28%, p<0.001), there was no difference in the proportion of HCC detected by surveillance (p=0.87). Similarly, the number of HCC nodules (p=0.47), maximum diameter (p=0.19), and presence of metastatic disease (p=0.39) were similar between Caucasians and non-Caucasians. Despite no difference in BCLC tumor stage at presentation (p=0.13), Caucasians were more likely to receive care at a transplant center (82% vs. 28%, p<0.001) and undergo curative treatments (25% vs. 14%, p=0.01). Caucasians also had shorter time from diagnosis to treatment (p=0.04), with therapeutic delays >3 months in 56% of Caucasians compared to 68% of non-Caucasians. Caucasians had longer survival than non-Caucasians, although this did not reach statistical significance (median 11.5 vs. 7.8 months, p=0.28).

Conclusion: Non-Caucasian patients experience lower rates of curative treatment and higher rates of therapeutic delays despite similar HCC stage at presentation, resulting in worse survival. These process failures represent targets for interventions that can reduce racial/ethnic disparities in HCC outcomes.

Disclosure of Interest: None Declared

P-125 ACCURACY OF SQAMOUS CELL CARCINOMA ANTIGEN- IMMUNOGLOBULIN M COMPLEXES IN THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

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Introduction: Early detection of hepatocellular carcinoma (HCC), one of the most common and deadly tumors worldwide, is still difficult due to the lack of adequate biomarkers that show high sensitivity and specificity. The serum squamous cell carcinoma antigen complexed with IgM (SCCA-IgM) has been reported as a promising serological marker for hepatocellular carcinoma (HCC). The aim of this study was to assess the diagnostic accuracy of serum SERPINE3 (SCCA-IgM) in different stages of liver disease, including HCC.

Methods: Cross-sectional study of three groups of patients with liver disease: chronic hepatitis (Group 1), liver cirrhosis (Group 2) and HCC (Group 3) and a control group (blood donors group 4). Serum SCCA-IgM immune complexes concentration were determined using ELISA kit (Lexma-IgM, Xeptagen, Italy). Descriptive statistics, uni and multivariate analysis, logistic regression and ROC curves analysis were performed using IBM SPSS Statistics 20 p with p < 0.05 deemed to be statistically significant.

Results: In this study were included 50 males and 26 females with a median age of 56 years (QR: 47 - 63), with the following distribution: 19 patients with chronic hepatitis in group 1; 20 cirrhotic patients in group 2; 18 patients with HCC in group 3; 19 blood donors in group 4. In group 4 the SCCA-IgM levels were lower levels compared to individuals with liver disease (p = 0.002). There were no statistically significant differences across groups with liver disease (median SCCA-IgM levels: 61 ± 41 vs. 83 Al/mL, group 1, 2, and 3, respectively, p > 0.05). The SCCA-IgM levels showed good predictive utility for the diagnosis of HCC with AUCROC of 0.71 (p = 0.008). The cut-off of 38 Al/mL presented a sensitivity of 69%, specificity of 57%, positive predictive value of 38%, and negative predictive value of 94%, in predicting HCC.

Conclusion: SCCA-IgM is a sensitive marker in HCC patients with cirrhosis even though lacking in specificity. This study demonstrates that SCCA-IgM can increase the diagnostic sensitivity of HCC and may be useful to identify individuals at increased risk.


Disclosure of Interest: None Declared

P-126 MIXED HEPATO-CHOLANGIOCELLULAR CARCINOMA: A DISTINCT ENTITY OF PRIMARY LIVER CANCER

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Introduction: Mixed hepatoc-choolangiocellular carcinoma (HCC-CC) accounts for up to 5% of primary liver cancer (PLC). Currently HCC-CC is thought to be a unique entity which deserves comprehensive distinction. Still a number of clinical and pathological issues are unaddressed for a more comprehensive understanding of this tumor.

Methods: We reviewed all PLC surgically resected at Humanitas Cancer Center since 1996 and we identified 32 cases satisfying the criteria for the diagnosis of mixed HCC-CC morphology (i.e. primary liver malignancy showing not separate or collision areas of glandular and hepatocellular differentiation).

Conclusion: Non-Caucasian patients experience lower rates of curative treatment and higher rates of therapeutic delays despite similar HCC stage at presentation, resulting in worse survival. These process failures represent targets for interventions that can reduce racial/ethnic disparities in HCC outcomes.
The following tumoral features were quantified on H&E staining: classical HCC and CC areas, stem-like cells (small epithelial malignant cells with a high N:C ratio), cholangiolocarcinoma component (malignant ducts with anti-keratin pattern). The diagnosis was further supplemented by immunohistochemical markers of hepatocellular (Hepar1, anginase, CD10, pCEA), cholangiocellular (CK7, CK19) and stem cells (NGCAM, c-kit) origin.

The radiological features of each case were also reviewed in 22 cases, and reported typical/probable HCC or CC. Follow-up and clinical information were also available in 29 patients.

Results: Patients were mostly men (2:1) with a mean age of 71 years (range 48-85) and a severe Republic Of Korean population. and hepatocellular carcinoma (HCC) have not been studied, yet. In this study, we investigated these tumors while classical morphology plays a major role. The significance of stem-like cells and intermediate behavior between HCC and CC. Imaging is still limited in the correct identification of these tumors. Stem-like cells (small epithelial malignant cells with a high N:C ratio), cholangiolocarcinoma component was seen in 5 cases (15%). Immunomarkers were used to confirm a hepatoc/choangi- cellular differentiation.

The outcome of mixed HCC-CC was compared to that of the whole series of surgically removed classical HCC (>25%) and CC (60%) seen at our Institution during the same period and expressed as overall survival (OS) and disease free survival (DFS). The DFS of mixed HCC-CC was in between that of HCC and CC and significantly different from HCC (p: 0.002) and CC (p:<0.001). The OS of mixed HCC-CC showed a similar behavior but it was not statistically different from HCC and CC. The presence of stem cell or cholangiolocarcinoma features did not have any clinical impact on OS and DFS.

Conclusion: This study supports the notion that mixed HCC-CC is a peculiar entity with an intermediate behavior between HCC and CC. Imaging is still limited in the correct identification of these tumors while classical morphology plays a major role. The significance of stem-like cells and cholangiocellular components need to be addressed in larger series.

Disclosure of Interest: None Declared

P-128 ROLES OF SS18L1 POLYMORPHISMS IN PREDICTING PROGNOSIS OF HEPATOCELLULAR CARCINOMA IN PATIENTS

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Introduction: Recently, many studies have been performed to analyze single nucleotide polymorphisms (SNPs) as a genetic marker of HCC. Syntial sarcoma translocation gene on chromosome 18-like 1 (SS18L1), a calcium-responsive transactivator has been found to be associated with cancer development and progression. However, the relationships between SS18L1 and hepatocellular carcinoma (HCC) have not been studied, yet. In this study, we investigated whether single nucleotide polymorphisms (SNPs) of SS18L1 gene are associated with HCC in a Korean population.

Methods: We genotyped four SNPs (rs6142970, rs60061450, rs6142969 and rs2295207) using direct sequencing in 189 HCC patients and 194 controls. Clinicians were fulfilled detailed clinical features such as cancer size, stage of cancer and radiologic morphology. To analyze the genetic data, SNPAnalyzer and SNstats were used. Multiple logistic regression models (codominant, dominant, recessive and log-additive) were performed for odds ratio, 95% confidence interval, and p value. Age and gender as covariates were adjusted to obtain statistical significance.

Results: No SNPs of the SS18L1 gene were found to be associated with the risk of HCC development. Next, the relationships between SS18L1 SNPs and the clinical characteristics of HCC were investigated. rs6142970 was associated with tumor size, significantly (p: 0.034). Also, rs60061450 and rs6142969 were associated with HCC stage and tumor size. rs2295207 was associated with serum AFP level, significantly (p:0.042).

Conclusion: In conclusion, we found that SS18L1 may have a significant role in predicting the prognosis of HCC. This is the first study to demonstrate that SS18L1 polymorphisms may be associated with susceptibility to HCC in the Korean population. Further studies in different populations or other SNPs of SS18L1 will be needed.

Disclosure of Interest: None Declared

P-129 EVALUATION FOR CANCER SPREAD VIA PORTAL SYSTEM OF HEPATOCELLULAR CARCINOMA BY 3-DIMENSIONAL CT MAPPING

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Introduction: It is well established that intrahepatic metastasis (im) can spread by microvascular invasion of portal vein (vp) in hepatocellular carcinoma (HCC), therefore anatomic resection based on portal territory may be preferred in terms of curability. To assess the tumor spreading is theoretically. Several reports documented that im/vps associated with recurrence after resection of HCC repeatedly, the spread pattern and extent of histological im and vp im/vp is not fully clarified. To evaluate the optimal resection extent for HCC, we assessed the distribution of histological im/vps visually by 3-dimensional computed tomography (3D-CT) mapping.

Methods: We analyzed prospectively 66 patients who performed hepatic resection for HCC during January to September 2015 in our institution. The object of this study was primary-single HCC, less than 50mm in tumor size, with adequate extent of anatomical resection, without preoperative treatment. Anatomical resection was defined as resection including the 1st-, 2nd- and 3rd-order portal venous territory.

1. In selected cases out of 66 patients according to criteria, histological im/vps were inspected in whole resected 5mm thick sliced specimens, and projected to preoperative 3D-CT. We evaluated the interrelation between im/vps and portal segments visually.

2. We counted the all im/vps, subsequently measured the distance of im/vps from the tumor margin to assess the extent of tumor spreading.

Results: Of the 66 patients who underwent hepatic resection for HCC, 36 cases met the entry criteria. Excluded 17 cases for recurrent, 6 cases for multiple, 3 cases for tumor size, 3 cases for preoperative treatment, 1 case for inadequate margin) Of these 36 cases, 17 cases performed anatomical resection. 10 cases of seventeen have no evidence of im/vp histologically. Finally, 7 cases out of 66 patients (11%), that is, anatomical resected primary-single HCC cases with histological im/vps less than 50mm in tumor size were examined. Tumor sizes were less than 30mm in 4 cases (Group-B), and 31- 50mm in 3 cases (Group-B).

1. All histological im/vps were located in only portaluromal area regardless of portal branches in Group A, whereas several histological im/vps were seemed to spread via portal 3rd order branches, which served as drainage vessel, visually in Group B.

2. Altogether, 225 im/vps were identified in this series. The total numbers of histological im/vps in Group B were seen more frequently than in Group A (161; Group B vs 64; Group A). In Group A, all histological im/vps were localized within 1cm from tumor margin. Among 3 cases in Group B, 2 cases showed that several histological im/vps were scattered over 2cm from tumor margin.

Conclusion: 3D mapping revealed that histological im/vps were extensively extended along portal branches in several HCC>30mm cases. Anatomical resection with adequate surgical extent based portal territory may be preferred in terms of curability. To assess the tumor spreading is useful to predict the optimal resection extent for HCC.

Disclosure of Interest: None Declared

Posters

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P-130 LONG NON-CODING RNA00364 REPRESSIONS PROLIFERATION VIA P-STAT3-ITF2 AXIS IN HEPATOCELLULAR CARCINOMA

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Introduction: It has long been known that the effects of interferon are extensively investigated in HCC, but the mechanism of roles of long non-coding RNAs involving interferon are still not completely understood in HCC.

Methods: LncRNA00364 was identified by microarray and validated by realtime PCR. The mRNA level of LncRNA00364 was performed by realtime PCR assay in 27 paired HCC samples. The LncRNA00364 expression was manipulated in HepG2 and LM3 cells using siRNA and overexpression plasmids and performed assays for cell viability, cell cycle and apoptosis. Western blot, RIP assays were conducted to evaluate the interaction between LncRNA00364 and STAT3.

Results: We identified IFNβ-induced upregulated LncRNA, LncRNA00364, in hepatocellular carcinoma. We found that LncRNA00364 was downregulated in HCC and promoted apoptosis of HCC cell in culture, whereas overexpression of LncRNA00364 dramatically inhibited cell proliferation (P<0.05). LncRNA00364 specifically binded the STAT3, which resulted in inhibition of STAT3 phosphorylation and upregulated expression of IFIT2. Phosphorylation of STAT3 was obviously enhanced in Si-LncRNA00364 cells and decreased in Ce-LncRNA00364 cells, but phosphorylation of STAT1 and AKT was not apparently changed. Depilation or overexpression of LncRNA00364 did not show any apparent effect on the expression of OAS1 and ISG15. Clinically, the level of LncRNA00364 in HCC specimens was positively correlated with RT2 (P<0.05).

Conclusion: These findings suggest that upregulated LncRNA00364 induced by IFNβ could inhibit cell proliferation and promote apoptosis by blocking phosphorylated STAT3. Consequently, it exhibits exciting anticancer effects and provides new insights into a possible therapeutic target.

Disclosure of Interest: None Declared

P-131 KINETICS OF THERAPEUTIC EFFICACY AND PROGNOSTIC VALUE OF PIVKA-II IN A FRENCH COHORT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC)

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Disclosure of Interest: None Declared

P-132 PRONOSTIC IMPACT OF HEPATITIS B VIRUS INFECTION IN PATIENTS WITH INTRAHEPATIC CHOLAGIOCARCINOMA

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Disclosure of Interest: None Declared

P-133 SOMATIC GENETIC ALTERATIONS IN HEPATOCELLULAR CARCINOMA FROM EGYPTIAN PATIENTS

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Disclosure of Interest: None Declared
frequency. Our findings suggest a low contribution of aflatoxin B1 in the etiology of HCC in this cohort. Future studies, including correlation of these defined genetic alterations with prognosis and response to therapies will be needed.

Disclosure of Interest: None Declared

P-134 PHASE II TRIAL OF NEO-ADJUVANT OXALIPLATIN/ADRIAMYCIN/5-FU/INTERFERON A-2B (OXAFA) COMBINATION IN LIVER-LIMITED UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: Surgical resection offers potential cure in patients (pts) with HCC. The PAE regimen was active in HCC but its use was limited by toxicity. The OXAFI regimen was a modification to improve its tolerability. We previously published the feasibility of OXAFI in advanced HCC. We now evaluate OXAFI as neo-adjuvant conversion therapy in a single centre, open label study.

Methods: Previously untreated pts with histologically proven, liver-limited HCC deemed unresectable by a multidisciplinary team, adequate organ function, AST and ALT ≤ 5X ULN, bilirubin ≤ 50μmol/L, albumin > 30g/l, were eligible. I oxaliplatin (80mg/m2) and adriamycin (25mg/m2) on days 1, 8 and 15 in a 28-day cycle, continuous 5-FU (200mg/m2) and s.c interferon 5 MU 3x/wk were given up to 8 cycles. Evaluations was repeated every 2 cycles by CT and surgery was performed if curative resection was feasible. The primary end point was response rate by RECIST 1.0. Secondary end points were progression free survival (PFS), overall survival (OS), resection rate and toxicities graded by CTCAE 3.0.

Results: 12 pts of median age 55yrs (range 35 to 67) were recruited. 8 pts were Hep B carriers and 7 took lamivudine; 1 patient had Hep C; Child-Pugh status was AVB in 2/2 pts. The median cycles of treatment was 2 (range 1 to 4). Median relative dose intensity for oxaliplatin, adriamycin, 5-FU and interferon was 69%/67%/95%/92% respectively. 5 pts required dose reduction and all pts required a dose delay or interruption for at least one drug. 3 pts (25%) had a partial response after 2 cycles, of which 2 underwent R0 resection. 5 pts had stable disease and 3 had progressive disease. With a median follow-up of 7.7 mo to early study closure from poor accrual, median PFS and OS was 9.1m and 11.7m respectively. Observed Grade 3/4 adverse events were non-febrile neutropenia (58%), mucositis (17%), depression (8%), varicale bleed (8%) and infection (6%), 1 possible Hep B flare resolved with lamivudine.

Conclusion: OXAFI has activity in liver-limited HCC and conversion to resectability is achievable in selected patients. Toxicities were manageable with appropriate dose modification. The study was supported by National Medical Research Council 5SG ClinicalTrials.gov Identifier: NCT00471484

Disclosure of Interest: None Declared

P-135 TRANS-ARTERIAL ADMINISTRATION RESULTS IN LOWER DELIVERY OF PARTICLES TO PORTAL TUMOR THROMBUS RELATIVE TO INTRA-HEPATIC HCC TUMOR

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Introduction: Patients with Hepatocellular Carcinoma (HCC) with portal vein tumor thrombus (PVTT) are often treated with Yttrium-90 radioembolization (Y-90). However, despite response to therapy seen in the intra-hepatic portion of the HCC, the PVTT often displays progression. We sought to discover a potential mechanism for this phenomenon by studying the relative delivery of arterially administered Technicium-99 labeled micro-aggregated albumin (MAA) using single photon emission CT (SPECT) scans performed as routine mapping prior to Y-90.

Methods: From 10/2013 – 1/2016, all patients with HCC with PVTT in the main portal vein or 1st/2nd order branches underwent MAA scan prior to Y-90. Particles (10-150 microns) were injected into the branches of the hepatic artery supplying the tumor. SPECT scan was performed within 90 minutes after injection. Relative counts were measured over the PVTT. Relative counts were measured over three separate points on the main intra-hepatic HCC and an average calculated. A ratio of PVTT/ intra-hepatic HCC counts was calculated for each patient. Paired T-test was used to determine significance of differences in uptake between PVTT and intra-hepatic HCC in each patient.

Results: During the study, 11 patients meeting the inclusion criteria were enrolled. Patient and tumor characteristics are provided in Table 1. The mean ratio of uptake PVTT/HCC was 0.418 (range 0.052-0.702). In no case was uptake higher in PVTT compared to intra-hepatic HCC. Paired T-test revealed significantly lower relative counts in PVTT compared to the main intra-hepatic HCC (p<0.16).

Table 1

<table>
<thead>
<tr>
<th>Range</th>
<th>Mean</th>
<th>Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56-96</td>
<td>65</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>4.1-15.0</td>
<td>8.7</td>
</tr>
<tr>
<td>AFP (ng/ml)</td>
<td>3.4-4,285</td>
<td>1,112</td>
</tr>
<tr>
<td>Counts intra-hepatic HCC</td>
<td>2,692-61,957</td>
<td>11,656</td>
</tr>
<tr>
<td>Counts PVTT</td>
<td>201-39,934</td>
<td>6,482</td>
</tr>
<tr>
<td>Ratio PVTT/intra-hepatic HVV</td>
<td>0.05-0.70</td>
<td>0.41</td>
</tr>
<tr>
<td>Extent of PVTT</td>
<td>Main PV n=3</td>
<td>1st order n=5</td>
</tr>
</tbody>
</table>

Conclusion: Trans-arterial delivery of radio-labeled particles to HCC with PVTT seems to result in significantly lower delivery to the PVTT. On average, the PVTT receives less than half, and in some cases as little as 5%, of the radiation dose relative to the intra-hepatic HCC. This may explain the relative resistance of the PVTT portion of these tumors to Y-90 and argues for treatment of the intra-vascular portion of these tumors with higher doses of Y-90 or in combination with external beam radiation.

Disclosure of Interest: None Declared

P-136 DPP4 INHIBITION REVEALS EOSINOPHIL-MEDIATED TUMOR IMMUNITY IN A MODEL OF HEPATOCELLULAR CARCINOMA

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Introduction: Dipeptidylpeptidase 4 (DPP4) compromises leucocyte trafficking by cleaving and therefore inhibiting several chemokines including the alpha-chemokine CXCL10, which mediates lymphocyte migration towards inflamed tissues (1). DPP4 inhibitors have been shown to improve tumor immunity by preserving agonist forms of CXCL10, in turn enhancing the migration of CXCR3-expressing T cells into the tumor parenchyma (2).

Methods: In an effort to extend our initial findings, we developed a mouse model of hepatocellular carcinoma where we injected one million of Hepa-1-6 cells in mice treated or not with a DPP4 inhibitor (Sitagliptin directly incorporated in food). Enzymatic assays and Elisa were used to characterize pharmacokinetic and pharmacodynamic biomarkers; analysis of cellular infiltration of tumors were performed using multiparametric cytometry; and experimental studies using blocking antibodies and mouse strains knocked out for relevant genes were used. Methodology and design for human clinical study can be found on http://clinicaltrials.gov (Study # NCT02650427)

Results: We discovered that DPP4 inhibition by sitagliptin delays growth of hepatocellular carcinoma (HCC), yet surprisingly it works via a unique mechanism. Notably, tumor immunity to Hepa-1-6 remained intact in sitagliptin-treated animals, even when CXCR3 blockade was utilized or in Rag2/-/- mice. Further analyses revealed increased trafficking of eosinophils into the tumors of mice treated with DPP4 inhibitors. Eosinophil-mediated tumor immunity was dependent on the chemokine CCL11 (eotaxin-1), interacting with its receptor CCR3. CCL11 possesses the consensual X-P-diplopetide motif and we confirmed its being a substrate for DPP4, and further demonstrated that treatment of mice with DPP4 inhibitors enhanced in vivo CCL11 recruitment of eosinophils. Our study provides new understanding for how eosinophils may contribute to tumor immunity when endogenous mechanisms of immune regulation are inhibited. These preclinical data allowed us to conduct a prospective phase Ib clinical study where patients with hepatocellular carcinoma awaiting surgery are treated with Sitagliptin. Inclusion of patients is ongoing, and preliminary results from the first two patients indicate CCR3 downregulation and eosinophil depletion from circulation, both suggestive of their migration from circulating blood towards parenchymal sites of infection. interim analysis of the patients receiving low dose Sitagliptin will be presented.
P-138  EVALUATION OF ACTH (ASSESSMENT FOR CONTINUOUS TREATMENT WITH HEPATIC ARTERIAL INFUSION CHEMOTHERAPY) SCORE IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Introduction: The prognosis of advanced hepatocellular carcinoma (HCC) remains poor. In advanced HCC patients who did not receive active therapy, the median survival time (MST) was 5.2 months in the nationwide survey of Primary Liver Cancer in Japan. For advanced HCC patients, sorafenib is recommended as standard of care. In contrast, hepatic arterial infusion chemotherapy (HAIC) is a treatment option in Asia. Recently, we developed the ACTH score to guide the decision for a continuous HAIC treatment. This score is first established in the therapeutic assessment of HCC patients receiving HAIC and consists of 3 simple parameters which have been used commonly; Child-Pugh score, alpha-fetoprotein (AFP), and des-gamma-carboxy prothrombin (DCP). Patients stratified into two groups according to this score showed significantly different prognoses (c1 vs. c2: MST, 15.1 vs. 8.7 months; p = 0.003). In this study, we aimed to evaluate the efficacy of the ACTH score in a validation cohort.

Methods: One-hundred and thirty-one advanced HCC patients with elevated baseline levels of AFP (>40 ng/mL) and/or elevated baseline levels of DCP (>200 mAU/mL) were enrolled in this study (90 patients in the training group and 41 in the validation group). Patients received HAIC using low dose cisplatin and 5-fluorouracil based regimen. This point score is calculated as follows: Child-Pugh score (A = 0, B = 1), AFP response (yes = 0, no = 1), and DCP response (yes = 0, no = 1), ranging from 0 to 3. AFP and DCP responses were assessed at 2 weeks after HAIC induction; a positive-response was defined as a reduction of ≥20% from baseline. We analyzed the treatment response and survival according to the ACTH score in the validation cohort compared with the training cohort.

Results: In the validation cohort, DCP response was significantly associated with treatment response (p = 0.002), and the MST was longer in patients with a score ≥2 (n = 20, 15.9 months) than in those with a score ≤1 (n = 21, 7.0 months, p = 0.010). In all patients, they were stratified according to this score; the MST with the ACTH score of 0 (n = 17), 1 (n = 50), 2 (n = 49), and 3 (n = 15) points was 21.7, 14.4, 9.5, and 3.8 months, respectively.

Conclusion: We showed the usefulness of the ACTH score in the validation cohort. The ACTH score can aid in the therapeutic assessment of HCC patients receiving HAIC. Furthermore, it may promote the efficiency in advanced HCC therapies.

Disclosure of Interest: None Declared

P-139  OBESITY AND THE RISK OF MORTALITY IN NEWLY-DIAGNOSED HEPATOCELLULAR CARCINOMA

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Introduction: The influence of body mass index (BMI) on the outcome of patients with hepatocellular carcinoma (HCC) is unclear, particularly in a hepatitis B virus endemic area. We investigated the influence of BMI on survival of newly-diagnosed HCC patients.

Methods: A total of 3,104 patients with HCC were analyzed. Patients were stratified into four BMI groups: underweight (<18.5 kg/m²), normal (18.5-22.9 kg/m²), overweight (23.0-24.9 kg/m²), and obese (≥ 25.0 kg/m²).

Results: The median survival was significantly different according to BMI: 2.3, 3.8, 4.2 and 5.2 years for the groups, underweight, normal, overweight and obese, respectively (p < 0.001). Compared to normal BMI group, the underweight group showed higher risk for mortality (Hazard ratio [HR], 95% confidence interval [CI]: 1.37, 1.04-1.82, p = 0.025), the overweight group showed marginal association with mortality (HR, 95% CI: 0.90, 0.80-1.01, p = 0.057), and the obese group showed lower risk for mortality (HR, 95% CI: 0.82, 0.73-0.91, p < 0.001). However, tumor stage and liver function were more favorable in overweight/obese patients than normal weight patients, while both were less favorable in underweight patients. In a multiple-regression model, there was no independent association between BMI and patient survival.

Conclusion: The survival of obese patients was longer than normal weight patients while it was shortest in underweight patients. However, the observed survival difference was mediated by multiple other clinical characteristics at presentation, and BMI did not independently influence overall survival of HCC patients.

Disclosure of Interest: None Declared

P-137  USEFULNESS OF ALBUMIN-BILIRUBIN GRADE FOR EVALUATION OF PROGNOSIS IN SURGICALLY TREATED HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma is commonly associated with chronic liver disease which is one of major prognostic factors that has been assessed with the Child-Pugh (C-P) grade. Recently, Albumin-bilirubin (ALBI) grade was introduced as a new, simple and objective system for assessing the liver function. The aim of this study is to evaluate the usefulness of ALBI grade in patients with surgically treated HCC, in comparison with C-P grade.

Methods: This retrospective cohort study reviewed 242 patients with surgically treated HCC at Jikei University Hospital between January 2000 and December 2014. The liver function of the patients assessed by C-P and ALBI grading systems were compared to clarify the utility of ALBI grade.

Results: For all patients, the median age was 64 years (29 – 90), Male : Female = 206 : 36. Type of resection was anatomical in 137 patients and partial in 105 patients. Median overall survival and disease-free survival was 971.5 days and 544 days, respectively. When applying the C-P grade, 227 patients were classified as C-P grade A and 15 patients in C-P grade B. The median overall survival (OS) and 5-year survival rates were 974.5 days and 74.8% for C-P grade A and 920 days and 40.0% for C-P grade B patients, respectively (p = 0.031). When ALBI scoring grade was used for assessing liver function, 113 patients were classified as ALBI grade 1 and 126 patients as ALBI grade 2. The median OS and 5-year survival rates were 1,113 days and 62.7% for ALBI grade 1 and 864 days and 62.4% for ALBI grade 2 patients, respectively (p = 0.031).

Conclusion: ALBI grading score was a simple, objective system which is useful for predicting prognosis of surgically treated HCC, compared with C-P grade which requires subjective variables such as ascites and encephalopathy.

Disclosure of Interest: None Declared

P-140 PREVALENCE AND CLINICAL OUTCOME OF HBSAG-NEGATIVE AND HBCRAG-POSITIVE HEPATOCELLULAR CARCINOMA TREATED WITH TRANSARTERIAL CHEMOEMBOLIZATION

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Introduction: Elevation of serum hepatitis B virus core-related antigen (HBcrAg), a new surrogate marker of intrahepatic covalently closed circular DNA (cccDNA), has been shown to be associated with the development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). Interestingly, the presence of HBcrAg levels is observed in a proportion of patients with CHB achieving HBsAg clearance. However, the prevalence and clinical characteristics of HCC patients with HBcrAg-negative but HBcrAg-positive have not been well defined.

Methods: A total of 196 consecutive Thai patients with HCC who had undergone transarterial chemoembolization (TACE) as initial treatment and had long-term follow up were included. The etiologies of underlying liver diseases were CHB (n=132), chronic hepatitis C (CHC with anti-HCV positivity, n=36) and alcoholic steatohepatitis (ASH)/non-alcoholic steatohepatitis (NAS) (n=28). Baseline HBsAg and HBcrAg levels were determined by chemiluminescence enzyme immunoassay, with the lower limit of detection levels of 0.05 IU/ml and 100 IU/ml, respectively.

Results: Serum HBsAg and HBcrAg levels were positive in 132 (67.3%) and 164 (83.7%), respectively. Among those with HBsAg negativity (64 patients), HBcrAg levels were detected in 32 (50%). Among the CHC and ASH/NASH groups, the positivity of HBcrAg was 11 (30.8%) and 21 (75.0%), respectively. HBcrAg levels were positively correlated with HBsAg (r=0.611, P<0.001) and HBV DNA (r=0.551, P<0.001), but were negatively correlated with patients’ age (r=-0.344, P<0.001). There were no difference in baseline clinical characteristics, tumor size, Child-Pugh score, BCLC tumor stage and overall survival between the HBsAg-positive group and HBsAg-negative/ HBcrAg-positive group. Similar results of patients’ parameters and survival were also found in the CHC group regarding the positivity of HBcrAg. Among the ASH/NASH group, patients with HBcrAg positivity tended to have a shorter overall survival than those without detectable HBsAg (11.5 vs 23.0 months), although there was no significant difference (P=0.088).

Conclusion: The prevalence of the HBsAg-negative/HBcrAg-positive marker was high among Thai patients with HCC, particularly those with underlying ASH/NASH. The existence of this serological profile might represent the so called ‘occult hepatitis B infection’ and could had an impact on the overall survival of patients undergoing TACE.


Disclosure of Interest: None Declared

P-141 COMBINATION OF TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION WITH SORAFENIB IMPROVED SURVIVAL THAN SORAFENIB ALONE IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA – A NATIONWIDE COHORT STUDY

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Introduction: Only early stage of hepatocellular carcinoma (HCC) could be treated by curative methods. Intermediate HCC patients are recommended to be treated with transcatheter arterial chemoembolization. However, tumor progressed to advanced stage with vascular invasion and/or distant site metastases despite treatment. Currently, Sorafenib is the only available target therapy to treat HCC when tumor progressed to advanced stage. Effect of combination therapy for HCC treatment in advanced stage is unknown. This study evaluated the effect of adding transcatheter arterial chemoembolization on HCC patients receiving sorafenib treatment.

Methods: Data from the National Health Insurance (NH) database cancer registry database and mortality database of The Collaboration Center of Health Information Application, Taiwan, were analyzed. We enrolled the HCC patients who were diagnosed between August 1, 2012 and December 31, 2014, and followed them to the December 31, 2015. The inclusion criteria were advanced HCC patients with liver cirrhosis Child-Fugh class A receiving sorafenib target therapy. The associated comorbidity and previous treatment of TACE were retrospectively reviewed for 5 years.

Results: Totally 4390 HCC patients who received sorafenib were enrolled. The median follow-up duration was 4.87 months. Among them, 3655 patients received sorafenib alone and the other 735 patients received TACE treatment after starting sorafenib, respectively. Advanced HCC patients who received combined sorafenib with TACE had longer survival than sorafenib alone (8.47months v.s. 4.12months). Frequency of TACE after sorafenib was correlated with the increase of survival.

Conclusion: For patient of advanced HCC with maintained liver reservation, TACE with combination of sorafenib usage prolongs the survival. Adjuvant therapy with TACE demonstrated therapeutic benefit in treating advanced HCC.


Disclosure of Interest: None Declared

P-142 PRETREATMENT RISK FACTORS, INCLUDING FIBROSIS STAGE, AND TIME TO DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (HCC) AFTER ERADICATION OF HEPATITIS C VIRUS WITH INTERFERON AND RIBAVIRIN.

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Introduction: There is a debate on whether surveillance for HCC should be performed in patients with liver fibrosis following a SVR (Sustained Virological Response) for hepatitis C.

The aim of the present study was to investigate a possible correlation between HCC development and the liver fibrosis pretreatment stage, age, alcohol consumption, and some laboratory parameters, in patients, successfully treated for chronic HCV infection.

Methods: The records of 357 (284M, 73F) consecutive patients that underwent successful treatment for chronic HCV infection with pegylated interferon α and ribavirin between the years 2004-2014 were reviewed. Age, sex, alcohol consumption, viral genotype and pre-treatment levels of viral load, platelets, γ-globulins, INR, HbAlc, AFP, CA 19-9 and also fibrosis stage were taken into account in the performed multivariate analysis. Patients were followed routinely every six months with liver ultrasound and AFP levels. The median follow up after SVR was 62 months (range 11-120).

Results: During the follow-up period 141 (13M, 3.92%) out of 357 patients developed HCC. The median period from SVR to HCC diagnosis was 35 months (range 21-139). Alcohol consumption (HR 7.3: 95% CI 3-15.9; P<0.0001), age ≥55 years (HR 3.3: 95% CI 1.5-6.4: P=0.009) and pretreatment fibrosis stage (HR 7.3: 95% CI 1.8-26; P<0.0001) were identified as independent and statistically significant factors for development of HCC after successful eradication of HCV.

Conclusion: Pretreatment advanced fibrosis stage, alcohol consumption and age can consider as significantly factors correlated with the development of HCC in non-viremic HCV patients prior treated with interferon a and ribavirin.

Disclosure of Interest: None Declared

P-144 ROBOT-ASSISTED LAPAROSCOPIC HEPATECTOMY FOR HEPATOCELLULAR CARCINOMA: THE HENRI-MONDOR EXPERIENCE

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Introduction: Laparoscopic hepatectomy remains technically challenging especially on cirrhosis. The recent introduction of robotic surgical systems has revolutionized the field of minimally invasive surgery in many different surgical specialties in regards to 3-dimensional images and better instrumentations.

Methods: Between July 2011 and November 2014, we performed 15 hepatic resections for hepatocellular carcinoma by robot-assisted laparoscopic approach (left lateral segmentectomy n=5, atypical resection segment 2 n=2, atypical resection segment 3 n=3, atypical resection segment...
4 n=1, atypical resection segment 5 n=1, atypical resection segment 6 n=3). Cirrhosis Child Pugh A was present in 14 patients and one patient had a normal liver parenchyma. A Da Vinci Robotic Surgical System (Intuitive Surgical, Mountain View, CA, USA) with three arms was used and two additional laparoscopic ports for the assistant surgeons were added. No Pringle maneuver was used. The dissection was carried out with the bipolar forceps and the Harmonic curved shears. In case of left lateral sectionectomy, the division of the vascular pedicles for segments 2 and 3 was performed with EndoGIA staplers. Prospectively collected data was analyzed retrospectively.

Results: Overall mean operative time was 170.1 ± 70.5 minutes (range: 60-290). Overall mean intraoperative blood loss was 208 ± 240 ml (range: 20-900). Two open conversions (13.3%) were needed due to bleeding. One patient (6.6%) had postoperative complications (biliary fistula treated conservatively). There was no mortality and no reoperations. Mean hospital stay was 5.6 ± 2 days (range: 3-10). All patients had RD resection with a mean margin of 13.3 ± 16 mm (range: 1-65 mm). Four patients had resection as a bridge to liver transplantation and were transplanted safely with minimal adhesions at the time of transplantation.

Conclusion: Robotic-assisted laparoscopic hepatectomy for hepatocellular carcinoma is feasible and safe. Further evaluation with clinical trials is required to assess for improvement in outcomes and to validate its real benefits. Long-term oncologic outcomes are still pending.

Disclosure of Interest: None Declared

P-145 MORBIDITY FOLLOWING HEPATECTOMY FOR HEPATOCELLULAR CARCINOMA: PREDICTORS AND IMPACT ON LONG TERM OUTCOMES

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Introduction: The impact of morbidity on long term outcomes following HCC resection remains controversial among existing series.

Methods: All consecutive HCC resected at a single center were included in analysis. Patients who experienced morbidity were compared to those without in terms of demographics, pathology, management, overall survival (OS) and disease free survival (DFS). Cox-regression models were developed for identifying prognostic factors. Independent predictors of morbidity were identified.

Results: Among 341 patients, overall morbidity rate was 34% (n=118) and grade III-IV morbidity rate was 14.4% (n=48). Morbidity was associated with OS and DFS in univariable analysis (Figure 1). Morbidity was an independent negative factor for OS (HR= 1.40, 95% CI 1.12-2.26, p=0.009) with BCLC stage, the need for combined procedure, intraoperative transfusion and the Metavir score of the underlying parenchyma. Similarly, morbidity was independently associated with DFS (HR= 1.59, 95% CI 1.18-2.15, p=0.002). Other independent predictors for DFS were the presence of portal hypertension, BCLC stage, the presence of satellite nodules. After population stratification by BCLC stage, the negative impact of morbidity on OS and DFS reached statistical significance in the BCLC stage A subset only (p=0.026 and p=0.001, respectively). Open resection, intraoperative transfusion and the existence of underlying fibrosis or cirrhosis were independent predictors of morbidity.

Image:

No morbidity 217 152 118 88 65
Morbidity 108 60 39 25 18

Conclusion: Morbidity should be considered as a prognostic factor especially for early HCC. Careful patient selection requiring underlying liver assessment and appropriate strategy such as mini-invasive surgery and restricted transfusion policy might be promoted to prevent morbidity.

Disclosure of Interest: None Declared

P-146 THE SHORT TERM AND LONG TERM OUTCOMES OF LAPAROSCOPIC HEPATECTOMY AND MICROWAVE ABLATION FOR SMALL HEPATOCELLULAR CARCINOMA: 5-YEARS EXPERIENCE OF A SINGLE CENTER

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Introduction: Laparoscopic hepatectomy (LH) and microwave ablation (MWA) are two widely used minimally invasive methods to treat hepatocellular carcinoma (HCC). However, few studies have compared their short- and long-term outcomes in small HCC. The aim of this study was to investigate their effectiveness when treating different location small HCCs.

Methods: The data were reviewed from 193 patients with HCCs measuring 3 cm or smaller (BCLC stage 0 or A) who received LH (n=133), or MWA (n=60) in our research center from 2005-2010. Short-term outcomes included intraoperative blood loss, operation time, and length of hospital stay. The disease-free survival and overall survival rates were analyzed as long-term outcomes. Subgroup analysis were used for different location tumors.

Results: The patients in the MWA groups showed better short-term outcomes compared with the LH group for the tumor located in the liver surface. There were no significant differences in overall survival rates among the two treatments. The LH group showed significantly lower recurrence rates than the MWA group (p=0.0146).

Conclusion: LH seems to be a better option for patients with a small HCC located in the deep liver parenchyma and left lateral lobe in experienced hands when compared with MWA for it can not only provide satisfied traumas but also can remove the tumor completely at the same time. The short-term outcome and overall survival rates of MWA is promising, although the high risk of local recurrence after the operation should be considered when planning treatment.

Disclosure of Interest: None Declared

P-147 TREATMENT OF RECURRENT HEPATOCELLULAR CARCINOMA: LAPAROSCOPIC SURGERY VERSUS RADIOFREQUENCY ABLATION IN A LARGE RETROSPECTIVE COMPARATIVE MULTICENTER STUDY USING PROPENSITY SCORE MATCHING

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Introduction: Treatment strategy for recurrent hepatocellular carcinoma (HCC) remains controversial. Radiofrequency ablation (RFA) has been widely adopted to treat recurrent HCC and the use of laparoscopic surgery (LS) is rising. The comparison of these two curative treatments for recurrent HCC is critical and has not yet been evaluated.

No morbidity 214 169 134 99 77
Morbidity 108 69 52 34 25
Methods: In this retrospective, multicenter study, 485 patients with small recurrent HCC in left lateral lobe or subcapsule of liver were treated either by LS (n=118) or by RFA (n=377). From 2007 to 2015. The long-term survivals were compared between these two groups via Kaplan Meier method before and after propensity score matching. Complications including morbidity and mortality were also evaluated.

Results: Before matching, the 1-, 3-, 5- year overall survivals after LS and RFA were 84.9%, 62.0%, 45.6% and 66.3%, 43.0%, 34.8% (p <0.001), the corresponding recurrence-free survivals were 76.8%, 41.5%, 33.2% and 55.5%, 26.5%, 26.5% (p =0.001). After matching, the 1-, 3-, 5- year overall survivals after LS (n=107) and RFA (n=107) were 83.7%, 63.3%, 46.3% and 57.6%, 35.9%, 33.5% (p <0.001), the corresponding recurrence-free survivals were 77.1%, 41.5%, 33.4% and 56.7%, 28.5%, 26.5% (p =0.003). No treatment-related death was observed in both groups. The morbidity after matching was 8.4% in the LS group and 11.2% in the RFA group, which had no statistical significance (p =0.649). Multivariate analyses showed that treatment allocation was the significant prognostic factors for overall survival (HR=0.592; 95% CI, 0.381-0.904; P=0.015) and recurrence-free survival (HR=0.668; 95% CI, 0.474-0.936; P=0.019).

Conclusion: Compared with RFA, LS may have advantages of oncological outcomes for small recurrent HCC in left lateral lobe or subcapsule of liver.


P-148 SAFETY AND EFFICACY OF ANTIVIRAL THERAPY IN CHRONIC HEPATITIS C PATIENTS WITH FOCAL HEPATIC LESION

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Introduction: Antiviral treatment for chronic hepatitis C (CHC) patients with focal hepatic lesion (FHL) is an important issue. We evaluated the safety and efficacy of the direct acting antiviral (DAA) regimens in CHC patients with FHL including well ablated HCC.

Methods: 32 adult patients (21 male,11 female) (21 Child-Pugh class A,11 class B) with CHC were treated using the available DAA regimens (Sofosbuvir+Ribavirin for 6 months in 12 patients, Sofosbuvir+Rebetivir+Daclatasvir for 16 patients, Sofosbuvir+Daclatasvir in 19 patients, Sofosbuvir+Simeprevir for 3 months in 2 patients and Sofosbuvir+Ledipasvir+Rebetivir for 3 months in 2 patients). 13 patients had prior HCC (HCC group) which was ablated by either TACE (11 patients) or RFA (2 patients). The other 19 patients (non HCC group) included patients with dysplastic nodules (12 patients), hepatic hemangiomas (5 patients) hepatic cyst (1 patient) and liver metastasis (1 patient). HCC was confirmed by real time (RT) PCR for HCV RNA. The presence and nature of FHL was confirmed by contrast enhanced abdominal CT/CE CT, MRI or both, according to EASL criteria. (1). The response to loco-regional therapy in HCC group was evaluated, before starting antiviral therapy, by CE CT, MR or both using the modified REGIST criteria (1). Hepatic functional reserve and degree of liver fibrosis were evaluated before and after antiviral therapy in all patients using Child-Pugh (CP) score, MELD score and APRI, FIB4 and fibrosis index (FI) respectively. Response to antiviral therapy was evaluated by RT PCR at the end of week 2 of antiviral treatment, end of treatment and 12 weeks post treatment (SVR12) (2). Serious adverse events including refractory ascites, hepatorenal syndrome, hepatic encephalopathy, GI bleeding and death were recorded. Recurrence of HCC (HCC group) or change of the nature of focal hepatic lesion (non HCC group) were evaluated by CE CT, MRI or both every 3 months (1).

Results: After 2 weeks of antiviral treatment, RT PCR was below detection limit (BDL) (12 IU/ml) in 97.1% of cases without significant difference between both groups (p=0.367). At the end of treatment, RT PCR was BDL in 95% of cases (19 of the 20 who reached the end of treatment date) without significant difference between both groups (p=0.257). The SVR 12 weeks RT PCR was BDL in 72.7% of the 11 who reached SVR12 evaluation date without significant difference between both groups (p=0.621). In both groups, there was significant improvement in APRI and FIB4 scores (p=0.005, 0.017 respectively). In HCC group, there was also significant improvement of FI (p=0.01). In both groups, there was no significant change in MELD or CP score. Varied bleeding occurred in one patient in each group, without significant difference between both groups. No death was recorded in both groups during follow up. No recurrence of HCC occurred during follow up in HCC group. Change of the nature of focal hepatic lesion from dysplastic nodule to HCC occurred in two cases (10.5% of non HCC group), both of them achieved on treatment response but failed to achieve SVR12.

Disclosure of Interest: None Declared

P-149 A STUDY OF PATIENTS DEVELOPING HEPATOCELULAR CARCINOMA DURING DIRECT-ACTING ANTIVIRALS (DAA S) FOR HEPATITIS C VIRUS

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Introduction: DAAs for the hepatitis C virus (HCV) is safe, effective with short term treatment, so may be used to treat patients with high risk for hepatocellular carcinoma (HCC), such as the elderly or with liver cirrhosis (LC), as well as with treated-HCC. In this study, we evaluated the factors influencing on hepatocarcinogenesis after DAAs treatment.

Methods: We evaluated 136 patients (median age: 72 years) who received DAA for HCV between October 1, 2014 and January 31, 2016 (daclatasvir/asunaprevir: 80 patients; sofosbuvir/ledipasvir: 32 patients, and sofosbuvir/ribavirin: 24 patients). Patients profiles were as follows: male/female: 65/71 cases; chronic hepatitis (CH)/LC: 42/54 cases; interferon treatment history yes/no: 20/116 cases; and HCC treatment history yes/no: 33/103 cases. Cumulative time to HCC onset after initiating oral drug treatment was evaluated with the Kaplan-Meier method, while multivariate analysis with Cox regression analysis was used to evaluate factors related to HCC. Differences between patients who developed HCC and those who did not were compared with the Mann-Whitney U test.

Results: Five patients (median age: 73 years) developed HCC. Patients profiles of the 5 patients were as follows: genotype 1/2: 4/1 cases; male/female: 3/2 cases; CH/LC: 3/2 cases; interferon treatment history yes/no: 1/4 cases; and HCC treatment history yes/no: 3 hepatocarcinoma: 1; RFA: 1; TACE: 1/2 cases. All 5 patients were SVR5 tested negative for HCV after 4 weeks. Time to HCC onset from initiation of DAA treatment was 4, 4, 8, 8, and 10 months, respectively. Multivariate analysis revealed no factors significantly related to hepatocarcinogenesis. The only significant difference between those patients who developed HCC and those who did not was AFP values prior to DAA treatment. Patients who developed HCC had higher AFP values: median AFP was 30.3 ng/mL for those with HCC and 6.1 ng/mL for those without, respectively.

Conclusion: Direct acting antiviral regimens are safe in chronic hepatitis C patients with focal hepatic lesions, including patients with well ablated HCC. The over all SVR12 is 72.7% without significant difference between HCC and non HCC group. There was significant improvement in fibrosis markers, especially APRI and FIB4 scores in both groups.

Disclosure of Interest: None Declared
P-150  ASSESSMENT OF THE TREATMENT MAINLY USING INTRAOPERATIVE MICROWAVE COAGULO-NECROTIC THERAPY (MCN) FOR BILOBULAR MULTIPLE HEPATOCELLULAR CARCINOMA

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Introduction: Embolization or chemotherapy is generally recommended for hepatic tumours (HTC) patients with 4 or more tumours. However, we consider intraoperative microwave coagulo-necrotic therapy (MCN) a useful treatment method with similar local management effects as hepatic resection (HR) and have aggressively used even for multiple bilobar HCC. Now we evaluated therapeutic results and report on the usefulness of this treatment.

Methods: Among a total of 2677 HCC patients treated surgically at our department from 1994 to 2014, 1182 patients were newly diagnosed with HCC. Among these, 174 patients with 4 or more HCC tumours in both lobes were included. Overall survival (OS), disease-free survival (DFS), liver function, and tumor features were evaluated. MCN was performed in 151 patients, HR+MCN in 21, and HR in 2.

Results: The mean age of the 174 patients included was 67.4 years and 77.6% had hepatitis C. The mean tumor diameter of the main nodule was 28.6 mm (11.3 - 130.0 mm). The 1-, 3-, 5-, and 10-year OS (%) of these patients were 95.9, 72.9, 44.7, and 22.0, respectively, and 1-, 3-, 5-, 10-year DFS (%) were 77.2, 62.6, 10.0, and 6.8, respectively.

Analyses based on the number of positive tumor markers showed no significant differences in OS and DFS (p = 0.2373 and p = 0.4631, respectively). In the evaluation of individual markers, compared with patients with PIVKA-II < 400 (129 patients), those with PIVKA-II ≥ 400 (25 patients) showed significantly less favorable DFS and a 3-year DFS of 0% (p < 0.001). The 3-year/5-year OS of patients with PIVKA-II ≥ 400 (35.2/17.6%) was significantly lower than those with PIVKA-II < 400 (78.3/49.4%) (p = 0.0002). In patients with PIVKA-II ≥ 400, the rate of recurrence was high and treatment after the recurrence was difficult: local treatment could only be performed again in 2 patients (9.5%) or by number of tumors (4 vs. 8 vs. 10 vs. > 10; p = 0.9638 and p = 0.6881, respectively).

Conclusion: MCN-based treatment strategies are useful in multiple HCC. Favorable liver function (CP-A) is necessary for long-term survival. Surgical treatment should be aggressively selected for patients with PIVKA-II < 400, while for patients with PIVKA-II ≥ 400, the frequency of recurrence is high and post-operative multimodal therapy is required.

Disclosure of Interest: None Declared

P-151  EFFECTS OF ENDOSCOPIC VARICEAL LIGATION FOR THE ESOPHAGEAL VARIX IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA AND PORTAL VEIN TUMOR THROMBOSIS

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Introduction: The outcomes of endoscopic varical ligature (EVL) treatment of esophageal varices in patients with hepatocellular carcinoma (HCC) and portal vein tumour thrombus (PVT) are unclear. We evaluated the short term (7-, 15-, 30-day) outcomes of emergency and prophylactic esophageal variceal band ligation (EVL) in HCC patients with PVT.

Methods: From 2010 to 2012, 424 sessions of EVL were conducted in 242 HCC patients with esophageal varices. Clinical findings and outcomes were reviewed retrospectively. We assessed the bleeding-free and overall survival, and related prognostic factors were analyzed using the Kaplan-Meier method and a Cox proportional hazard model.

Results: All EVL sessions were conducted in patients with liver function Child-Pugh class A (159 sessions, 37.5%), class B (220 sessions, 51.9%), class C (45 sessions, 10.6%), and in modified UICC stage III (138 sessions, 32.5%), stage IV (83 sessions, 21.9%). Ninety-three (21.9%) sessions were conducted in the state of complete remission of HCC. Total 172 sessions of EVL were conducted in patients with PVT; 115 (66.9%) sessions in patients with PVT at the main portal trunk (VP4) or first-order branch of the portal vein (VP3). Major PVT (VP4 or VP3) was predictive of esophageal varical bleeding hazard ratio 8.14, p < 0.0001. The 7-, 15-, 30-day bleeding-free survival rates of patients with major PVT were 91.2%, 75.0%, 56.9% and they are significantly lower than that of patients without PVT (98.0%, 95.6%, 92.0%, p < 0.0001, respectively).

Conclusion: After successful hemostasis with EVL, the bleeding-free survival rate was significantly lower in patients with major PVT in comparison to patients without major PVT. Non-invasive treatment may be first considered for esophageal varix in advanced HCC patients with main PVT.

Disclosure of Interest: None Declared


P-152  THE PROGNOSIS OF SECOND-LINE SORAFENIB TREATMENT AFTER TRANSARTERIAL CHEMOEMBOLIZATION COMPARED TO FIRST-LINE SORAFENIB TREATMENT IN ADVANCED STAGE HEPATOCELLULAR CARCINOMA.

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Introduction: Although international guidelines recommend sorafenib as a first-line treatment, still many Asian-Pacific centers perform transarterial chemoembolization (TACE) as the first treatment for advanced hepatocellular carcinoma (HCC). In this study, we aimed to evaluate whether the second-line sorafenib treatment after TACE treatment is inferior to first-line sorafenib treatment.

Methods: Consecutive patients treated with sorafenib for >4 weeks without TACE for advanced HCC at Seoul National University Hospital (Seoul, Korea) were included. Treatment response was analyzed according to modified Response Evaluation Criteria in Solid Tumors.

Results: Sorafenib was administered as a first-line treatment in 110 patients (70 were treated with sorafenib only, 40 treated with sorafenib followed by TACE; the sorafenib-first group) and a second-line therapy in 122 patients (the TACE-first group). Overall mean age was 61.2 ± 10.4, 84.5% were male. There were no significant differences of baseline characteristics including TNM classification and the presence and of portal vein thrombosis (PVT) in the first-line and the second-line groups, respectively. Objective response rates were comparable (0.11 vs 10.2%, P=0.66) between the sorafenib-first group and the TACE-first group, respectively. The time-to-progression (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.86–1.57; P=0.31), and the overall survival (HR, 0.81; 95% CI, 0.60–1.09; P=0.17) was not significantly different in the TACE-first group compared to the sorafenib-first group. After multivariate analysis, presence of ascites, infiltrative tumor morphology, and alpha-fetoprotein (AFP) > 200 ng/mL was related to overall survival. Subgroup analysis revealed that TACE first strategy was favored in age < 60 (HR, 0.51; 95% CI, 0.32–0.79; P<0.01), patients with PVT (HR, 0.56; 95% CI, 0.37–0.85; P<0.01), infiltrative tumor morphology (HR, 0.33; 95% CI, 0.17–0.67; P<0.01), bilobar tumor distribution (HR, 0.62; 95% CI, 0.39–0.99; P=0.04), and AFP > 200 ng/mL (HR, 0.55; 95% CI, 0.37–0.82; P<0.01).

Conclusion: For patients with advanced HCC, sorafenib treatment as a second-line treatment following TACE has comparable efficacy to a first-line sorafenib treatment with/without subsequent TACE with comparable tumor response and overall survival. And TACE first strategy was favored in age < 60, patients with PVT, infiltrative tumor morphology, bilobar tumor distribution, and AFP > 200 ng/mL.

Disclosure of Interest: None Declared
Introduction: Sorafenib remains the only approved molecular targeted agent for hepatocellular carcinoma (HCC); however, reliable biomarkers are still lacking. The aim of this study was to explore the predictive role of stemness-related markers for sorafenib response in patients with HCC.

Methods: Forty-seven patients with HCC who had available tumor samples before starting sorafenib treatment were enrolled. RNA was extracted from formalin-fixed, paraffin-embedded samples, and real-time PCR was used to quantify mRNA expression of EpCAM, CD133, CK8, CK24, CD248, CD90, CD133, SALL4, ALDH1A1, albumin, and alpha-fetoprotein.

Results: Of 47 patients, 3 had combined HCC and cholangiocarcinoma. The predominant etiology for HCC was hepatitis B virus (72.3%). Most patients had preserved liver function (Child-Pugh class A, 89%), and 14.9% and 74.5% had vascular invasion or extracapsular spread, respectively. No intrahepatic tumors were present in 34.0% of the patients. Patients with low CD133 expression tended to have longer progression-free survival (PFS) compared to those with high CD133 expression (5.5 months vs. 4.0 months, respectively; P=0.087), but this was not statistically significant. The expression of other markers was not associated with PFS. When combining two markers, patients with both low CD133 expression and low EpCAM expression demonstrated better PFS compared to those who did not (7.0 months vs. 4.2 months, respectively; P=0.037).

Conclusion: Among patients with HCC given sorafenib, dual expression with CD 133 and EpCAM in tissue had a negative correlation with better prognosis. Expression of stemness-related markers CD133 and EpCAM may provide new insights about biomarkers for sorafenib therapy.

Disclosure of Interest: None Declared

P-154 AN INTERNATIONAL OBSERVATIONAL STUDY TO ASSESS THE USE OF SORAFENIB AFTER TRANSARTERIAL CHEMOEMBOLIZATION (TACE) IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC): OPTIMIS INTERIM ANALYSIS

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Introduction: Transcatheter arterial embolization (TACE) is recommended for the treatment of patients with intermediate-stage HCC (BCLC stage B). However, several retrospective studies indicated continuation of TACE after TACE refractoriness/failure may be harmful to the patient.

Methods: OPTIMIS is a global observational study of patients who are treated with TACE followed by sorafenib or without sorafenib after TACE. The study enrolled ~1700 pts with HCC who are classified as BCLC stage B or higher and for whom a decision to treat with TACE is made at time of study entry. This interim analysis describing patient characteristics, TACE, suitability for TACE, and post-TACE liver dysfunction was performed when 1000 pts were observed for ~6 months. TACE suitability was defined and analyzed using definitions from recognized international guidelines.

Results: Of 998 eligible pts, 977 received TACE and were included in this analysis from the following regions: Europe/Canada n=327, Asia (excluding Japan/China) n=218, Japan n=173, and China n=138. The majority of the pts are Asian (68%). At baseline, 866 (70%) pts were BCLC B and 227(23%) were BCLC C. Additional patient characteristics are provided in the table. At time of the first TACE, the percentage of pts not indicated for TACE according to international guideline/consensus was high (43% overall, 62% China, 52% Asia, 39% Europe, 37% Korea, and 15% Japan). Conditions not indicated for TACE in greater than 10% of pts included the presence of ECOG PS >1 (20%), BCLC C (24%), Child-Pugh C (1%), and vascular invasion (11%). Prior to the first TACE, 59 (6%) pts already had extracapsular spread. Selectively of TACE location varied across regions; patients in China tended to receive broader TACE, while subsegmental/segmental TACE was more common in Korea/Japan. Mean time from first TACE treatment to initiation of other treatment was 178 days. The median interval between 1st and 2nd TACE varied by region and ranged from 49 days in China to 97 days in Japan. The median time to TACE unsuitable from first TACE according to the protocol definition was 120 days with the shortest time interval occurring in China. Detereoration of liver dysfunction parameters was observed after TACE (34% for first TACE, 51% for second TACE). At the cut-off, only 27% (267/977) of pts had received sorafenib.

Conclusion: These real-life data indicate TACE practice is very heterogeneous and different from international guidelines. The percentage of patients unsuitable for TACE at treatment start is high (more than half of patients), especially in China. Locations/selectivity of TACE varies across regions. It is important to evaluate outcomes of patients from various practices with TACE and other treatments.


P-155 THE HIGHLY SELECTIVE C-MET INHIBITOR TEPOTINIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA PREVIOUSLY TREATED WITH SORAFENIB: PHASE IB SAFETY AND EFFICACY

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Introduction: No systemic therapy is currently approved for patients (pts) with advanced hepatocellular carcinoma (HCC) after failure of sorafenib. HCC may express high levels of c-Met, a receptor tyrosine kinase that is implicated in tumor growth. The highly selective c-Met inhibitor tepotinib has shown activity as first-line treatment for patients with c-Met-positive HCC. Here, we report safety and efficacy data for patients with advanced HCC who had received first-line sorafenib and were enrolled into the phase Ib part of a phase Ib/Ii trial of second-line tepotinib (NCT02115373). All patients have completed a dose-limiting toxicity evaluation period.

Methods: Adult patients with confirmed HCC and Child-Pugh Class A liver function, ECOG PS 0-1, in whom sorafenib treatment (duration ≥4 weeks, treatment ceased ≥2 weeks before tepotinib...
Results: Seventeen patients were enrolled into the phase II part: four patients received tepotinib 300 mg/day, 13 patients 500 mg/day. The RP2D of tepotinib was confirmed as 500 mg/day. Fourteen patients had treatment-related treatment-emergent adverse events (TRAEs), with five having grade 3 events: two patients experienced peripheral edema, two patients acute kidney injury, and one patient lipase increase. One patient at each dose level discontinued treatment due to a TRAE not related to tepotinib (grade 3 blood bilirubin increase, grade 4 hepatic encephalopathy). The best overall response (BOR) was partial response (PR) in two patients; three patients had a BOR of stable disease (SD). Duration of response was up to 57 weeks (one response ongoing). In the two patients with BOR of PR, baseline serum alpha-fetoprotein (AFP) levels were 15,923 and 7.2 µg/L, respectively. In the patient with abnormally high baseline AFP levels, these had decreased by 90% by the beginning of cycle 2 and remained <3,000 µg/L until end of treatment; in the second patient, AFP levels decreased to 4.4 µg/L after one cycle of treatment and remained at this level. No pattern of change in AFP levels was apparent in the three patients with a BOR of SD.

Conclusion: The RP2D of tepotinib was confirmed as 500 mg/day in patients with advanced HCC who had received first-line sorafenib therapy. Activity was observed and was tolerable. The phase II part of this trial is investigating the efficacy and safety of tepotinib in 48 patients with sorafenib-pre-treated HCC who are required to have a C-Met-positive disease.


Conclusion: Adequate surveillance was performed in less than one third of newly diagnosed Korean HCC patients, in whom, 75% of HCC detected at early stage, which may improve survival of those patients. Comprehensive efforts to optimize the surveillance program for the target population should be urgently established.

Disclosure of Interest: None Declared

P-159 GLUTATHIONE SPECIES AND METABOLIC Prints IN SUBJECTS WITH LIVER DISEASE AS BIOLOGICAL MARKERS FOR THE DETECTION OF HEPATOCELLULAR CARCINOMA

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Introduction: The incidence of liver disease is increasing in USA. We have shown in animal models Glutathione species in plasma reflects liver glutathione state and it could be a surrogate for the detection of hepatic tumors. The present study aimed to translate methods to the human for exploring the role of glutathione species and metabolic prints in the progression of liver dysfunction and in the detection of HCC.

Methods: Treated plasma from healthy subjects (n=20), patients with ESLD (n=99) and patients after LTx (n=7) were analyzed by GC-MS or LC/MS-MS. Glutathione labelling profile was measured by isotope analyzer of H2O enriched plasma. Principal Component Analyses were used to determine metabolic prints.

Results: There was a significant difference in healthy controls fast vs fed in their glutathione levels and metabolic prints in the progression of liver dysfunction and in the detection of HCC.

Conclusion: Glutathione species and metabolic prints defined liver disease progression and serve as surrogate for the early detection of HCC in patients with established cirrhosis.

Disclosure of Interest: None Declared

P-160 GLUTATHIONE SPECIES AND METABOLIC Prints IN SUBJECTS WITH LIVER DISEASE AS BIOLOGICAL MARKERS FOR THE EARLY DETECTION OF HEPATOCELLULAR CARCINOMA

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Introduction: The incidence of liver disease in the Western is increasing mainly as a result of viral infections and obesity. We have showed in animal models Glutathione sp. in plasma reflects hepatic disease progression and serve as surrogate for the early detection of HCC in patients with established cirrhosis.
P-162 HEPATIC STEATOSIS MEASURED BY CONTROLLED ATTENUATION PARAMETER (CAP) USING FIBROSCAN® IS DIFFERENT ACCORDING TO THE PRESENCE OF HEPATOCELLULAR CARCINOMA AMONG PATIENTS WITH THE SAME DEGREE OF HEPATIC FIBROSIS

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Introduction: Progression of hepatic fibrosis to cirrhosis is one of the most important cause of hepatocellular carcinoma (HCC). However, prevalences of HCC are not consistent in among patients with the same degree of hepatic fibrosis. Intrahepatic steatosis has been considered another contributing factor to HCC. To clarify the effect of steatosis to the development of HCC, we attempted to compare degree of steatosis among patients with or without HCC whose stage of hepatic fibrosis were in same range.

Methods: We retrospectively reviewed controlled attenuation parameter (CAP) and liver stiffness (kHz) of patients with chronic hepatitis B and chronic hepatitis measured by Fibroscan®, who diagnosed as HCC between January 2013 and March 2016 at Pusan national university Yangsan hospital and compared parameters with sex- and stiffness (kHz)-matched control group.

Results: Of 74 patients with HCC, 60 were male and 14 were female. When we compared degree of steatosis in 60 male patients with 120 control group, mean value of CAP was significantly lower in HCC group. We divided patients in two groups according to the presence of hepatic steatosis using cut-off value 230 dB/m of CAP, the number of patients with steatosis was significantly less prevalent in HCC group, according to comparitional analysis. However, results of above were not documented in female group.

Table: Degree of hepatic fibrosis and steatosis according to hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Age (mean ± 2SD)</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>59 ± 10</td>
<td>34 ± 9</td>
<td>30 ± 9</td>
<td>0.203</td>
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<table>
<thead>
<tr>
<th>Method</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>58 ± 11</td>
<td>59 ± 8</td>
<td>0.036</td>
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|x-Redox state and it could be a surrogate for the early detection of hepatic tumors. The present study aimed to translate methods to the human in order to explore the role of both glutathione sp and metabolic prints in the progression of liver dysfunction and in the early detection of HCC in patients with liver disease.

Methods: Treated plasma from healthy subjects (n=20), patients with diverse MELD score and end stage liver disease (n=99) and patients after liver transplantation (n=29) were analyzed by Gas or LC/MS/MS and identification of metabolites was performed using metabolic libraries. Glutathione sp. synthesis rate was calculated by isotope pattern analysis of 2H-labeled compounds. Parametric analytical tests were performed to compare groups and Principal Component Analyses (PCA) and Partial Least Square Discriminant Analysis (PLS-DA) were implemented.

Results: There was a significant difference in healthy controls fast vs fed in their glutathione (GSH, GS-SG, ratio and Da) and Tier 1 metabolite profile (p<0.05). There was a significant difference in glutathione sp and Tier 1, 2, and 3 of metabolic prints from patients with ESLD when compared to healthy subjects and patients after liver transplantation (p<0.05). Patients with ESLD and HCC(+) had a significant different oxi-redox status and metabolic profile when compared to patients with ESLD and HCC(-), to healthy subjects and to patients after liver transplantation (p<0.05). It was observed a significant different profile on patients with ESLD when stratified by MELD score or by etiology. Patients with ESLD had a significant decreased in GSH synthesis and increased GS-SG production when compared to healthy subjects and to patients after liver transplantation (p<0.05).

Conclusion: Glutathione sp and metabolic prints defined liver disease progression and served as surrogate for the early development of HCC in patients with established cirrhosis.

Disclosure of Interest: None Declared

P-164 USEFULNESS OF BASELINE CRP LEVEL FOR PREDICTING THE PROGNOSIS OF PATIENTS WHO UNDERWENT SURFARENIF AND TACE

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Introduction: The serum CRP level were considered as a surrogate marker of systemic inflammation. The aim of this study is to clarify the usefulness of serum CRP level to predict the prognosis of patients who administered sorafenib. Moreover we analyzed patients who underwent conventional TACE (cTACE) to clarify the clinical significance of baseline CRP levels for intermediate stage HCC.

Results: Degree of hepatic steatosis were different according to the presence of HCC among patients with the same stage of hepatic fibrosis, especially in male patients. It may be interpreted that hepatic fibrosis without contribution of steatosis is at higher risk for the development of HCC.

Disclosure of Interest: None Declared
Methods: One hundred and ninety-seven patients who were administered sorafenib and one hundred ninety-six patients who underwent TACE were retrospectively analyzed. Tumor burden was assessed by Up-to-7 (UTS) criteria. Baseline characteristics including CRP levels before sorafenib administration and 1st TACE were analyzed.

Results: Among patients who administered sorafenib, 26 were within UTS, and 111 were out of UTS. Serum CRP levels were higher in those within UTS than those out of UTS. Multivariate analysis revealed serum CRP was an independent factor for overall survival with UTS and serum AFP level. In patients out of UTS, those with baseline CRP level 1.0 mg/dl showed significantly shorter survival than those less than 1.0 mg/dl (MST 190 days vs. 350 days, p<0.0001). Among patients who underwent TACE, baseline median CRP level was 0.16 mg/dl and 11 patients showed CRP over 1.0 mg/dl. Sixty six patients were inside Up-to-7 criteria and 130 were outside the criteria. Among patients inside the criteria, the median time to Child-Pugh B exacerbation was longer (745 days) than those out of the criteria (612 days). Among patients outside the criteria, those with CRP level before TACE less than 1.0 mg/dl showed significantly longer duration to exacerbate to Child-Pugh B than those more than 1.0 mg/dl (median 630 days vs. 330 days).

Conclusion: Higher baseline CRP level was an independent prognostic factor for patients who administered sorafenib in addition to those who underwent TACE. Patients beyond UTS who underwent TACE time to exacerbation of Child-Pugh grade and GS was shorter than those within the criteria. Among patients beyond UTS, those with CRP level more than 1.0 mg/dl have higher risk of early declaration of liver function and should not miss the timing of shifting treatment modality other than TACE.

Disclosure of Interest: None Declared

P-165 THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR PORTAL VEIN TUMOR THROMBOSIS IN ADVANCED HEPATOCELLULAR CARCINOMA

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Introduction: We sought to evaluate the clinical outcomes of 3-dimensional conformal radiation therapy (3D-CRT) for portal vein tumor thrombosis (PVTT) with or without inferior vena cava tumor thrombosis in patients with advanced hepatocellular carcinoma.

Methods: We retrospectively analyzed data on 99 patients who received 3D-CRT for PVTT alone between June 2002 and December 2015. Response was evaluated following the Response Evaluation Criteria in Solid Tumors.

Results: Twenty one patients (21.2%) had age over 65 years and forty patients (40.4%) had Child-Pugh class B. The Eastern Cooperative Oncology Group performance status was 2 in 23 patients (23%). Forty eight patients (48.5%) had main or bilateral PVTT. The median irradiation dose was 46.5%. PVTT response was significantly associated with number of radiation fraction (p=0.044). Overall objective tumor response was significantly associated with number of radiation fraction (p=0.016). For the difference in overall survival were –0.067 ~ 0.229 years between RFA and SBRT. This study demonstrated that the expected overall survival for RFA and SBRT were nearly identical.

Conclusion: Intraoperative radiofrequency ablation (RFA) is one of the treatment options for hepatocellular carcinoma (HCC) patients with relatively poor liver function to undergo surgical resection or when percutaneous approach for RFA is not feasible due to the difficult location of the tumor. The aim of this study is to investigate the clinical outcomes of intraoperative RFA compared to surgical resection.

Methods: A total of 76 consecutive patients who received either intraoperative RFA (n=23) or surgical resection (n=53) with curative intent at the Incheon St Mary’s hospital from June 2012 to September 2015 were enrolled. Disease free survival and overall survival rates were analyzed.

Results: The median follow-up period was 20.1 months (range, 0.9-41.5). The mean baseline Model for End-Stage Liver Disease (MELD) score was higher in the RFA group compared to the resection group (11.5±4.7 vs. 7.8±3.5, p=0.001). The resection group consisted of larger tumors with the median diameter of 2.7cm (range, 1.1-16) compared to 2cm (range, 1-5) of the RFA group (p=0.002). However, there was no difference in the number of tumors and the tumor stage between the two groups. The disease free survival rates at 6 and 12 months were 81.6%, 74.8% in the RFA group and 92.2%, 86.2% in the resection group, respectively (p=0.256). The overall survival rates at one year were 91.3% in the RFA group and 94.3% in the resection group, respectively (p=0.635). In the RFA group, 5 patients (21.7%) received liver transplantation (LT) after median interval of 10.9 months (range, 9.2-26.4) since the intraoperative RFA.

Conclusion: The patients who received intraoperative RFA presented with relatively poor liver function but the disease free survival and overall survival rates were non-inferior compared to the patients who underwent resection. Therefore, intraoperative RFA may be considered as a useful option for patients ineligible to percutaneous RFA and surgical resection, or as a bridge therapy before liver transplantation.

Disclosure of Interest: None Declared

P-166 CLINICAL OUTCOMES OF INTRAOPERATIVE RADIOFREQUENCY ABLATION IN HEPATOCELLULAR CARCINOMA PATIENTS INELIGIBLE FOR PERCUTANEOUS RADIOFREQUENCY ABLATION OR SURGICAL RESECTION

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Introduction: No randomized trials have been reported for a comparison between radiofrequency ablation (RFA) versus stereotactic body radiotherapy (SBRT) for the treatment of patients with small hepatocellular carcinoma (HCC) less than 3 cm.

Methods: A Markov cohort model was developed to simulate a cohort of patients aged 60-65 years with small HCC who have undergone either RFA or SBRT and followed over a time horizon of their remaining life expectancy. Incision criteria as follows: (i) any solitary HCC ≤ 3 cm in diameter and no more than three tumor nodules; (ii) no intrahepatic metastasis; (iii) no portal/hepatic vein invasion; (iv) liver function equal or better than Child-Pugh Class B. Exclusion criteria were patients with decompensated liver cirrhosis and previous HCC treatment. Each arm was allocated with a hypothetical cohort of 10,000 patients. The primary endpoint was overall survival. The estimates of the variables were extracted from published articles after a systematic review.

Results: RFA was the preferred strategy in small HCC as the mean expected survival was 6.452 years and 6.371 years for RFA and SBRT group, respectively. One-way sensitivity analysis demonstrated that the probability of 1 year local recurrence with RFA was greater than 7.3% or probability of 1 year local recurrence with SBRT was less than 1.6%. In the second-order Monte Carlo simulation, the probability distributions of overall survival for the cohort in this study demonstrated that the expected overall survival for RFA and SBRT were nearly identical.

The 95% confidence intervals were 6.250-6.658 and 6.168-6.590 years for RFA and SBRT, respectively. The difference between RFA and SBRT was insignificant (p = 0.2384) as the 95% confidence intervals for the difference in overall survival were ~0.067 – 0.229 years between RFA and SBRT.

Image:
Survival Functions

Conclusion: SBRT was nearly identical to primary percutaneous RFA for the overall survival of compensated cirrhotic patients with small HCC less than 3 cm. This outcome would provide the baseline data to proceed randomized phase III study in the future.

Disclosure of Interest: None Declared

P-168 SURVIVAL RATES AND PROGNOSTIC FACTORS FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA AFTER TRANS-ARTERIAL CHEMOEMBOLIZATION

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Introduction: Transcatheter arterial chemoembolization (TACE) is recommended as palliative treatment for unresectable Hepatocellular carcinoma (HCC). In Pakistan most of the patients with HCC present at advance stage and when curative treatment could not be offered, TACE is a viable option for such patients. However, no data is available from Pakistan to assess the usefulness and outcome of TACE in local scenario. Aims: To estimate the survival of the patients with unresectable HCC treated with TACE and to analyze the prognostic factors affecting survival.

Methods: All patients diagnosed with unresectable HCC who underwent for TACE during 2000–2015 at The Aga Khan University Hospital, Karachi, Pakistan were reviewed. Information was collected regarding demographic characteristics, baseline laboratory parameters, tumor characteristics and staging, response to TACE and survival. Survival at 1, 3 and 5 years and the predictors for survival were estimated.

Results: TACE was performed in 599 patients with HCC. Mean age was 56.6±9.9 years and 74.1% were males. Hepatitis C was the most prevalent (67.1%) etiological factor. Mean Childs and MELD score was 6.6±1.3 and 9.9±2.7 respectively. Median AFP was 449.13 IU/ml. The average maximum tumor size was 5.54±3.4cm. Majority of the patients (51.6%) single lesion while paucifocal or infiltrative lesions were found in 2/3 of cases. Advanced HCC were found in 63.8% with FVT in 4.5% cases. A total of 664 sessions of TACE (range 1-7) were carried out. 323 (56.6%) patients received one, 24.2% received two sessions of TACE. After first session of TACE, 11.9% achieved complete response, while 23.2%, 9.7% and 27.4% had partial response, stable disease and progressive disease respectively. Median follow up was 7 months (range 1-168 months). The overall mean survival was 84.6±7.02 (CI 95%: 80.83-108.3). The cumulative 1-year, 2-year, 3-year and 5-year survival rates were 62%, 54%, 43% and 37% respectively. Overall survival was better for those who achieved complete or partial response after 1st session of TACE (figure 1). MELD score (Hazard ratio 1.1, 95% CI 1.02-1.2, P<0.01), male gender (HR 1.8, CI 1.1-3.1, P<0.01), lower albumin level (HR 2.57, CI 1.2-5.2), AFP>200IU/ml (HR 1.8; CI 1.17-3.1; P=0.01) and sessions of TACE (>1) hazard ratio 2.1 (95% CI 1.05-4.2, P=0.03) were the factors associated with a poor survival.

Image: Comparison of survival after first session of TACE

Conclusion: TACE was found useful and well tolerated palliative therapy for our patients with unresectable HCC. Additional treatment with TACE and serial multiple sessions of TACE could improve survival. However, higher MELD score, male gender, lower albumin level, AFP>200IU/ml were the factors associated with a poor survival.

References:

Disclosure of Interest: None Declared

P-169 PHASE 3 RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY OF RADIOFREQUENCY ABLATION +/- LYSO-THERMOSENSITIVE LIPOSOMAL DOXORUBICIN FOR UNRESECTABLE 3-CM HEPATOCELLULAR CARCINOMA (HCC) LESIONS- TRIALS IN PROGRESS

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Introduction: Radiofrequency ablation (RFA) can safely treat hepatocellular carcinoma (HCC) lesions up to 7cm maximum diameter (dmax), but recurrences are common when dmax is >3cm.2 Lysosome-thermosensitive liposomal doxorubicin (LTLD, ThermoDox®) consists of the heat-enhanced cytotoxic doxorubicin within a heat-activated liposome. When treated to >40ºC, LTLD produces a local doxilbubulin tumor concentration up to 25 times that of free (non- liposomal) doxilbubulin at the same doses.2 Preclinical studies suggest that LTLD greatly enhances efficacy when RFA dwell time is at least 45 minutes.3 Among 285 patients with a solitary 3-7cm HCC lesion who received ≥45 minutes RFA dwell time, the overall survival hazard ratio was 0.63 (95% CI 0.41-0.96, P=0.04). We hypothesize that LTLD and ≥45 minutes RFA will substantially prolong survival in 3-7cm dmax HCC.

Methods: We are now conducting the OPTIMA Study (NCT02112656), a 550-patient randomized controlled trial. All subjects will have a solitary HCC lesion 3-7cm dmax and be Child-Pugh A without vascular invasion or extrahepatic disease. All will receive ≥45 minutes RFA, half will also receive 50 mg/m2 LTLD and half a dummy infusion. Overall survival is the primary endpoint while progression-free survival and safety are secondary endpoints. Randomization and analysis will be stratified by dmax (<3cm versus >3-7cm) and by RFA approach (laparoscopic, open surgical, percutaneous). The OPTIMA Study is designed to detect with 80% power a hazard ratio for OS of 0.67 (33% risk reduction) in the LTLD arm compared with the control arm with an overall 1 sided type 1 error of 0.025. Two interim analyses, both for efficacy and futility, are planned for the study. The first is planned after 60% of the target events (118 deaths) and the second after 80% of the events (158 deaths) have occurred.

Results: Trial enrolment is in progress.

Conclusion: Primary analysis is scheduled for 2019 with interim analysis projected in 2018.


P-170  BRAF EXPRESSION IN HCV RELATED CIRRHOSIS AND HEPATOCELLULAR CARCINOMA AND IT’S ASSOCIATION WITH PROGNOSTIC ANATOMOPATHOLOGICAL FEATURES

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Disclosure of Interest: None Declared

Introduction: The multistep process of hepatocarcinogenesis initiated by different external stimuli lead to genetic changes in hepatocytes resulting in neoplasia. However, the mechanisms of malignant transformation seem to differ widely. A comprehensive understanding of carcinogenesis mechanisms is essential to develop new target treatments and develop prevention methods. The aim of this study is to analyze BRAF immunopositivity in HCV related cirrhosis and hepatocellular carcinoma (HCC) and to associate their expression with some prognostic pathological features.

Methods: 36 patients with HCV related cirrhosis and HCC that underwent liver transplantation at Clinical Hospital – UFMG and 25 normal livers from the Hospital necropsy archives. Tumors were classified according to: number and diameter of nodules, vascular invasion and differentiation grade. BRAF expression was determined by immunohistochemistry in tumor and their cirrhotic adjacent parenchyma and in normal livers.

Results: BRAF was strongly expressed in the cytoplasm of hepatocytes of 17.1% of the cirrhotic livers and in 62.9% of the HCC samples (p = 0.017, RR = 3.67). There was no significant association between BRAF score and tumor differentiation grade, number and size nor with micro vascular invasion. There was an association between high grade tumors and the presence of vascular invasion (p = 0.014, RR = 7.27).

Conclusion: This data suggests that BRAF may play an important role in HCC carcinogenesis. Larger studies are needed to validate these observations.


Disclosure of Interest: None Declared

P-171  SURGICAL MANAGEMENT WITH PREOPERATIVE TREATMENT IMPROVED OUTCOMES OF HEPATOCELLULAR CARCINOMA WITH INFERIOR VENA CAVA TUMOR THROMBUS

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Introduction: Hepatocellular carcinoma (HCC) with inferior vena cava tumor thrombus (IVCTT) is usually inoperable because of the high risk of local and distant recurrence. There are limited studies analyzing surgical indication and perioperative treatments, have yet to be established.

Methods: To evaluate our surgical management incorporating preoperative treatment for hepatocellular carcinoma (HCC) with IVCTT we retrospectively reviewed. Patients were divided into the early period (EP) group (1994-2002, 24 patients) and late period (LP) group (2003-2015, 14 patients) according to the introduction of preoperative treatment for massive IVCTT or extraphepatic metastasis. Overall survival (OS) and recurrence free survival (RFS) were compared between the 2 groups.

Results: The frequency of extrahepatic metastasis was significantly lower in LP group than EP group (7.1% vs. 23.7%, respectively, P = 0.0499). None of the EP patients and 9 of the LP patients (64.3%) received preoperative treatment (P < 0.001). Extrahepatic metastasis disappeared by preoperative treatment in 3 patients. Both OS and RFS significantly improved in LP group compared to EP group (5-year OS rates: 50.5% vs. 16.7%, respectively, P = 0.0077; 5-year RFS rates: 42.0% vs. 5.8%, respectively, P < 0.001). Multivariate analysis revealed that preoperative treatment (hazard ratio (HR): 0.24) and extraphepatic metastasis (HR: 2.58) were independent prognostic factors for OS.

Conclusion: Our current surgical management significantly improved the long-term outcomes of HCC with IVCTT. Preoperative treatment should be initially administered to the patients with massive IVCTT or extraphepatic metastasis for disease control and selection for surgical indication.

Disclosure of Interest: None Declared

P-172  THYMIDYLATE SYNTHASE (TS) AND EXCISION REPAIR CROSS-COMPLEMENTATION GROUP 1 (ERCC1) HAVE THE SAME GENE EXPRESSION PATTERN IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular Carcinoma (HCC) has not shown response to therapy using platinum compounds or anti - folate agents, suggesting the involvement of thymidylate synthase (TS) and excision repair cross - complementation group 1 (ERCC1) genes in drug resistance (1,2).

Methods: The study was performed on surgical samples from a series of 10 patients (7 males, 3 females) who consecutively underwent surgical resection for macroscopic BCLC A HCC, we investigated the gene expression of TS and ERCC 1. RNA was extracted from FFPE tissue performing a manual macro - dissection of the tumor area. Five - hundred of total mRNA were reverse transcribed to cDNA. Quantitative Real - Time PCR was performed in triplicate with 3 microsaters of c: DNA results: were normalized to 18S RNA and gene expression quantification was performed with ΔΔCT method. We used as a calibrator a pool of normal tissues including lung, liver and colon. The correlation between TS and ERCC 1 gene expression was analysed by the Spearman’s correlation test, using the R statistical software. The level of significance was set at P=0.05.

Results: Gene expression analysis was successfully performed on all the samples of for both TS and ERCC 1 with mean mRNA values of 194.39 and 247.68 units respectively. TS expression was significantly lower in HCC compared to normal liver tissue (P<0.05). There was no association between TS and ERCC1 expression (Pearson’s correlation coefficient r = 0.24, P = 0.39).

Conclusion: Our current surgical management significantly improved the long-term outcomes of HCC with IVCTT. Preoperative treatment should be initially administered to the patients with massive IVCTT or extraphepatic metastasis for disease control and selection for surgical indication.

Disclosure of Interest: None Declared

P-173  ANALYSIS OF ALTERATION OF N-GLYCAN AND INVASIVENESS ASSOCIATED WITH U-PA EXPRESSION IN HEPATOCELLULAR CARCINOMA CELL-LINES

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Disclosure of Interest: None Declared
Introduction: α-N-glycan modifies proteins and controls many cascades in biological body. Alterations of α-N-glycan profiles influence malignancy as invasiveness in patients with several cancers. We reported that there are specific alterations of α-N-glycan in the serum of patients with hepatocellular carcinoma using Glycoblotting Method. The specific alternations are independent risk factors of patient survival and disease-free survival each other, and correlate with invasiveness by analysis of clinicopathological factors. On the other hand, it is known that urokinase type plasminogen activator (u-PA) is an important factor of fibrinolysis which controls invasiveness of cancer cell. We investigated correlation of alternations of α-N-glycan and invasiveness in hepatocellular carcinoma cell-lines.

Methods: We used two hepatocellular carcinoma cell-lines, HLE as a high invasive cell-line and HepG2 as a low invasive cell-line. Expression of u-PA were analyzed by real-time qPCR and Western blotting method. Invasiveness was analyzed by Matrigel invasion assay. We knocked down u-PA in cell-line which had high u-PA expression by RNA interference (RNAi) technology, and knocked out u-PA with CRISPR/Cas9 system. We overexpressed u-PA in cell-line which had low u-PA expression by using Lentivirus vector, and also constructed a mutant strain of HepG2 which overexpressed u-PA deficient in α-N-glycans, replacing amino-acid residue of glycosylation site. Profiles of α-N-glycans in cell-lines were analyzed by Glycoblotting Method.

Results: Expression of u-PA was up-regulated in HLE and down-regulated in HepG2. Invasiveness decreased in HLE after u-PA knockdown, and increased in HepG2 after u-PA over-expression. However, invasiveness of a mutant strain of HepG2 was not increased. Eighty six α-N-glycans were identified in cell-lines by analysis with Glycoblotting Method. The concentrations of 11 α-N-glycans in HLE were higher than that of HepG2. The concentrations of 13 α-N-glycans in HLE decreased after knockdown of u-PA and down-regulation of invasiveness. The concentrations of 22 α-N-glycans in HepG2 increased after overexpression of u-PA and up-regulation of invasiveness. However, in a mutant strain of HepG2 which overexpressed u-PA deficient in α-N-glycans, invasiveness was not up-regulated. There were two common α-N-glycans (m/z = 1851 and 1892) which correlated with these changes of invasiveness.

Conclusion: It is suggested that two α-N-glycans (m/z = 1851 and 1892) play important roles in invasiveness controlled by u-PA.

Disclosure of Interest: None Declared

P-174 EFFECTS OF 5-FU OR CARCINOMA HEPG2 CELLS

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Introduction: We previously reported the therapeutic effects of combination of interferon alpha (IFNα)-2b and 5-fluorouracil (5-FU) in advanced hepatocellular carcinoma (HCC) with portal venous invasion.1 Since transforming growth factor (TGF)-β plays a critical role in cancer cell invasion and metastasis,2,3 we studied whether the regulation of TGFβ is involved in the superior efficacy of the combination therapy.

Methods: 1. Analysis of serum levels of TGFβ1 in advanced HCC patients. Fifty three HCC patients (Stage IV-A/B) were treated using subcutaneous administration of Peg-IFNα-2b (50-100 μg on day 1 of each week for 4 weeks) and intra-arterial infusion of 5-FU (250 mg/m2 for 5 hours on days 1-5 of each week for 4 weeks). Levels of TGFβ1 in serum before and after the therapy were determined (Quantikine Human LIF (TGF)-F1 ELISA kit, R&D Systems, Inc.). Statistical comparisons were performed using a paired T-test. 2. Analysis of protein expression and secretion of TGFβ1 from normal human hepatocytes, Hepatoma cells (HepG2 and Huh7) and AML-12 normal mouse hepatocytes cells were treated with 5-FU, IFNα-2b, and the combination of 5-FU and IFNα-2b, respectively, as indicated. The protein expression level of TGFβ1 in culture supernatant were also determined.

Results: 1. The levels of TGFβ1 in serum after the therapy significantly (p<0.01) decreased in comparison to that before the therapy. 2. 5-FU increased TGFβ1 protein expression and secretion levels of TGFβ1 in hepatoma cells but not in normal hepatocyte cells. The combination of 5-FU and IFNα-2b decreased either the protein expression or the secretion levels of TGFβ1 in HepG2 cells. However, it only decreased the secretion levels of TGFβ1 in Huh7 cells.

Conclusion: Our data suggested that the efficacy of the 5-FU/IFNα-2b combination therapy was related to the regulation of TGFβ1.

Key words: TGFβ, 5-FU, IFNα-2b, HCC, Hepatocytes.


Disclosure of Interest: None Declared

P-175 ANTICANCER EFFECTS OF CROCIN ON HEPG2 CELLS BY CYCLIN D1 DOWN-REGULATION AND P53 AND P21 UP-REGULATION

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Introduction: Hepatocellular carcinoma is one of the most common cancers worldwide and most current therapies are of limited efficacy. There are tendency to use natural products such as crocin as anticancer agents. Understanding the molecular mechanisms of cytotoxic effects of crocin may improve the current therapeutic strategies against liver cancer. The goal of this study was to investigate the effects of crocin on the growth of human hepatocellular carcinoma (HepG2) cells and understand possible mechanisms of its action.

Methods: Viability and colony formation ability of HepG2 cells were measured by MTT and soft agar assays, respectively, after crocin treatments. Expression of genes related to cell cycle such as cyclin D1, P53 and P21 were determined by quantitative real-time polymerase chain reaction (qRT-PCR).

Results: Our MTT data indicated a significant dose- and time-dependent inhibition of HepG2 cell proliferation following crocin administration. This treatment decreased colony formation of cancer cells up to 85%. Moreover, qRT-PCR analyses markedly revealed the suppression of cyclin D1 and the enhancement of P53 and P21 expression in treated cells.

Conclusion: These results suggest that crocin exerted a significant cytotoxic effect on liver cancer cells through alteration of the expression of the genes that are involved in regulation of cell cycle. So crocin may represent a novel therapeutic bioactive component for prevention and treatment of liver cancer.


Disclosure of Interest: None Declared

P-176 ANTITUMOR AND PROAPOTPTIC EFFECTS OF CROCIN COMBINED WITH HYPERTHERMIA ON HUMAN HEPATOCELLULAR CARCINOMA HEPG2 CELLS

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Introduction: Hepatocellular carcinoma is currently one of the most common worldwide causes of cancer death. Medicinal plants for instance saffron and its secondary metabolites play an important role in cancer prevention and treatment. We investigated the suppressive effects of crocin in combination with hyperthermia (HT) on proliferation of liver cancer cells by apoptosis induction.

Methods: Cell viability and apoptosis were assessed by MTT, Hoechst 33258 staining, and percentage of lactate dehydrogenase (LDH) release methods, respectively. The mRNA levels Hsp70, Hsp90, Bax, and Bcl-2 were measured by quantitative real-time polymerase chain reaction (qRT-PCR). Hsp70 and Hsp90 proteins were determined using enzyme-linked immunosorbent assay (ELISA) technique.

Results: Crocin (0-1 mg/ml) in combination with HT significantly inhibited the proliferation of cancer cells in a dose- and time-dependent manner. There was a degree of synergism in the combined treatment. Changed nuclear morphology and increased LDH (58%) indicated that crocin (0.5 mg/ml) combined with HT has a more apoptotic effect than crocin alone after 48h. Data of Hoechst staining indicated that HT increased the apoptotic impact of crocin in a dose-dependent manner (55% and 78% of apoptotic cells of total cells after 0.2 and 0.5 mg/mL crocin treatments, respectively). Furthermore, Bax/Bcl-2 ratio markedly increased (4 fold), whereas expression of heat-induced genes decreased after crocin-HT treatment. Also, the Hsp70 and Hsp90 proteins were decreased in survivors of treated cells.

Conclusion: Our results are providing insight into the molecular mechanisms underlying the combination of crocin and HT - induced apoptosis in the HepG2 cells, rendering it as the potential anticancer agent. These data suggest that crocin with HT may benefit human liver cancer treatment.


Disclosure of Interest: None Declared
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RAMUCIRUMAB AS SECOND-LEVEL TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA: ANALYSIS OF REACH PATIENTS BY ALBUMIN-BILIRUBIN (ALBI) GRADE AND CHILD-PUGH SCORE

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Introduction: The REACH trial evaluated ramucirumab (RAM) as a second-line therapy in patients with advanced hepatocellular carcinoma (HCC) following first-line sorafenib. There was no significant improvement in overall survival (OS) in patients with baseline albumin ≥400 mg/dL, with a median OS of 7.8 months for RAM vs 4.2 months for placebo (hazard ratio [HR] 0.67, 95% CI 0.51-0.90; p = 0.006). Albumin-bilirubin (ALBI) grade is based only on objective criteria, and has been previously tested as an alternative method to the Child-Pugh (CP) system to categorize HCC burden by liver function. The aim of the present analyses was to compare the prognostic utility of CP score vs ALBI score in the randomized population of RAM in REACH.

Methods: Randomized patients (including the intent-to-treat population [PTA] and the exploratory population [EP]) were assigned to subgroups (EP: CP, EP+7, CP+8) based on baseline CP score, as determined from case report forms. Patients were also regrouped by ALBI grade 1, 2, or 3. OS was evaluated by the Kaplan-Meier method. The log-rank test was used to compare OS by CP scores and ALBI grades independent of treatment. A Cox model with CP score as a covariate for OS or ALBI score was used to generate the HR. Agreement between test methods was calculated by a simple Kappa test. Harrell’s C index score was also performed to check the discriminatory performance of CP score vs ALBI grade.

Results: For ALBI grade, the REACH population was divided into 3 groups: ALBI grade 1 (n=217), ALBI grade 2 (n=376), and ALBI grade 3 (n=37). For CP score, patients were separated into 3 groups: CP score 5 (n=357), CP score 6 (n=208), and CP score 7+8 (n=78). Baseline and pretreatment disease characteristics were similar in ALBI grade 1 and CP score 5 groups, ALBI grade 2 and CP score 6 groups, and ALBI grade 3 and CP score 7+8 groups. In general, the CP score 5 and ALBI grade 1 groups were both associated with an ECOG performance status 0, a higher proportion of hepatitis B, and less macrovascular invasion. Both ALBI grade and CP score were each able to differentiate 3 patient populations of progressively worse prognosis in REACH, OS curves by CP score 5 median (10.45 months), CP score 6 (5.55 months), and CP score 7+8 (3.81 months), and by ALBI grade 1 (10.87 months), ALBI grade 2 (6.04 months), and ALBI grade 3 (3.42 months). The pattern of adverse events was simple for patients with a CP score of 5 and ALBI grade 1, CP score of 6 and ALBI grade 2, or CP score of 7+8 and ALBI grade 3.

Conclusions: The baseline characteristics of the 3 REACH populations defined by CP score were similar to the 3 groups defined by ALBI grade. Both CP score and ALBI grade were each able to distinguish 3 populations with a differing prognosis. A comparable pattern of adverse events across the 3 patient populations defined by CP score or ALBI grade was also observed. Both CP score and ALBI grade were each able to distinguish 3 patient populations of progressively worse prognosis in REACH. OS curves by CP score 5 median (10.45 months), CP score 6 (5.55 months), and CP score 7+8 (3.81 months), and by ALBI grade 1 (10.87 months), ALBI grade 2 (6.04 months), and ALBI grade 3 (3.42 months) resembled each other. The pattern of adverse events was simple for patients with a CP score of 5 and ALBI grade 1, CP score of 6 and ALBI grade 2, or CP score of 7+8 and ALBI grade 3.

Disclosure of Interest: None Declared

P-178

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF RAMUCIRUMAB VERSUS PLACEBO AS SECOND-LEVEL TREATMENT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND ELEVATED BASELINE ALPHA-FETOPROTEIN FOLLOWING FIRST-LINE SORAFENIB (REACH-2)

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Introduction: Ramucirumab (RAM) is a humanized IgG1 monoclonal antibody that inhibits VEGF-A and C D activation of the vascular endothelial growth factor receptor 2 (VEGFR2). The phase 3 REACH study assessed RAM versus placebo (PBO) in the treatment of patients with advanced hepatocellular carcinoma (HCC) after prior sorafenib. Significant improvement in overall survival (OS) was observed in patients with baseline albumin ≥400 mg/dL (RAM 3400 ng/mL, PBO = 0.0069), with improvements in progression-free survival (PFS) in both RAM (HR 0.699, p = 0.0018) and PBO (0.7% vs 0.4% PBO, p = 0.0254). For OS treatment benefit was observed in patients with a baseline ALBI score < 400 ng/mL (N=310) HR = 0.93, 95% CI 0.836-1.428; p = 0.5059). Comparing the OS results in patients with baseline ALBI score ≥ 400 ng/mL, the subgroup-by-treatment interaction was significant (p = 0.0272). The safety profile of RAM vs PBO was considered manageable. In patients with elevated ALBI score ≥ 400 ng/mL, a strategy for delay in deterioration of patient reported symptoms (p = 0.054) and delay in performance status (PS) deterioration (p = 0.057) was also observed in patients treated with RAM compared to PBO.

Methods: REACH-2 is a randomized, double-blind, placebo-controlled, phase 3 study of RAM and best supportive care (BSC) versus PBO and BSC in patients with HCC and elevated baseline ALBI fraction following prior therapy with sorafenib. Eligible patients will be randomized 2:1 to receive RAM (8 mg/kg, id) or PBO on Day 1 of each 14-day cycle until disease progression or other discontinuation criteria. Eligible patients must have a diagnosis of HCC, disease or tumor with classical imaging criteria (present or future) prior to randomization; OS benefit for delay in deterioration of patient reported symptoms (p = 0.054) and delay in performance status (PS) deterioration (p = 0.057) was also observed in patients treated with RAM compared to PBO.

Disclosure of Interest: None Declared

P-179

DELTANP23 ISOMORPHS ARE INVOLVED IN THE IMMATURE PHENOTYPE OF LIVER CANCER CELLS

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Introduction: Hepatocellular carcinoma (HCC) is the third cause of cancer death worldwide. The presence of cancer stem cells (CSCs) in HCC tumours is thought to be responsible for cancer relapse and radio-chemotherapeutic resistance. Major efforts are thus being made to identify the pathways leading to the maintenance of CSCs, in order to develop specific targeted therapies. The p53 family (p53, p63, and p73) plays an important role in carcinogenesis and maintenance of cell stemness. These three genes encode several full-length and truncated isoforms (from alternative splicing and promoter usage), which exert opposite effects. The full-length isoforms (Ta) have tumor suppressor activity, whereas the truncated isoforms (DN) act both as dominant negative forms, and thus are considered as oncogenes, and as regulators of cell stemness. In physiological conditions, DNp63 and DNp73 expression is restricted to progenitor cells. Since p73 is expressed in liver cells, we analyzed its expression in a cohort of human HCC. We observed that the acquired expression of several truncated isoforms (collectively called DNp73), correlated with that of the stemness factor Nanog. This result suggests that DNp73 could be involved in the emergence of cancer cells with immature properties (CSCs).
**Posters**

The origin of liver CSCs is unknown. They could be generated by oncogenic events occurring either in a mature hepatocyte accompanied by a dedifferentiation process, or in a liver progenitor cell.

**Methods:** To address this question, we first characterized non-transformed and transformed liver stem cells by FACS analysis, colony- and sphere formation. We then ectopically expressed DNp73 in non-transformed progenitor cells that are subsequently differentiated in vitro, and in primary human hepatocytes.

**Results:** As expected, DNp73 overexpression was not sufficient per se to transform differentiated or progenitor liver cells. Nevertheless, we observed an altered differentiation program, supporting the role of DNp73 in progenitor maintenance. To go further, we ectopically expressed DNp73 in several HCC cell lines with different levels of differentiation and confirmed the correlation between stemness properties and DNp73 expression.

**Conclusion:** The next steps will consist of identifying the DNp73-dependent molecular mechanisms involved in immaturity/differentiation. The effect of DNp73 expression will be also evaluated in terms of tumor aggressiveness and metastasis formation in mouse.

**Disclosure of Interest:** None Declared

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**P-180 EFFECTIVENESS OF SORAFENIB WITH LIPIODOL DEPOSITION IMPROVEMENT AFTER TACE IN PATIENTS WITH UNRESECTABLE HCC**

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**Introduction:** Evidence indicates that transarterial chemoembolization (TACE) plus sorafenib could provide survival benefits over TACE monotherapy in unresectable HCC patients[1]. In our previous study, we demonstrated that after treated with TACE, the poor lipiodol retention might predict a poor survival outcome of the unresectable hepatocellular carcinoma (HCC) patients [2]. In this study, we aim to investigate whether sorafenib could improve the lipiodol retention in advanced HCC patients who received TACE.

**Methods:** This is a retrospective study. We enrolled 236 unresectable HCC patients of the 236 methods, 103 patients received TACE combined with sorafenib treatment and the other 133 patients treated with TACE monotherapy. Patients’ demographic data, Child-Pugh class, Barcelona Clinic Liver Cancer (BCLC) stages, Eastern Cooperative Oncology Group (ECOG) score, size/number of tumor, HBsAg, AFP, and TACE frequency were retrieved from medical charts. The lipiodol retention condition was analyzed after treatment. To evaluate the characteristics might effect lipiodol deposition patterns in patients after TACE, multivariate Logistic regression model was performed.

**Results:** There were 88 (35.44%) and 117 (80.77%) males in TACE combined with sorafenib and TACE group, respectively, and the mean age of each group was 53.88±12.25 and 57.35±11.88 years. After treatment, patients with more than 50% iodine oil deposition was more in TACE plus sorafenib group than that in TACE monotherapy group (70.87% vs. 45.11%, P=0.0001), which indicate that sorafenib might correlated with lipiodol retention. Furthermore, patients’ baseline characteristics were enrolled as independent variables and lipiodol deposition pattern was set as outcome, and the multiple regression results showed that TACE plus sorafenib may protect patients from poor lipiodol retention (OR=0.449, 95%CI=[0.208-0.906], P=0.041).

**Image:**

![Image: TACE+sorafenib](image)

**Conclusion:** In the present study, we found that more patients with better lipiodol retention pattern after treated with sorafenib, and TACE combined with sorafenib could provide benefits for good lipiodol retention in advanced HCC patients.

**References:**

**Disclosure of Interest:** None Declared

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**P-181 SCHISTOSOMA MANSONI INFECTION IN PATIENTS UNDERGOING LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: A CASE SERIES**

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**Introduction:** Schistosoma mansoni infection (SMI) affects about 258 million people worldwide, notably in Africa and Northeast of Brazil. Hepatoparenchymal form affects 4-7% of patients and is characterized by the formation of bands of perilobular fibrosis, in response to the inflammatory insult caused by the parasite’s eggs, that lead to preehilar portal hypertension. In most of cases, liver preserves its synthetic function, except when exposed to repeated ischemic injury or when there is another pathological insult, such as viral hepatitis or alcoholism. Studies from Egypt suggest a possible association between SMI and hepatocellular carcinoma (HCC), but the high prevalence of co-infection with hepatitis C virus in that population makes difficult the evaluation about the real role of SMI in oncogenesis. Helmintha-related carcinogenesis had been already studied, and the association between S. haemostobium and bladder cancer in well accepted. The present study intends to describe clinical characteristics of patients submitted to liver transplantation (LT) as treatment for HCC, in which SMI was detected.

**Methods:** Retrospective case series study, based on data collected from records of patients that received LT for HCC treatment in a reference center of Recife - Northeastern Brazil, between 2000 and 2015. Cases whose pathological examination of the explanted liver identified only Schistosomosis Liver Fibrosis (SLF), in the absence of cirrhosis or other conditions, were included.

**Results:** Among 149 patients analyzed, seven were defined as SLF (4.7%). Six of the seven cases were male (65.7%), with ages ranging from 34 to 74 years (median 53 years) and all of them reported contact with river waters of endemic areas from Northeastern Brazil. The reasons of LT choice as treatment for HCC were: hepatic failure signs, as ascitis and encephalopathy, in four patients, and the association between SMI and hepatocellular carcinoma (HCC), but the high prevalence of co-infection with hepatitis C virus in that population makes difficult the evaluation about the real role of SMI in oncogenesis. Helmintha-related carcinogenesis had been already studied, and the association between S. haemostobium and bladder cancer in well accepted. The present study intends to describe clinical characteristics of patients submitted to liver transplantation (LT) as treatment for HCC, in which SMI was detected.

**Conclusion:** The present case series, though small, is the first that describes the association between HCC and SMI, through in toto liver analysis, allowing exclusion of other etiological factors.

**References:**

**Disclosure of Interest:** None Declared

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**P-182 PREVALENCE AND RISK FACTORS OF HEPATOCELLULAR CARCINOMA IN EGYPTIAN CIRRHOTIC PATIENTS**

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**Introduction:** HCC is the commonest primary cancer of the liver. Geographical distribution of HCC varies throughout the world with an incidence rate ranging from 2.1 in Central America to 35.5 in Eastern Asia. The burden of HCC has been increasing in Egypt with a doubling in the incidence rate in the past 10 years. Aim of the study is to detect the prevalence and risk factors of hepatocellular carcinoma in Egyptian cirrhotic patients.

**Methods:** The study included 1514 patients with liver cirrhosis from Menoufa University Hospitals
Survival rates were analyzed by the generalized Wilcoxon test; all other factors were analyzed by the causes of HCC, hepatic reserve, stages of HCC, and HCC detection by screening. The relationship between regular hospital visits and survival rates, demographics, B of patients with regular visits to other hospital divisions, and group C of patients with no regular care system to improve the prognosis of HCC in community health.

Introduction: Egypt has a high incidence of HCC about 20% in cirrhotic Egyptian patients. HCV and HBV infections and smoking are the main determinants of HCC development in Egyptian cirrhotic patients. An active surveillance and secondary prevention programs for patients with chronic hepatitis are the most important steps to reduce the risk of HCC.

Conclusion: Egypt has a high incidence of HCC about 20% in cirrhotic Egyptian patients. HCV and HBV infections and smoking are the main determinants of HCC development in Egyptian cirrhotic patients. In the regional community, regular hospital visits, especially hepatologist visits, may improve the stage at initial diagnosis and prognosis of HCC. In particular, regular hospital visits for male and non-virally infected patients should be promoted, and simple diagnostic methods that enable other division clinicians to detect HCC should be developed.

Disclosure of Interest: None Declared

P-183 REGULAR HOSPITAL VISITS IMPROVE THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA AFTER INITIAL DIAGNOSIS IN REGIONAL COMMUNITY

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Introduction: The prognosis of hepatocellular carcinoma (HCC) remains poor despite advancements in diagnostic tools and treatments. The aim of this study is to investigate the relationship between regular hospital visits and the prognosis of HCC after initial diagnosis and to suggest an ideal medical care system to improve the prognosis of HCC in community health.

Methods: This study was conducted by a regional hospital in Japan which was equipped with multidetector computed tomography and magnetic resonance imaging, and offered treatments, excluding transplantation, to patients with HCC. Ninety patients who were initially diagnosed with HCC in January 2012 or later were classified into 3 groups based on hospital visits occurring 1 year before their diagnosis. Group A was composed of patients who had regular hepatologist visits, group B of patients with regular visits to other hospital divisions, and group C of patients with no regular hospital visits. The relationship between regular hospital visits and survival rates, demographics, causes of HCC, hepatic reserve, stages of HCC, and HCC detection by screening were analyzed. Survival rates were analyzed by the generalized Wilcoxon test; all other factors were analyzed by the χ² test. Multiple logistic regression analysis was performed using sex, cause, hepatic reserve, and staging as explanatory variables and group A, B, and C as the objective variable.

Results: The following results are presented as group A/ group B/ group C.
1) Survival rates: 6 months post-diagnosis, 93.8%/76.4%/45.7% survived; at 12 months, 93.8%/73.3%/44.7%; at 36 months, 93.8%/63.6%/43.6%. Survival rates were significantly higher in group A than B (P=0.011) and in group B than C (P=0.023).
2) Age: The number of patients ≤65 and >65 years old were 27/37/6 and 8/8/4, respectively (P=0.31).
3) Sex: The numbers of male and female were 17/36/7 and 18/9/3, respectively (P=0.012). Males had fewer regular hepatologist visits than females.
4) Causes: The number of virally infected and non-virally infected patients, having neither hepatitis C nor B were 24/15/5 and 11/30/3, respectively (P=0.008). Non-virally infected patients had fewer regular hepatologist visits.
5) Hepatic reserve: The number of patients with Child-Pugh grade A, including non-cirrhotic patients, was 23/33/3, and with grade B or C was 12/36/7 (P=0.033). Hepatic reserve was poor in group C.
6) TNM stage: The number of patients with stage 1 or 2 was 30/26/2; stage 3 or 4, 5/18/9 (P=0.003). TNM stage was poor in group C.
7) Japan integrated Staging (JIS) score: The number of patients with scores <4 and ≥4 was 33/9/5 and 26/3, respectively (P=0.002). JIS score was poor in group C.
8) Detection of HCC by regular screening was performed for all patients of group A, but only in 15.6% of group B (P=0.007).

Conclusion: Of 836 patients initially diagnosed with HCC at a single institution between January 2007 and December 2009, 651 patients with available documented history of alcohol intake were enrolled. The total amount of alcohol intake was calculated based on written questionnaires at the first clinic visit. Patients were categorized into 4 groups according to the etiology: Hepatitis B virus (HBV)-related (HBV+, n=462), Hepatitis C virus (HCV)-related (HCV+, n=53), both HBV and HCV-related (HBV+/HCV+, n=21), and non-virus-related (HBV-/HCV-, n=119). Clinical features and prognosis were analyzed according to the presence or absence of alcohol intake or the amount of alcohol intake.

Results: Of 651 patients, 431 had a history of drinking alcohol (alcohol group) and 220 had no history of drinking alcohol (non-alcohol group). There were no significant differences between the alcohol and non-alcohol groups in terms of tumor size, number of nodules, tumor stage, Child-Pugh class, or overall survival. Significant differences in tumor stage were observed between alcohol and non-alcohol groups for the HBV+ group in subgroup analysis (P=0.038); stage I (51.1% vs. 11.5%), stage II (31.3% vs. 31.5%), stage III (24.2% vs. 26.7%), stage IVa (4.6% vs. 15.8%), and stage IVb (14.8% vs. 14.6%). There were no other significant differences between the alcohol and non-alcohol groups across etiologies for HCC. The amount of alcohol intake also did not affect the tumor characteristics or prognosis of HCC.

Conclusion: In this cohort, the non-alcohol group of HBV-related HCC patients tended to have more stage I and less stage IVa diagnosis. However, there was no significant difference in tumor characteristics, Child-Pugh class, or overall survival according to the history or amount of alcohol intake reported in the questionnaire.

Disclosure of Interest: None Declared

P-185 THE CLINICAL OUTCOMES OF ADVANCED HCC PATIENTS RECEIVED SYSTEMIC CYTOTOXIC CHEMOTHERAPY AFTER SORAFENIB FAILURE

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Introduction: The role of systemic cytotoxic chemotherapy has not been elucidated in patients with advanced hepatocellular carcinoma (HCC) after sorafenib failure. We analyzed clinical outcomes of patients who received systemic cytotoxic chemotherapy after sorafenib failure.

Methods: Between 2007 and 2015, there were 47 advanced HCC patients treated with systemic chemotherapy after sorafenib at Korea University Guro Hospital. The most common regimen was doxorubicin, cisplatin and capcitabine containing regimen (87.2%). Data for each patient was collected retrospectively including demographic, laboratory, clinical, treatment and survival data. Tumor response was assessed by RECIST version 1.1. Overall survival and progression free survival were analyzed through Kaplan-Meier curve.

Results: In baseline characteristics, chronic hepatitis B (76.6%) was main etiologic factor in development of HCC. ECOG performance status 0 and 1 were 29.8% and 68.1%, 85.4% of patients were Child-Pugh class A. 40 patients (85.4%) had distant metastasis and lung was the most frequent metastatic organ (26 patients). Patients with portal vein invasion were 20 (42.5%). During follow up, 33 patients were died and overall median survival was 9.8 months (95% CI, 6.0-13.6) The median progression-free survival was 6.0 months (95% CI, 4.6-7.4). In analysis of
best response rate, no patient had CR, 10 patients had PR (21.3%), 14 patients had SD (29.6%), and 16 patients had PD (34.0%). The overall objective response rate was 21.3% and the disease control rate was 51.1%.

Conclusion: In this study, systemic cytotoxic chemotherapy showed favorable response. Therefore, systemic cytotoxic chemotherapy could be considered in patients with hepatocellular carcinoma after sorafenib failure in present situation that there is no option for second-line therapy.


Disclosure of Interest: None Declared

P-186 BIOLOGICAL, CLINICAL FEATURES AND OUTCOME OF HEPATOCELLULAR CARCINOMA DEVELOPING IN PATIENTS DURING LONG-TERM ANALOG THERAPY FOR HBV

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Introduction: Long-term oral nucleotide (NUL) therapy in patients with hepatitis B virus (HBV)-related compensated cirrhosis prevents clinical decompensation and improves portal hypertension but not the development of HCC (2.8% per year). While the biological and clinical characteristics of HCC in untreated HBV patients are well established, HCC arising in long-term NUL treated patients is poorly characterized as well as the diagnostic accuracy of alpha-fetoprotein (AFP) in this specific setting.

Methods: All HCC developing between 2005 and 2015 in NUL treated HBV patients were studied. HCC surveillance was performed every 6 months according to international guidelines. HCC occurring within the six month of NUL therapy were excluded. Endpoints of the study were biological and clinical features of HCC, AFP patterns and patients outcome.

Results: 66 patients developed a HCC after 7 years (1-16) of NUL therapy (71% on TDF or ETF). HCC was diagnosed by imaging in 85% and by fine needle liver biopsy in 15%. Age was 66 years (40-80), 82% male, 95% Caucasian, 95% HBV infected, 95% with undetectable HCV DNA, 89% genotype D, 77% with normal ALT levels, 75% had TE values <12 KPa, 88% with cirrhosis (91% CTP A, 9% CTP B, 17% with variables (73% F1), Median AFP level was 4 ng/ml (1-3615), with 62% of the patients with AFP <7 ng/ml. Of the 25 patients with elevated AFP, this marker increased above the normal values either before or at HCC diagnosis in 76% of cases. HCC was monocentric in 80%, had median diameter of 22 mm (range: 6-57), 74% <30 mm diameter, 92% BCLC 0 or A, 92% within Milan criteria, 95% within Up to Seven. 3% with neoplastic portal thrombosis. As first-line treatment, 66% received radical therapies (36% RFA, 27% surgical resection, 3% OLT). During 24 months (1-126) of follow-up, 18% died of HCC progression while 23% successfully underwent liver transplantation within a median of 6 months (2-77) from HCC diagnosis. The 4-year survival was 77% (O,LT=alive) or 59% (OLT=dead).

Conclusion: A majority of HCC developing in patients long-term treated with NUL are small tumors, within Milan criteria, BCLC O/A and therefore amenable to curative therapies.

Disclosure of Interest: None Declared

P-187 HAP SCORE IN PATIENTS UNDERGOING RADIOEMBOLIZATION TREATMENT FOR HEPATOCELLULAR CARCINOMA.

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Introduction: Chemoembolization is the usual treatment for patients with unresectable, unirradiated hepatocellular carcinoma and liver-limited disease. The HAP score establishes the prognosis of these patients using 4 variables: albumin <36 g/dL, bilirubin >17 µmol/L, AFP >400 ng/mL, tumor size >7 cm. This score was shown to differentiate 4 groups of patients treated with chemoembolization with progressively worse prognosis. Nevertheless, HAP has not been tested in radioembolized patients. In this context, the objective of this study is to evaluate the performance of the HAP score in this population.

Methods: We analyzed retrospectively all consecutive patients with hepatocellular carcinoma treated by radioembolization from 2003 to 2012. Patients not followed entirely in our center, those with a follow-up <3 months, and those in which the HAP score could not be calculated were excluded. Although the analysis is retrospective, most variables were prospectively recorded. Survival was plotted from the day of treatment until death or last visit using Kaplan-Meier method and compared by log-rank test. Cox-regression analysis was used for multivariate analysis.

Results: 116 patients analyzed had a mean age of 64 years and were predominantly males (82.8%), and cemirics (79%) in Child-Pugh class A (85.3%), 26.3% had portal vein thrombosis and 26.7% had AFP >400 U/ml. Patients were in BCLC stages A (16.4%), B (53.4%) or C (50.2%) and HAP groups A (14.7), B (31.9), C (37.1), and D (16.4). Survival stratified by HAP score showed a statistical difference in overall survival (P=0.017). However, there were no differences between groups HAP A (median: 19.2 months) and HAP B (21.1 months) or between groups HAP C (7.9 months) and HAP D (10.6 months). When the frequency of each component of the HAP score was compared, groups A and B differed significantly in the frequency of large tumor size (A:0% vs. B:27%) and high bilirubin (A:0% vs. B:46%), while groups C and D differed significantly in the frequency of large tumor size (C:44% vs. D:99%) and high AFP (C:32% vs. D:63%).

Conclusion: The HAP scoring system has not shown a good prognostic accuracy in a large series of patients treated with radioembolization. A benefit of radioembolization compared to chemoembolization in patients with large tumors or high AFP may partially explain this impaired prognostic ability.

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References:

Disclosure of Interest: None Declared
**P-189 COMBINED RADIOFREQUENCY ABLATION AND ETHANOL INJECTION VERSUS HEPATIC RESECTION FOR MEDIUM AND LARGE SOLITARY HEPATOCELLULAR CARCINOMAS**

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**Introduction:** To retrospectively compare survival outcomes of hepatic resection (HR) and combined use of percutaneous radiofrequency ablation and ethanol injection (RFA-PEI) in the treatment of resectable solitary hepatocellular carcinoma (HCC) with medium or large size (3.1-7.0cm).

**Methods:** Between June 2009 and June 2015, 201 consecutive HCC patients were enrolled, including 102 undergone RFA-PEI and 99 undergone HR. The differences in survivals between two groups and subgroups were compared with the Kaplan-Meier method and log-rank test. Univariate and multivariate analyses were performed to identify the potential predictors for survivals.

**Results:** Overall survival (OS) rates at 1, 3, and 5 years were 96.0%, 79.9% and 59.7% in RFA-PEI group and 81.8%, 59.6% and 48.1% in HR group, respectively (P=0.033). The corresponding 1-, 3-, and 5-year disease-free survival (DFS) after RFA-PEI were 75.3%, 59.0%, 52.2% and in HR group 54.5%, 43.4%, 39.3%, respectively (P=0.016). Subgroup analyses showed that the 1-, 3-, and 5-year OS in RFA-PEI group (97.5%, 67.2%, 71.8%) were significantly better than those in HR group (86.8%, 66.0%, 60.4%) with 3.1-5.0cm tumors (P=0.011), so did the 1-, 3-, and 5-year DFS (RFA-PEI vs. HR: 84.4%, 66.3% and 63.0% vs. 62.3%, 50.9% and 43.2%, respectively; P=0.009). There was no significant difference between these two groups regarding OS (P=0.209) and DFS (P=0.152) with 5.1-7.0cm tumors. Multivariate analyses showed that treatment type was the independent predictor for both the OS (P=0.022) and DFS (P=0.014), and the tumor size was also the significant prognostic factor for DFS (P=0.029).

**Conclusion:** RFA-PEI had the survival benefit over HR in the treatment of solitary HCC with medium size whereas showed comparable efficacy to HR in the treatment of HCC with large size.


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**P-190 EFFICACY OF SORAFENIB FOR EXTRAHEPATIC RECURRENTITY OF HEPATOCELLULAR CARCINOMA AFTER LIVER RESECTION**

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**Introduction:** Sorafenib is the first molecularly targeted drug recommended as a treatment for advanced hepatocellular carcinoma (HCC). But there is no evidence for survival after sorafenib treatment in patients with recurrence of HCC who have undergone curative resection.

**Methods:** Subjects were 47 patients who were diagnosed with recurrent HCC after liver resection and treated with sorafenib after surgical treatment from Sep 2004 to Mar 2015. We evaluated the overall response rate, disease control rate and median time to disease progression (TTP) according to dose intensity of sorafenib and recurrence site of HCC.

**Results:** The mean age of patients was 60 years with a male/female ratio of 42:5. The overall response rate was 17.5% (complete response: CR 1%, partial response: PR 6%, complete disease: SD 17, progressive disease: PD 13, SD beyond PD 3), and the disease control rate was 67.5%. Median TTP of 80mg dose group (n=17), reduced 400mg from 800mg dose group (n=13), and 400mg dose group (n=17) were 3.67 months, 4.00 months, and 5.23 months respectively. TTP according to sorafenib dose was not significant among the dose group (P=0.435). On the other hand, Median TTP of intrahepatic metastasis group (n=15), Intrahepatic and extrahepatic group (n=20), and only extrahepatic metastasis group (n=12) were 2.50 months, 4.95 months, and 5.25 months respectively. Median TTP of the group including extrahepatic metastasis was significant better than only intrahepatic metastasis group (P=0.034).

**Conclusion:** Sorafenib controlled the patients with extrahepatic recurrence of HCC more than with intrahepatic recurrence regardless of dose intensity. Therefore, Sorafenib may be an effective treatment for extrahepatic recurrence of HCC.

**Disclosure of Interest:** None Declared
P-193 TRANSFERENTIAL INFUSION OF EPIRUBICIN AND CISPLATIN COMBINED WITH SYSTEMIC INFUSION OF 5-FU FOR ADVANCED HEPATOCELLULAR CARCINOMA FRAGRATORY TO CONVENTIONAL TRANSFERENTIAL INFUSION WITH DOXORUBICIN


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Introduction: Transcatheter arterial chemoembolization (TACE) has been recognized as an effective therapy for advanced hepatocellular carcinoma (HCC). However, there are a few limited options including sorafenib in case of tumor progression after TACE with single agent, doxorubicin (TACE-DOX). As a novel therapeutic strategy, the efficacy of transfusional infusion of epirubicin and cisplatin combined with systemic infusion of 5-fluorouracil (5-FU) (TACE-ECF) in HCC patients with progression after TACE-DOX was investigated.

Methods: A total of 405 consecutive HCC patients who received TAC-DOX at the Catholic Medical Center between 2008 and 2015 were enrolled. Of these patients with the tumor progression after TACE-DOX (median 3 times, range 1-15 times), 34 patients who had treated with TAC-ECF were finally analyzed. TAC-ECF consisted of transarterial infusion of epirubicin (50 mg/m2) and cisplatin combined with systemic infusion of 5-fluorouracil (5-FU) (TACE-ECF) in HCC patients with progression after TACE-DOX was investigated.

Results: All patients presented with Eastern Co-operative Group performance status (ECOG) 0-2 and the Child-Pugh classification with A and B. The stage (modified UICC stage) of 34 patients was followed by stage III (n=5), IV (n=15), and 17 (n=16). Median follow-up period was 145 days (range, 40-635 days). The tumor response for TACE-ECF was completely resolution (CR) in 1 patient (2.9%), partial response (PR) in 2 patients (5.9%), stable disease (SD) in 14 patients (41.2%) and progression disease (PD) in 17 patients (50.0%). The median progression-free survival (PFS) during TACE-ECF was 105 days (95% CI 34.4-175.5). The overall survival was 152 days (95% CI 119.2-184.7). The overall survival rate in the objective response (CR, PR, SD) and progression disease (PD) was significantly higher than in the PD group (median 223 days vs. 119 days, p<0.001).

Conclusion: TACE-ECF therapy achieved acceptable progression free survival in the patients who progressed after TACE-DOX. It also showed higher survival rate in the patients with objective response than the patients with progressive disease. Therefore, TACE-ECF may be considered as an effective treatment option for patients with advanced HCC refractory to TACE-DOX.

Disclosure of Interest: None Declared

P-194 EVALUATION OF PREOPERATIVE RISK FACTORS FOR POSTHEPATECTOMY LIVER FAILURE AFTER RIGHT HEPATECTOMY FOR HEPATOCELULAR CARCINOMA

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Introduction: Liver cirrhosis, portal hypertension, and residual liver volume are well-known crucial factors for posthepatectomy liver failure (PHFL) in the patients with hepatocellular carcinoma (HCC). This study aimed to estimate safe cut-off levels of preoperative factors to avoid PHFL after right hepatectomy for HCC.

Methods: 90 patients underwent right hepatectomy for hepatocellular carcinoma from March 2008 to December 2013 at Yonsei University College of Medicine. We defined clinical relevant PHLF (CR-PHLF) more than grade B according the International Study Group of Liver Surgery. Logistic regression analysis was performed for perioperative risk factors to CR-PHLF, such as platelet counts, bilirubin level, ICG R15, liver stiffness measurement, the ratio of the future remnant liver volume to the total functional liver volume (RLV/TLV) and the ratio of the future remnant liver volume to body weight (RLV/BW).

Results: Among 90 patients, there were 15 patients (16.7%) with CR-PHLF. 75 patients (83.3%) without CR-PHLF were enrolled. CR-PHLF group. In the CR-PHLF group, platelet counts was lower (121.0 vs. 169.5X10^9/L, p=0.003), total bilirubin was higher (0.8 vs. 0.7 mg/dL, p=0.033), liver stiffness score was higher (12.1 vs. 9.9 kPa, p=0.025), RLV/TLV was smaller (31.8 vs. 38.9 %, p=0.001) and RLV/BW was smaller (0.51 vs. 0.69 %, p=0.022) than in the No CR-PHLF group. Platelet counts less than 138X10^9/L (Exp (B) = 4.814, 95% CI: 2.771-79.181, p = 0.002) and RLV/TLV less than 34.79% (Exp (B) = 9.302, 95% CI: 1.644-52.652, p = 0.012) were independent predictive factors for CR-PHLF according to multivariate analysis.

Conclusion: Platelet counts and RLV/TLV are powerful parameters to predict CR-PHLF after right hepatectomy for HCC.

Disclosure of Interest: None Declared

P-195 DEVELOPMENT OF AN ANIMAL MODEL OF ATROPHY-HYPERTROPHY AFTER PARTIAL LIVER RADIOEMBOLIZATION

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Introduction: Treatment intensity can be increased in lobar radioembolization (RE) and this is usually followed by atrophy due to damage of the treated lobe and hypertrophy of the non-targeted contralateral lobe. In fact RE is increasingly used as an alternative to portal vein embolization to increase the future liver remnant and allow resection in patients with liver tumors that are unresectable at diagnosis.

Aim: To develop an animal model of liver damage and atrophy-hypertrophy (AH) after lobar RE.

Methods: Increasing amounts of resin microspheres loaded with yttrium90 (Sirtex Medical, Sydney) were delivered to the 3 cranial lobes (right, left medial and left lateral) of 3-kg New Zealand female rabbits after portal vein catheterization via inferior mesenteric vein liver laboratory. An attempt to use the intrahepatic route failed because of the low capacity of the vessel. Injected activities of 0.3, 0.6 and 1.2 GBq were aimed to deliver doses of radiation of 200, 400, and 800 Gy to the cranial lobes. Body weight and liver function tests were obtained at different times after RE, liver volumes were measured before RE and at sacrifice on a CT scan, and liver weight was recorded at sacrifice. Animals were euthanized when they looked severely ill.

Results: Sparing of the caudal lobe was confirmed in 4 animals using decayed, fluorine18-labeled microspheres in a micro-CT. No AH was observed in 5 animals 2 weeks after injection of non-radioactive microspheres. 5 animals that received 1.2 GBq died 2 to 4 weeks after RE before CT. 5 animals that received 0.6 GBq developed weight loss by week 2, and AH (median injection in caudal lobe volume 35%) was observed in all animals at sacrifice, 2 to 4 weeks after RE. 4 animals that received 0.3 GBq showed mild weight loss and AH (median increase in caudal lobe volume 300%) was observed 1 to 2 months after RE, being maximal at month 2 after RE. Gastric ulcers in the vicinity of the irradiated cranial lobes were observed in 4/5 animals of the 0.6 GBq group and 0/4 animals of the 0.3 GBq group.

Conclusion: Selective portal vein injection of 0.3 to 0.6 GBq of yttrium90-loaded microspheres to the cranial lobes of rabbits consistently induces liver damage and AH that resembles human observations. This animal model can be used to study surgical rescue as well as liver protection strategies with translational purposes.

Disclosure of Interest: None Declared

P-196 SORAFENIB ASSOCIATED SURVIVAL IN TREATMENT NAÏVE VERSUS TREATMENT EXPERIENCED PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Introduction: Sorafenib treatment is associated with a survival benefit in patients with advanced hepatocellular carcinoma (HCC) Whether this survival benefit is present as a second-line therapy in patients who have progressive HCC after receipt of locoregional therapies remains unclear. We aimed to compare the survival and side effect profile associated with sorafenib treatment in patients with advanced stage HCC as a second-line therapy in patients who progressed after prior locoregional therapy versus treated with sorafenib as first-line therapy.

Methods: We performed a retrospective analysis of patients at a tertiary care academic medical center between 1/2007- 6/2014. We performed a stratified survival analysis using Kaplan-Meier with log rank testing and performed a multivariate Cox proportional hazard analysis to determine the survival benefit of sorafenib therapy. We collected data on side effects as defined by the Common Terminology Criteria for Adverse Events (CTCAE).
Results: There were 40 patients were in the sorafenib as initial therapy (G1) group and 43 patients in the sorafenib after previous therapy (G2) group. Baseline demographic and staging variables for the cohorts are shown in Table 1. The cohorts had similar mean ages and were both predominantly male and white. There were a higher proportion of patients with Child-Pugh class A cirrhosis in the SPT group, however there were no overall differences in Child-Pugh class between the cohorts. Patients G2 group had a higher incidence of ascites (p=0.039), portal venous invasion (p=0.001), distant metastasis (p=0.023), and a higher median ECOG score (p=0.049). The median survival after sorafenib treatment initiation was 89 days in the G1 group versus 131 days in the SPT group (p=0.001). However, there were no overall differences in actuarial survival as shown in Figure 1 (p=0.676). In our multivariate analysis, survival was not significantly impacted by treatment with sorafenib as a second-line therapy (HR: 0.82, 95% CI 0.37-1.81). SPT patients were more likely to experience one or more side effect of any grade (p=0.018). However, there was no significant difference in the severity of side effects or the likelihood that the side effects would result in sorafenib treatment discontinuation.

Conclusion: Short-term mortality differs between the cohorts, however no differences were seen when adjusting for demographic differences, Child-Pugh class, and ECOG status. The survival benefit associated with sorafenib is modest but similar in patients when used as a second-line therapy versus first-line. Locoregional treatment naïve patients experience fewer treatment related side effects than treatment experienced patients.

Disclosure of Interest: None Declared

P-197 LOW UTILITY OF FDG-PET CT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA BEFORE LIVER TRANSPLANTATION

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Introduction: Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide, and the burden of this devastating disease is expected to increase, HCC is the third most common cause of cancer-related deaths worldwide, and each year, approximately 750,000 new cases are diagnosed. Risk factors include pre-existing infection with hepatitis B and cirrhosis. Hepatocellular carcinoma is one of the most common cancers in parts of Africa and the Far East. In developed countries, the peak incidence is between the ages of 40 and 60, but in those developing countries where the disease is common, most cases occur between 20 and 40.

The diagnosis of HCC in our study was made based on the radiological according to the AASLD guidelines. Positron emission tomography (PET) is a non-invasive imaging modality for whole-body imaging of cellular and metabolic functions and has been utilized in some patients. Several investigators have reported controversial conclusions and an inadequate sensitivity for PET in the detection of various malignancies. Our program utilizes FDG-PET CT routinely in the pre-transplant evaluation of patients with hepatocellular carcinoma (HCC). The aim of our study is to evaluate the utility of FDG-PET CT in the setting of the pre-transplant liver workup in HCC patients.

Methods: This is a retrospective chart review of our liver transplant (LT) database from January 2011 to December 2014 of all patients with HCC who had LT. Collected data included age, gender, etiology of liver disease, imaging (CT or MR), FDG-PET CT, explant tissue analysis, type of transplant and transplant outcome.

Results: During the study period, 275 LTs were performed. Fifty-three patients had HCC, of whom 41 underwent FDG-PET CT. The average age was 58 (22-72), and 28 patients were males. The etiology of liver disease was hepatitis B (24 patients), cryptogenic cirrhosis (12 patients) and HBV (5 patients). Twenty-five patients had HCC within the Milan, 7 within UCSF criteria, and 8 patients were beyond the UCSF criteria. Twenty-nine patients underwent LDLT, whereas 12 patients underwent DDLT. Of the 40 patients, 11 patients had positive FDG-PET CT (27%) with evidence of HCC in the explant. The remaining 29 patients had negative FDG-PET CT (73%). The FDG-PET CT was positive in 16% of patients within the Milan criteria, 40% of patients within and 62% of patients beyond the UCSF criteria.

Table 1: Accuracy of PET CT scan in detecting HCC

<table>
<thead>
<tr>
<th>Test</th>
<th>HCC present</th>
<th>HCC absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-PET CT Positive</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>FDG-PET CT Positive</td>
<td>29</td>
<td>1</td>
</tr>
</tbody>
</table>

Sensitivity 27.5% Specificity 100% Positive predictive value 100% Negative predictive value 3.3%

Conclusion: FDG-PET CT has a low utility in patients with HCC within the Milan criteria and should not be routinely used as part of the liver transplant workup.

Disclosure of Interest: None Declared

P-198 METASTATIC DE NOVO HEPATOCELLULAR CARCINOMA OR AGGRESSIVE RECURRENCE IN CHRONIC HEPATITIS C PATIENTS TREATED WITH DAA’S

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Introduction: The goal of chronic hepatitis C therapy with direct-acting antivirals (DAAs) is to delay progression of the disease and decrease the incidence of Hepatocellular Carcinoma (HCC). Recently there has been new data showing either De novo HCC or aggressive recurrence in chronic hepatitis C patients who had been treated with DAAs (1,2). Aim: To highlight De novo HCC or aggressive recurrence in patients who achieved SVR after treatment with DAAs.

Methods: Between July 2014, and December 2015, 503 patients either before or after liver transplantation have received DAAs, at our center with an average rate of Sustained Virological Response (SVR) of 92%. Our cohort of patients included patients with liver cirrhosis up to Child-Pugh C and post liver transplant patients with Chronic Hepatitis C recurrence after liver transplant. We reported two cases with De novo HCC or aggressive recurrence after successful treatment with DAAs achieving SVR.

Results: 2 Patients have been identified; first case was a 67 year old female underwent liver transplant in March 2013 for HCV related liver cirrhosis and hepatocellular carcinoma (single lesion measuring 4.1), status post successful Loco-regional Therapy as evidenced by the explant which showed extensive necrosis and no lymphovascular invasion. In April 2014 she received 12 week of Peginterferon Alpha 2-a/Ribavirin/Sofosbuvir, to which she relapsed. In November 2014 she was started on Sofosbuvir/Daclatasvir, but at week 8 she was still have detectable HCV RNA, so she was changed in January 2015 to a regimen of Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir for 12 weeks to which she achieved SVR. In December 2014 Computerized Tomography (CT) of the abdomen was negative for any liver lesions. In August 2015, a CT of the abdomen showed a single lesion in the liver with characteristics of HCC, and in September 2015 CT Chest showed Mediastinal Lymphadenopathy, which was confirmed later by biopsy to be metastatic HCC. The second case was a 62-year-old male with compensated HCV cirrhosis, genotype 4 treatment Naive. In November 2014, and May 2015 he had 2 CT’s of the abdomen and pelvis as part of routine screening for
HCC, and both were negative for any liver lesions. In November 2015 he received a 12 week course of Ledipasvir/Sofosbuvir with Ribavirin after which he achieved SVR. He presented about in April 2016 to the emergency room with fracture of the right Humerus; X-ray showed a pathological fracture. In view of that, a CT abdomen and pelvis was done on April 2016, which showed infiltrative diffuse bone metastasis with pathological fracture of the right Humerus and the right Femur. Both cases had metastatic disease on presentation shortly after finishing treatment.

Conclusion: There is a growing concern about increased risk of metastatic De novo HCC or aggressive recurrence after treatment with DAAs. Highlighting the importance of prospectively following the large cohort of patients who received this treatment to prove or refute this finding.


Disclosure of Interest: None Declared

P-199 PRETREATMENT LOW CIRCULATING MICRONRNA-29A EXPRESSION LEVEL AS POOR PROGNOSTIC MARKER IN PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO UNDERWENT HEPATIC RESECTION OR RADIOfREQUENCY ABLATION

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Introduction: As therapy for chronic hepatitis B (CHB) can reduce the risk of hepatocellular carcinoma (HCC), ideally, there should be no HCC development who are not indicated for therapy.

Methods: A simple HCC risk score was developed from 9872 CHB patients with elevated HBV DNA levels who are outside of current treatment criteria due to alanine aminotransferase (ALT) levels <2 upper limit of normal if whom 26 patients developed HCC during follow-up. Variables included in the risk score were serum HBV DNA levels (used twice), age and sex (DA2S score). Score was validated from independent cohort of 507 patients from other hospital (of whom 15 patients developed HCC).

Results: A 4-point risk scale was developed, with HCC risk ranging from 0% to 29.1% at 3 years, and 0% to 30.9% at 5 years for lowest and highest risk score. DA2S score had highest area under receiver operating curves (AUROC) for the prediction of HCC development at 3/5 years (0.895/0.844, compared with REACH-B 0.814/0.812, FB-4 0.759/0.712, age 0.780/0.718, ALT 0.666/0.766) and HBV DNA (0.559/0.556) levels. The calculated AUROC to predict HCC development at 3/5 years was 0.889 (95% CI: 0.786-0.983) and 0.876 (95% CI: 0.738-0.963) in the validation cohort, with a 5-year HCC incidence of 0%, 0.63%, and 19.2% for very low, low, high and very high DA2S score, respectively.

Conclusion: HCC developed in patients with elevated HBV DNA levels who are outside of current treatment criteria due to normal or subnormal ALT levels. For them, DA2S risk score can play a valuable role in the risk stratification, and may guide clinical decision over enhanced surveillance or treatment to reduce HCC risk.

Disclosure of Interest: None Declared

P-201 D2AS SCORE TO PREDICT HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CHRONIC HEPATITIS B PATIENTS WITH ELEVATED HEPATITIS B VIRUS DNA LEVELS WHO ARE OUTSIDE OF CURRENT TREATMENT RECOMMENDATION

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1Medical, Samsung medical center, Internal Medicine and Liver Research Institute, Seoul University college of medicine, 2Biostatics and Clinical Epidemiology Center, Samsung medical center, 3Internal Medicine, Konkuk University School of Medicine, Seoul, Korea, Republic of Korea

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Results: A 4-point risk scale was developed, with HCC risk ranging from 0% to 29.1% at 3 years, and 0% to 30.9% at 5 years for lowest and highest risk score. DA2S score had highest area under receiver operating curves (AUROC) for the prediction of HCC development at 3/5 years (0.895/0.844, compared with REACH-B 0.814/0.812, FB-4 0.759/0.712, age 0.780/0.718, ALT 0.666/0.766) and HBV DNA (0.559/0.556) levels. The calculated AUROC to predict HCC development at 3/5 years was 0.889 (95% CI: 0.786-0.983) and 0.876 (95% CI: 0.738-0.963) in the validation cohort, with a 5-year HCC incidence of 0%, 0.63%, and 19.2% for very low, low, high and very high DA2S score, respectively.

Conclusion: HCC developed in patients with elevated HBV DNA levels who are outside of current treatment criteria due to normal or subnormal ALT levels. For them, DA2S risk score can play a valuable role in the risk stratification, and may guide clinical decision over enhanced surveillance or treatment to reduce HCC risk.

Disclosure of Interest: None Declared

P-200 DOUBLING TIME OF SERUM TUMOR MARKER IN HCC PATIENTS PREDICTS RECURRENCE AFTER CURATIVE TREATMENT

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Introduction: We aimed to evaluate prognostic implication of circulating microRNA (miR)-21, 26a, and 29a in patients with hepatocellular carcinoma (HCC) who underwent hepatic resection or radiofrequency ablation (RFA) for curative treatment.

Methods: A total of 120 patients with hepatitis B virus (HBV)-related HCC who underwent hepatic resection and 29a in patients with hepatozellular carcinoma undergoing interferon-free therapy: a note of caution. Journal of Hepatology, 2018;S0168-0278(16)30113-1

Disclosure of Interest: None Declared

P-199 PRETREATMENT LOW CIRCULATING MICRONRNA-29A EXPRESSION LEVEL AS POOR PROGNOSTIC MARKER IN PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO UNDERWENT HEPATIC RESECTION OR RADIOfREQUENCY ABLATION

Posters


Disclosure of Interest: None Declared

P-201 D2AS SCORE TO PREDICT HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CHRONIC HEPATITIS B PATIENTS WITH ELEVATED HEPATITIS B VIRUS DNA LEVELS WHO ARE OUTSIDE OF CURRENT TREATMENT RECOMMENDATION

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Introduction: Hepatocellular adenomas (HCA) and focal nodular hyperplasias (FNH) are benign hepatocellular tumors and their distinction is of crucial importance in clinical care.

Objective: Correlate the imaging of HCA and FNH after injection of liver-specific contrast agents MRI (Gd-BOPTA, Multihance, Bracco) with pathological features.

Disclosure of Interest: None Declared

P-202 BENIGN HEPATOCELLULAR TUMORS AND HEPATOMOBILIARY MRI CONTRAST AGENTS: IMMUNOHISTOCHEMICAL AND RADIOLOGICAL CORRELATION

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Methods: Twenty three patients with 27 lesions (9 FHN; 18 HCA) were included in the study. All patients had their lesions treated with HAIC. MRI with hepaticobiliary phase (BPH) after injection of Gd-BOPTA, a pathological documentation and an immunohistochemical analysis were performed in all patients. A qualitative analysis of the lesion to liver contrast Enhancement Ratio (LCCR) was performed and compared between HCA subtypes and FHN (Mann Whitney). The organic anion-transporting polypeptide (OATP) and Glutamin Synthetase (GS) expression levels were compared between HCA subtypes and FHN (Mann Whitney).

Results: All FHN were hypointense in BPH of MRI against 69% of HCA. In the FHN the degree of hepatocyte capture in BPH was significantly higher in the HCA (relative mean LCCR of 10.05% vs. 10.8%; p=0.01). In HCA the degree of hepatocyte capture in BPH was significantly higher in the treatment-naive group than in other HCA (relative mean LCCR of 15.1% vs. 10.8%; p=0.02). The expression of OATP was higher in FHN than in HCA (45.5% vs 17.2%, p<0.01). Among the HCA, the percentage of neoplastic cells expressing OATP was more important in the treatment-naive HCA compared to other subtypes (72% vs 8%; p<0.01). OATP expression was correlated with Wnt/β-catenin pathway activation, as assessed by GS expression (p=0.001).

Conclusion: Specific patterns of hepatobiliary capture with hepato-specific contrast agents are highly correlated to the rate of OATP receptor expression. OATP expression is related to GS expression, marker known to reflect Wnt/β-catenin pathway activation. Finally Gd-BOPTA MRI contrast agent is able to differentiate β-catenin mutated HCA from other HCA subtypes and FHN.

Disclosure of Interest: None Declared

P-203 EVALUATION OF CHEMOTHERAPY INDUCED LIVER INJURY IN PATIENTS WITH COLORECTAL CANCER LIVER METASTASES

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Introduction: Adjuvant chemotherapy improves survival in patients with curatively resected colorectal cancer. But up to 50% of patients will develop hepatic metastases during their course of disease. Surgical resection of liver is the only potentially curative treatment for patients with liver metastases. However, giving the chemotherapy before resection of colorectal carcinoma liver metastases may cause hepatic injury and affect postoperative outcome. The aim of this study is to show that commonly used chemotherapy drug are associated chemotherapy induced liver injury which was recognized to impair the function of the remnant liver.

Methods: Between June 2007 and March 2012, data of 29 liver resection performed for colorectal liver metastases were analyzed, retrospectively. Eleven patients had liver resection without chemotherapy, while 18 patients had history of adjuvant, neo-adjuvant chemotherapy before liver resection. We analyzed patients’ clinical data, histopathology of resected liver and post-operative outcome between two groups.

Results: In the comparison of patients’ clinical data, there was no statistically significant difference in the sex, age, extent of hepatopathy, ICG-R15, PIVKA-II, CEA, pre-operative AST, cholesterol, bilirubin, INR and fatty liver score of preoperative CT between non-chemotherapy group and chemotherapy group. Whereas, patients in the chemotherapy group had higher pre-operative α-fetoprotein (AFP), pre-operative γ-glutamyl transpeptidase (GGT), AST, ALT, total bilirubin, INR, ICG-R15, PIVKA-II, CEA, C-reactive protein (CRP), AST, ALT, pre-operative AST, cholesterol, pre-operative cholesterol, pre-operative total bilirubin and the fatty liver score of preoperative CT compared to patients in the non-chemotherapy group. In the comparison of histopathology of resected liver including steatosis grade, steatohepatitis grade, ALT(p=0.043), lower PLT level(p=0.032) compared to patients in the non-chemotherapy group. Whereas, patients in the chemotherapy group had higher pre-operative bilirubin, PT, INR and fatty liver score of preoperative CT between non-chemotherapy group and chemotherapy group. Since 2012 to 2015, altogether 14 patients treated with HAIC were retrospectively enrolled. The patients were divided into the treatment-naive group (n=8) and the treatment-experienced group (n=6). Baseline characteristics, progression free survival (PFS) and overall survival (OS) were compared between the treatment-naive and treatment-experienced groups. In the treatment-experienced group, starting day of analysis was defined as the day decided to HAIC.

Results: The treatment-naive group and the salvage group were similar in baseline characteristics and tumor stages. The average number of cycles treated with HAIC were 6.5±4.8 and 7.0±4.3 cycles for the treatment-naive and the treatment-experienced group, respectively (p=0.950). Median OS of the treatment-naive and the treatment-experienced group were 300.0±245.8 and 302.5±124.5 days, respectively (p=0.739). Median PFS were 198±165.9 and 392±128.3 days, respectively (p=0.282).

Conclusion: In this study, chemotherapy induced liver injury in patients with colorectal cancer liver metastases was not associated with the treatment method. The study shows there were no significant differences in OS and PFS between the treatment-naive group and the treatment-experienced group. In conclusion, regardless of the treatment status of HCC, survival gain of HAIC in advanced HCC was similar.

Disclosure of Interest: None Declared

P-206 UPTAKE OF LARGE DNA FRAGMENTS BY HEPATOMACELLULAR CARCINOMA CELLS AND IN VIVO STUDY IN ANIMALS

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Introduction: Advanced hepatocellular carcinoma (HCC) is incurable and deadly; there is no effective therapy at the present time. It would be ideal to develop a carrier labeled with an isotope specifically targeting cancer cells with minimal side effects on normal cells. In this study, we tested a group of DNA fragments as the potential carriers to deliver Phosphorus-32(32P) to cancer cells.

Methods: The DNA fragments were modified with phosphorothioates ends to protect enzyme digestion for in vivo studies. The stability and therapeutic efficacy of 32P labeled DNA fragments was further tested in animal models. A group of DNA fragments of different lengths were screened for their capacity to selectively target HCC cells rather than normal liver cells.

Results: The data demonstrated that HCC cells and about 1/3 of non-HCC cancer cells possess the ability to take in large DNA fragments without the aid of a transfection reagent. The uptake study revealed that fluorescence was mainly located on the membrane. Combined with the 32P labeled DNA study, the mechanism of uptake of large DNA by cancer cells is likely endocytosis, which does not exist in normal cells. A in vivo study in a mouse model demonstrated that the application of compound remarkably suppresses tumor growth.

Conclusion: Our approach of using a modified DNA fragment as an isotope carrier to treat HCC is tested to be safe and effective. This application broadens the current concept of gene therapy in which gene-expressing vectors are employed, and provides a promising therapeutic modality for HCC.

Disclosure of Interest: Y. Kong Advisory Board of: Bulloughs Biomedical Technology, J. Liu: None Declared, X. Zhang: None Declared

P-207 TOXICITY TEST OF EMODIN IN ICR MICE

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Introduction: Radiosensitivity in the tumor and radiotoxicity in the non tumorous liver significantly restrict efficient radiotherapy of hepatocellular carcinoma (HCC). It is therefore important to study the radiosensitivity mechanism and development of radiosensitization to optimize the effect of irradiation.
on cancer cells. Emodin (1,3,8-trihydroxy-6-methylanthraquinone), a family of plant derived polyphenol has been proven to have anticancer properties. In the previous study we proved that emodin attenuated radiosensitivity by fractionated irradiation (Supplement 1) or hypoxia (Supplement 2) in human HepG2 cell line and enhanced radiation killing effect in BALB/c nude mice (Supplement 3) via upregulation of apoptosis. Therefore we performed toxicity study of emodin in the view of new drug development.

**Methods:** ICR mice was used in this study. Male & female mice were treated with five different manners; none (control), 5mg/kg, 50mg/kg, 100mg/kg, 250mg/kg of emodin. 10 mice were distributed in the each group. Emodin was administered only one time and we investigated body weight, activity, food intake of mice and harvested them within one month. Then we measured organ weight & gross morphology.

**Results:** No systemic and organ toxicity of emodin was found in ICR mice (Figure 1), but hematologic toxicity as subtle anemia and thrombocytopenia was suspicious in 250mg/kg injected group (Figure 2, 3).

**Image:**

**Conclusion:** Therefore, our findings may provide that emodin can be developed as new tolerable radiosensitizer in HCC and may aid in the design of new therapeutic strategies for the radiosensitive HCC. A further clinical study to prove toxicity & efficacy of emodin in HCC patients is recommended.


**Disclosure of Interest:** None Declared

**P-208** EXPRESSION OF EPIDERMAL GROWTH FACTOR RECEPTOR IN PRIMARY LIVER CANCER WITH OR WITHOUT VIRAL HEPATITIS

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**Introduction:** According to researches, there are many discordant data about the prognostic and treatment significance of epidermal growth factor receptor in Primary Liver Cancer (HCC) with or without viral Hepatitis.

**Methods:** The intensity of Epidermal Growth Factor Receptor (EGFR) expression in HCC with or without viral Hepatitis was the focus of our study. 34 patients have been investigated morphologically (Cytology). For cytological study the material was collected by Circulated Tumor Cells from Blood of each Patient by Oncoquick Test system. Cytological and Immuno-cytological studies were performed as well. The numeric data obtained were processed statistically using the SPSS-12 program.

**Results:** Based on the results, expression of epidermal growth factor receptor was diagnosed in 100% of the patients. Of them, mild EGFR expression was documented in 35.2% (p<0.1), while sharp EGFR expression – in 64.8 % (p<0.1) of patients. With that, EGFR-immunoreactivity was observed in HCC cells both with or without viral Hepatitis. In HCC without viral Hepatitis EGFR was expressed with different intensity, however in most cases, i.e. in 11 out of 19 patients (57.8%) EGFR was expressed with low intensity (p<0.1), in 8 patients (42.1%) high intensity of EGFR expression was revealed (p<0.1). In HCC with viral Hepatitis EGFR was expressed both with low and high intensity: in 8 patients out of 15 (53.3%) EGFR was sharply expressed (p<0.1), 7 patients (46.7%) showed mild EGFR expression (p<0.1). The results of the study suggest that in HCC with viral Hepatitis mild EGFR expression predominates, while sharp EGFR expression is mostly typical of HCC with viral Hepatitis.

**Conclusion:** At the same time, EGFR staining intensity increases with the severity of grade of HCC differentiation. The results show that the Viruses affect on the expression of the growth factors genes, it allows us to think that the viruses might have become a part to targeting treatment agents with EFGR blockers for liver cancer.

**Disclosure of Interest:** None Declared
Conclusion: Our study suggests that SBRT can be effective and safe modality that achieves promising rates of long-term local control and survival in HCC refractory or unsuitable for other therapeutic options, even with vascular or bile duct invasion. A further well controlled, large scaled study to reduce toxicity (esp. gastrointestinal and pulmonary and hepatic toxicity) is recommended.

Disclosure of Interest: None Declared

P-212 NEXVAR FOR TREATMENT OF ADVANCED HCC, REAL-LIFE DATA FROM SAUDI ARABIA

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Introduction: Management of advanced hepatocellular carcinoma (HCC) is still a challenge to physicians. The disease carries a very poor prognosis with an expected survival of 4-6 months. Till recently, no chemotherapeutic agent has been proven to improve the clinical outcome in such patients. Sorafenib, a multikinase inhibitor, has emerged as the only effective treatment with significant improvement in survival in patients with advanced HCC based on two large randomized clinical trials. The aim of this trial is to assess the efficacy and safety of sorafenib in the treatment of advanced HCC outside clinical trials.

Methods: A retrospective chart review of patients with advanced HCC treated with Sorafenib in a single tertiary centre between June 2008 and June 2015 was carried out. Patients were included if they were prescribed sorafenib and had at least one follow up after starting treatment. Demographic, clinical, biochemical and radiological data were collected. Primary end point was the overall survival. Side effects were recorded whenever available together with radiological response

Results: A total of 74 patients were included in the analysis. Males were 57 (77.0%) and the mean age was 66.4±6.9 years. Forty-seven percent of patients were diabetic and 62 pts (84%) were cirrhotic. HBV infection was the primary cause of liver disease in 25 pts (33.8%) while HCV was the cause in 27 pts (36.5%). Distant Metastasis was found in 18 pts (24.3%), lymph node enlargement in 16 pts (21.6%) and portal vein thrombosis in 6 pts (8.1%). Thirty patients (40.5%) had previous procedures. Fifty-three patients (71.8%) had Child A disease at the start of treatment and 21 pts (28.2%) were Child B. The median overall survival was 10.0 months (11.6 and 9.8 months in child A and B respectively, p=0.012). Survival at 1 year of treatment was 35%. Side effects were reported in 20 patients and the commonest were diarrhea and skin rash. Poor predictors of survival were Child B score above 6 and distant metastasis.

Conclusions: Efficacy of sorafenib in treating advanced HCC in real-life data was very similar to phase III clinical trials. Impaired synthetic liver function predicts shorter survival and thus selection of patients is important to optimize the response to treatment.


Disclosure of Interest: None Declared

P-214 SAFETY AND TOLERABILITY OF COMBINATION MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR (mTOR) AND SORAFENIB FOR RECURRENT HEPATOCELLULAR CARCINOMA (HCC) AFTER LIVER TRANSPLANT

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Introduction: Recurrence of HCC complicates up to 10 percent of liver transplants and the best way to manage these patients is unclear. Mammalian target of rapamycin (mTOR) Inhibitors possess antiproliferative properties and sorafenib has survival benefit in patients with advanced unresectable HCC. Combination therapy with an mTOR inhibitor and sorafenib could potentially be synergistic in the prevention and/or treatment of recurrent HCC after liver transplant.

Methods: This retrospective study included adult patients transplanted for a history of HCC at our tertiary center, with post-transplant HCC recurrence between 2005 and 2015. Patients were selected for further analysis if they were on combination therapy of sorafenib and an mTOR inhibitor for management of recurrent HCC. This study served to assess the tolerability of combination therapy and descriptive statistics were utilized to analyze clinical outcomes.

Results: Of the 162 patients transplanted for HCC, 10 patients had recurrent HCC after transplant in the specified time frame. Six patients simultaneously received both sorafenib and an mTOR inhibitor (4 patients on everolimus and 2 on sirolimus) for greater than 30 days. Among the 4 patients who did not receive combination therapy, 2 were started on palliative chemotherapy instead, 1 failed everolimus conversion due to fatigue, and 1 experienced a prolonged intraabdominal infection that precluded additional immunosuppression. For all patients on combination therapy, the mTOR inhibitor was started prior to sorafenib. Sorafenib was titrated to a maximum of 400 mg bid in all patients except patient 3 who received 600 mg bid. Of the 6 patients, 1 patient was not on a calcineurin inhibitor (CNI), while 5 patients received combination of low-dose CNI (4 on tacrolimus and 1 on cyclosporine) with an mTOR inhibitor and sorafenib. On therapy, diarrhea was reported in 66% of patients, while 33% of patients experienced fatigue, hyperglycemia, or hypertension and 17% had hand-foot syndrome, hyperbilirubinemia, GI bleed, hyperpotassemia, acute kidney injury, hepatic dysfunction, rash, or mouth sores (Table). Progression of HCC despite combination therapy was seen in four patients, with the other two patients continuing on combination therapy at the time of study completion.

Conclusion: In conclusion, sorafenib in combination with an mTOR inhibitor is feasible and should be considered for patients with recurrent HCC after liver transplant as well as patients at high-risk for HCC recurrence. Additional studies are needed to assess efficacy of this combination on disease progression.

Disclosure of Interest: None Declared

P-216 PREVIOUS TUMOR TREATMENT AND ELEVATED BILIRUBIN LEVELS ARE ASSOCIATED TO POST TRANSPLANT HCC RECURRENCE

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Introduction: Liver transplantation is being considered the treatment of choice for small hepatocellular carcinoma with cirrhosis. After the introduction of selective criteria based on number and size of tumors, the recurrence rate has decreased dramatically. However, even patients with small tumors still recur after transplantation, suggesting that current criteria fail in predicting oncological outcome. This study aimed to identify clinical, radiological and pathological characteristics of patients transplanted with hepatocellular carcinoma and correlate them with tumor recurrence after transplantation.

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Methods: The authors performed a retrospective study based on the review of 128 patients transplanted with hepatocellular carcinoma at Hospital das Clínicas da UFMG, between 1994 and 2014. Clinical, radiological and pathological characteristics of the patients were correlated with tumor recurrence after transplantation, intending to identify risk factors of poor oncological prognosis. Fischer exact test, Shapiro-Wilk, 1st Student and Mann-Whitney tests and the multivariate analysis were used to compare data. Statistical significance was determined with a p £ 0.05.

Results: 104 patients were male. Average of age was 56.3±8.5 years. The main underlying liver disease was hepatitis C cirrhosis (60.2%). Child-Pugh classification was 39.8% A, 32.0% B, and 17.2% C. Average of calculated MELD score was 14.1±5.6. 33 patients (25.8%) underwent pre transplant tumor treatment: chemoembolization (TACE) (n=28), radiofrequency ablation (n=2), surgical resection (n=2) or percutaneous ethanol injection (n=1). Eight patients were submitted to TACE for downstaging purposes. Univariate analysis showed higher HCC recurrence when pre transplant bilirubin levels were above 3mg/dl (p=0.08), ALT above 80U/L (p=0.046), pretransplant treatment was used (p=0.06). In multivariate analysis only bilirubin >3mg/dl and pretransplant treatment were associated with recurrence (p<0.05).

Conclusion: Patients whose tumors were treated before liver transplantation and patients with serum levels of total bilirubin above 3mg/dl before transplantation, should be considered as higher risk for tumor recurrence. These patients may benefit of rigorous surveillance strategies and even adjuvant therapy, after liver transplantation


Disclosure of Interest: None Declared

P-217 HBV DNA CLEARANCE WITHIN 6 MONTHS AFTER ANTIVIRAL THERAPY BENEFITS THE SURVIVAL OUTCOME OF ADVANCED HCC PATIENTS TREATED WITH SORAFENIB: A RETROSPECTIVE OBSERVATIONAL STUDY

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Introduction: As current available data clearly showed hepatitis B virus(HBV) viral load at baseline prior to sorafenib treatment was significant prognostic factor for tumor recurrence and disease survival(1). This retrospective cohort study investigated the impact of HBV antiviral therapy on the survival of patients with advanced hepatocellular carcinoma(HCC) treated with sorafenib.

Methods: In present study, 91 HCC patients received sorafenib and concurrent anti-HBV (lamivudine, entecavir, adefovir or telbivudine) treatment were identified retrospectively from 2006.07 to 2012.12 in Henan People’s Hospital. Demographic data, clinical/Child-Pugh class) and cancer(Barcelona Clinic Liver Cancer, BCLC) stages, tumor size/number, HBV viral load, AFP, and other clinical data were retrieved from medical charts. Primary endpoints included overall survival(OS). Secondary endpoints include progression free survival(PFS), aviremia, antiviral drug resistance, change of antiviral drugs and treatment-related adverse events(AEs) after beginning of antiviral therapy and time-to-antiviral drug resistance. Multivariate COX regression were used to identify factors associated with better prognosis.

Results: Twenty-two(24.2%) patients received adefovir treatment, 33(36.3%) patients treated with entecavir, 28(30.8%) patients with lamivudine and 8(8.8%) patients with telbivudine as the first line anti-HBV agent. After treated with anti-HBV agents, clearance of HBV DNA in 59(64.8%) patients within 6 months’ treatment. The median OS and PFS of all patients were 14.4 and 7.8 months respectively. The median OS of patients with HBV DNA clearance was longer than that without clearance within 6 months (17.1 vs. 13.7 months, P=0.012). In addition, 6-month-clearance also prolonged the median PFS of patients(9.00 vs. 6.94, P=0.006). In the multivariate analysis, BCLC B stage and AFP<400 μg/L also predict better OS and PFS outcome.

Conclusion: Subtyping of BCLC stage C by tumor size, major portal invasion, distant metastasis and underlying liver function may.


Disclosure of Interest: None Declared

P-218 THE SAFETY AND EFICACY OF TRANSTERIAL CHEMOEMBOLIZATION COMBINED WITH SORAFENIB AND Mono-Therapy of Sorafenib in BCLC Stage B/C HCC PATIENTS: A RETROSPECTIVE OBSERVATIONAL STUDY

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Introduction: Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world [1]. Both sorafenib and transarterial chemoembolization (TACE) are recommend therapies for Barcelona Clinic Liver Cancer (BCLC) stage B/C hepatocellular carcinoma (HCC) patients [2]. The efficacy of combining TACE with sorafenib compared with sorafenib alone is still under debating.

Methods: From august 2004 to November 2014, totally 104 BCLC stage B/C HCC patients were enrolled from Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University. The total 104 HCC patients, 56 were treated with sorafenib alone (sorafenib group) and 48 were treated with TACE plus sorafenib (TACE + sorafenib). The baseline information of patients including demographic information and clinical features were included. The primary
outcome was median overall survival (OS). Second outcomes were progression-free survival (PFS), the overall response rate (ORR) and the sorafenib-related adverse events (AEs). The baseline characteristics associated with disease prognosis were analyzed with multivariate Cox hazards regression model.

Results: Among the 104 patients, there are 94 males (90.38%), and the mean age is 49.02 ± 12.29 years. For the baseline information of patients in each group, only albumin (ALB) level and Child-Pugh stage showed significantly differences (P = 0.028 and P = 0.017, respectively). No difference observed in the median OS of patients in sorafenib and TACE + sorafenib groups (18 vs. 22 months, P = 0.223). While the median PFS of patients treated with sorafenib was significantly shorter than patients treated with TACE + sorafenib (8 vs. 8 months, P = 0.034). Furthermore, we investigated the tumor responses of patients in two groups after 6 months’ treatment. The ORR in sorafenib group was similar with TACE + sorafenib group (12.5% vs. 18.7%, P = 0.425). The numbers of grade III–IV adverse events in sorafenib group and TACE + sorafenib group were without difference (21.4% vs. 27.1%, P = 0.35). In addition, we analyzed the factors associated with OS and PFS of patients, which indicated that TACE plus sorafenib regimen, no vascular invasion and Child-pugh stage A are protective factors of patients’ OS (HR=0.498, 95%CI=0.278-0.892, HR=0.354, 95%CI=0.183-0.685 and HR=0.308, 95%CI=0.141-0.674, respectively), in which TACE plus sorafenib regimen and no vascular invasion are also protective to patients’ PFS (HR=0.461, 95%CI=0.273-0.780 and HR=0.557, 95%CI=0.314-0.988, respectively), while bigger tumor number was risk factor of OS (HR=1.286, 95%CI=1.031-1.604).

Conclusion: Combined TACE with sorafenib would prolong survival outcome and delay disease progression when compared with sorafenib alone. Better survival outcome could also be seen in patients without vascular invasion and with Child-pugh stage A, while patients with bigger tumor number would suffer poor outcome.


Disclosure of Interest: None Declared

P-219 HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANTATION: CASE SERIES AND SURVIVAL ANALYSIS

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Introduction: Liver transplantation (LT) is the treatment of choice for hepatocellular carcinoma (HCC) in cirrhotic patients and the outcome depends on the risk of recurrence, that ranges from 15 to 25%. HCC recurrence is associated with poor prognosis, median survival is 7-10 months, which varies according to the affected organ and the disease-free survival. There is no established adjuvant treatment and the therapeutic possibilities are restricted and individualized according to the affected site. The aim of this study is to report the pattern of HCC recurrence in patients submitted to LT between 2000 and 2015 at a reference center in northeastern Brazil and to determine disease-free and post-recurrence survivals, stratifying by: site and time of recurrence and treatment.

Methods: Descriptive study of patients who relapsed OHC after LT and survival analysis, with informations obtained from medical records and death certificates. Statistical analysis was performed using R for Windows program, with construction of Kaplan Meier curves and Cox proportional regression.

Results: The sample consisted of 22 patients, 21 of them were male (95.4%) and the median age was 62 years (53-75 years). Indications for LT were: Hepatitis C (36.4%), alcoholic disease (27.3%), Hepatitis B (18.2%) and the association Hepatitis C plus alcohol (18.2%). Pathological examination of the explanted liver revealed that only 40% of the cases were inside Milan criteria. Disease-free survival ranged from 54 to 2068 days (median 563 days), with 50% of patients presenting relapse during the first year post-LT. Liver was the first site of recurrence in 4 patients and throughout all the evolution, it was involved in 10 patients (45.4%). 19 patients had extrahepatic recurrence (86.3%), in 8 of which this was the first manifestation. The extrahepatic sites involved were: bone (47.4%), lung (36.8%), lymph nodes and peritoneum (21%), adrenal gland (15.8%), abdominal wall (10.5%), spleen (5.3%) and brain (5.3%). Recurrence affected multiple organs in 13 cases (59%), 44% of bone and 62% of adrenal recurrences occurred in the first year post-LT (early recurrence). Patients with tumors within Milan criteria presented a longer disease-free survival (673 vs. 309 days, p = 0.015). Early recurrences were observed in only 12.5% of the cases within the criteria versus 86.7% of the cases outside (p = 0.019). There was no association between Milan criteria and site of recurrence. The survival post-recurrence (SPR) varied from 10 to 1899 days, with median of 304 days. SPR in patients with early recurrence was 200 days whereas in the late recurrence group was 636 days (p = 0.09). 13 patients (59.1%) underwent anti-tumor therapy. Six patients underwent locoregional therapy (radiofrequency ablation(RFA), sphenectomy, adrenalectomy, lung and abdominal wall nodule resections) and 10 used sorafenib. Patients undergoing any treatment had SPR of 636 days, compared to only 82 days in those who underwent only supportive treatment (p = 0.017). Patients who used sorafenib had a median SPR of 636 days compared to 82 days for patients who underwent only supportive therapy, conforming a hazard ratio of 0.13 (IC 95% 0.03 - 0.49 - p = 0.02).

Conclusion: This study finds an association between explant’s tumor staging and the disease-free survival post-LT. The SPR was higher in patients whose recurrence occurred after the first year and in patients who undergone some treatment, both locoregional as sorafenib.


Disclosure of Interest: None Declared

P-220 THERAPEUTIC RESPONSE ASSESSMENT AND OUTCOME OF RADIOFREQUENCY ABLATION FOR HEPATOCELLULAR CARCINOMA: CORRELATION WITH HISTOPATHOLOGICAL PATTERN

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Introduction: Radiofrequency ablation (RFA) is commonly applied for the treatment of early hepatocellular carcinoma (HCC). Few studies assessed the relation between histological characteristics of HCC and prognosis after RFA. Whether the histopathologic characteristics of HCC can predict local recurrence, overall survival (OS) and time to progression (TTP) after RFA were assessed in this study.

Methods: Twenty five patients with nodular HCC were treated with RFA in a tertiary referral center in Egypt. All patients underwent sonography-guided percutaneous tumor biopsy and were classified as Edmondson-Steiner grade I HCC (n = 13), grade II HCC (n = 7), or grade III HCC (n = 5). All patients underwent contrast-enhanced triphasic CT examination before and one and six
P-221  IMPACT OF RETREATMENT MODALITY FOR INTRAHEPATIC RECURRENT OF HEPATOCELLULAR CARCINOMA

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Introduction: Prognostic factors after treatment for intrahepatic recurrence of hepatocellular carcinoma (HCC) are controversial. Our study aimed to examine the impact of treatment modality on the prognosis of intrahepatic recurrence of HCC following hepatic resection (Hx).

Methods: The subjects consisted of 77 patients who underwent single treatment for intrahepatic recurrence of HCC between 2000 and 2011 by repeat Hx (n=24), ablation (n=11) or transarterial chemoembolization or transcatheter arterial infusion (TACE/TAI) (n=42). We retrospectively investigated the relation between types of treatment for recurrent HCC and overall survival (OS) as well as disease-free survival (DFS).

Results: In univariate analysis, OS of repeat Hx group was significantly better than that of TACE group (hazard ratio [HR]=0.2340; 95% confidential interval [CI], 0.1398-0.7683), but not significantly different from that of ablation group (HR=0.4831; 95% CI, 0.08738-2.671). On the other hand, DFS of repeat Hx group was significantly better than that of TACE or ablation group, respectively (HR=0.3197; 95% CI, 1.052-5.013 and HR=0.4509; 95% CI, 0.1512-0.9806, respectively). In multivariate analysis, the poor prognostic factors in OS after re-treatment were ICC-R15 (15%) (HR=4.266; 95% CI, 1.562-11.649, pathologic portal or hepatic vein invasion upon initial Hx (HR=3.472; 95% CI, 1.237-9.747) and DFI (≤1 year) (HR=3.435; 95% CI, 1.302-9.058) and those in DFS after retreatment were DFI (≤1 year) (HR=2.567; 95% CI 1.413-4.663) and type of treatment for recurrence (TACE/TAI) (HR of the TACE group to repeat Hx = 3.188; 95% CI 1.442-7.050).

Conclusion: DFS (≤1 year) was an independent poor prognostic factor in both DFS and OS. Repeat Hx seems to achieve the most reliable local control of intrahepatic recurrence of HCC.

Disclosure of Interest: None Declared

P-223  OBESITY AND HEPATOCELLULAR CARCINOMA IN PATIENTS RECEIVING ENTECAVIR FOR CHRONIC HEPATITIS B

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Introduction: This study aimed to clarify the effect of obesity on the development of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients receiving antiviral treatment.

Methods: This study was retrospectively analyzed based on a historical cohort in Bundang Jesaeng Hospital. A total of 102 CHB patients were treated with entecavir as an initial treatment for CHB and checked with body composition analyzer (electrical biocomposition analysis) for obesity. Hepatic steatosis was measured semi-quantitatively using Hamaguchi’s scoring system in ultrasonography. Risk factors including obesity-related factors (body mass index, waist circumference, waist-to-hip ratio, visceral fat area, and hepatic steatosis) were analyzed for HCC development.

Results: The median follow-up duration of the patients was 45.2 (interquartile range: 36.0–58.3) months. The cumulative incidence rates of HCC at 1 year, 3 years, and 5 years were 0%, 5.3%, and 9.0%, respectively. Univariable analysis revealed that the risk factors for HCC development were platelet count <120,000 mm(3) (HR 5.21, p=0.031), HBeAg negativity (HR 5.61, p=0.039), and liver cirrhosis (HR 10.26, p=0.031). Multivariable analysis showed that the significant risk factor for HCC development was liver cirrhosis (HR 9.07, p=0.042). However, none of obesity-related risk factors were significantly associated with HCC: BMI >25 kg/m2 (HR 0.90, p=0.894), waist circumference ≥90 cm (HR 1.10, p=0.912), waist-to-hip ratio ≥0.9 (HR 1.94, p=0.386), visceral fat area ≥100 cm2 (HR 1.69, p=0.495), and hepatic steatosis (HR 0.57, p=0.602).

Conclusion: HCC development is associated with liver cirrhosis but not obesity-related factors in CHB patients receiving entecavir.

Disclosure of Interest: None Declared
Introduction: Whether esophageal varices (EV) could determine the outcomes of patients with hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) is still obscure. This study aimed to assess the impact of EV on the prognosis of HCC patients who underwent RFA. Besides, we also aimed to identify the indication of RFA for HCC patients with EV.

Methods: We enrolled 280 treatment-naïve HCC patients who also received upper gastrointestinal endoscopy examination at the time of HCC diagnosis. EV was diagnosed by upper gastrointestinal endoscopy. Factors determining overall survival and recurrence after RFA were analyzed by Cox proportional hazards model and propensity score matching analysis.

Results: A total of 140 (50.0%) patients had EV. Compared to their counterpart, patients with EV had relatively poor liver functional reserve, including lower serum albumin levels and platelet counts, and higher serum bilirubin levels. After a median follow-up of 23.5 months, the cumulative five-year survival rates were 46.9% and 65.4% in patients with and without EV, respectively (p=0.026). By multivariate analysis, age > 65 years (hazard ratio (HR) 1.740, p=0.025), serum albumin levels < 3.5 g/dL (HR 2.186, p<0.001), and multinodularity (HR 1.693, p=0.046), but not EV, were independent risk factors associated with poor overall survival after RFA. The overall survival rate was comparable between patients with and without EV after adjusting the confounding factors by propensity score matching analysis. Moreover, the overall survival rates were comparable between patients without EV and patients with EV who had serum albumin levels > 3.5 g/dL, both of these groups had significantly better prognoses after RFA than patients with EV and serum albumin levels < 3.5 g/dL. Regarding recurrence, multivariate analysis showed that age > 65 years (HR 1.604, 95% CI 1.136-2.265, p=0.007), male gender (HR 1.885, 95% CI 1.161-2.447, p=0.006), and tumor size > 2 cm (HR 1.681, 95% CI 1.190-2.375, p=0.003), but not EV were the risk factors that predicted poor recurrence-free survival after RFA.

Conclusion: EV was not an independent risk factor predicting overall survival and recurrence for patients with small HCC undergoing RFA by multivariate analysis and propensity score matching analysis. It was not a contra-indication for RFA, especially if patients had a serum albumin levels > 3.5 g/dL.

Disclosure of Interest: None Declared

P-225 MELD SCORE PREDICTS OUTCOME OF PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH SORAFENIB

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Introduction: The Model for End-Stage Liver Disease (MELD) score was initially created to predict survival in patients with complications from portal hypertension submitted to elective placement of transjugular intrahepatic portosystemic shunts (TIPS). It is calculated using a mathematical formula incorporating 3 routine blood test results (serum creatinine, bilirubin, and INR). The score was subsequently validated as a predictor of survival in several independent cohorts of patients with varying degrees of liver disease severity, but not in patients treated with sorafenib. The purpose of this study was to examine the predictive value of the pre-sorafenib MELD score in patients with advanced hepatocellular carcinoma (HCC).

Methods: Our study included a training cohort of 67 HCC patients and a validation cohort of 61 HCC patients receiving sorafenib. The MELD score was measured before starting sorafenib.

Results: In the training cohort, an optimal cutoff of 12 for the MELD score stratified HCC patients into high (n=12) and low MELD score (<12) groups. In univariate analysis, training cohort patients with MELD score ≥12 had a lower median PFS and OS than those with MELD score <12 (1.8 vs. 3.3 months, p=0.004; 6.9 vs.8.7 months, p = 0.235, respectively). These data were confirmed in the validation set in which patients with MELD score ≥12 had a lower median PFS (1.4 vs 5.6 months, p<0.0001) and OS (5.0 vs 13.9 months, p=0.0035) than those with MELD score <12. Multivariate analysis confirmed MELD score as the only independent prognostic factor in terms of PFS and OS.

Conclusion: In our study, the MELD score was a powerful prognostic indicator of poor outcome in patients with advanced HCC treated with sorafenib. The fact that it is calculated from the results of a simple blood test makes the score a promising clinical tool to evaluate prognosis in HCC patients.

Disclosure of Interest: None Declared
P-229 APPLICATION OF MR SCAN PROTOCOLS FOR TRANS-FUSIMO LIVER TUMOUR TREATMENT CONTROLLER

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Introduction: MRgFUS is an attractive non-invasive treatment method. MRgFUS enables the treatment of liver for the parts that are poorly accessible for conventional surgery. Application of this treatment requires development of MR scan protocols compatible with Transfusimo Treatment Controller (TTC) to monitor temperature during successful application of MRgFUS (Schwenke et al., 2015).

Methods: Novel TTC designed by (Medis, Fraunhofer) interacts with MR Scanner (Signa 1.5T; GE Healthcare, USA) to acquire images. On MR scanner, 3D localiser scan is followed by axial, sagittal, and coronal scanning to check for airbubbles. Transducer calibration imaging is completed on the scanner with Coronal Fast Spin Echo (FFSE-XL), TE: 88.9 ms, TR: 800 ms. Transducer images are transferred to TTC. Operator checks the transducer positioning for image registration. TTC directly controls the Conformal Bone System (CBS) transducer (InSightei, Ltd, Tirat Carmel, Israel). Planning imaging requires calibration scan of the liver, with 3D FIESTA, in sagittal and coronal planes with TE: 1.3 ms, flip angle: 60°. Next, operator plans the treatment for sonication location, sonication duration and sonication power using by TTC. Monitoring scan requires asset calibration and EPI Scan with single-shot ASSET EPI 100 phases per location, interleaved, acceleration factor: 2, TE: 26.4 ms, TR: 100 ms. Finally, sonication is completed by activating execute sonication command. Tumour ablation is completed.

Results: Feasibility tests show that scan protocols used during the application of MRgFUS by using TTC, enables successful application ablation process on PAx pamphlets, and explanted sheep livers. Next step is to use this novel methodology in pig experiments, based on the successful pre-clinical evaluation of the controller.

Conclusion: MR imaging is crucial for successful application of MRgFUS. Pre-clinical evaluation is a must before animal testing for ethical reasons. Following animal studies, volunteer treatment studies are planned for successful ablation of liver tumours.


Disclosure of Interest: None Declared

P-230 PROGNOSTIC IMPLICATION OF PDL1 EXPRESSION IN HEPATOCELLULAR CARCINOMA

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Introduction: Liver cancer is the fifth and ninth most common cancer in men and women and second cause of cancer death worldwide. Hepatocellular carcinoma is a primary malignancy of liver and often associated with existing chronic liver disease including hepatitis B and C viral infection resulting the highest prevalence in East and South-East Asia. Tumor immunotherapy is currently focusing on the signaling pathway of the programmed death protein 1 (PD-1) binding with programmed death ligand-1 (PD-L1).

Methods: We examined immunohistochemical expression of PD-1 and PD-L1 in hepatocellular carcinoma samples and analyzed with clinicopathologic factors.

Results: A total of 284 samples were enrolled in this study. Expression of PD-1 and PD-L1 was observed in 23% and 21% of samples, respectively. PD-L1 expression was associated with higher AJCC stages. In the univariate analysis of disease free survival and overall survival, PD-L1 expression was a poor prognostic factor (P<0.001). PD-1 expression did not show statistical significance in the survival analysis. In the multivariate analysis, PD-L1 expression was an independent poor prognostic factor of disease free survival and overall survival (p=0.41 and p=0.42, respectively).

Conclusion: As a negative regulator of activated T-cells, PD-L1/PD-1 pathway has been evaluated as a target for immunotherapy. In this study, PD-L1 expression in hepatocellular carcinoma demonstrated correlation with clinicopathologic factors of poor prognosis. In the survival analysis PD-L1 expression was an independent poor prognostic factor. Recently, tumor immunotherapy is arising as an alternative therapeutics substituting conventional chemotherapy in various types of cancers. This study results implies PD-L1 expression as a poor prognostic marker and a possible therapeutic markers for tumor immunotherapy in advanced hepatocellular carcinomas.

Disclosure of Interest: None Declared

P-231 CLINICOPATHOLOGICAL FEATURES OF INTRADUCTAL PAPILLARY NEOPLASM OF THE BILE DUCT IN 27 PATIENTS

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Introduction: Intraductal papillary neoplasms of the bile duct (IPNB) show papillary proliferation in the bile duct with mucin secretion. However, a few studies have compared clinicopathological features between intraductal papillary (IPNB, intra-IPNB) and extrabiliary IPNB (extra-IPNB). In this study, we addressed this issue.

Methods: We used 27 patients from 27 patients (intra-IPNB: 10 patients, extra-IPNB: 17 patients) who underwent pancreaticoduodenectomy or hepatectomy for IPNB. Pathologic diagnosis was made according to the WHO classification. Clinicopathological features were compared between intra-IPNB and extra-IPNB. Immunohistochemical staining for mucin markers (MUC1, MUC2, MUC5AC and MUC6) was also performed. We examined the KRAS mutation in all tumors by real-time polymerase chain reaction.

Results: Mean age was 65.6±8.8 in the intra-IPNB and 69.8±8.1 in the extra-IPNB (P=0.209). The male/ female ratios were 8:2 and 12:5, respectively (P=0.993). Macroscopically, 6 tumors (60%, 6/10) in the intra-IPNB were cystic type associated with mucin hypersecretion, however, there were no cystic type in the extra-IPNB (P<0.001). Histologically, Invasion was found in four tumors (40%, 4/10) in intra-IPNB and in 10 tumors (59%, 10/17) in extra-IPNB (P=0.001). Immunohistochemically, MUC5AC was expressed in 9 tumors (90%, 9/10) in the intra-IPNB, but was expressed only in 7 tumors in extra-IPNB (41%, 7/17) (P=0.09). There were no differences in the expression of MUC1, MUC2 and MUC6 between intra-IPNB and extra-IPNB. KRAS mutation was 14% (1/7) in intra-IPNB and 6% (1/16) in extra-IPNB (P=0.529). There were no significant differences in overall survival between intra-IPNB and extra-IPNB (P=0.698). One intra-IPNB patient (10%, 1/10) with tumor-free surgical margin recurred and the recurrent tumor showed the similar histological features to the primary tumor.

Conclusion: This study revealed that intra-IPNB and extra-IPNB present mostly the common clinicopathological features, but are only significantly different in the frequency of cystic type and MUC5AC expression.

Disclosure of Interest: None Declared

P-232 IMPACT OF BLOOD TRANSFUSION ON SHORT AND LONG-TERM OUTCOMES AFTER RESECTION OF INTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: The impact of intraoperative blood transfusion (IT) on short and long term outcomes following intrahepatic cholangiocarcinoma (IHCC) resection remains to be determined.

OBJECTIVE: To evaluate the impact of IT upon short and long term outcomes after curative hepatectomy for HCC.

Methods: In this multicenter retrospective study (n = 569), patients from the IT (n = 191) and non-IT (n = 378) groups were compared in terms of short- and long-term outcomes using the propensity score method (PSM). The impact of IT on short and long-term mortality was determined using the multivariate analysis. Independent predictors factors of IT were also assessed.

Results: Using PSM, 104/191 IT patients could be matched with 104/378 non-IT patients to analyze the short-term outcomes. Overall morbidity was significantly higher in the IT than in the non IT groups (p = 0.01), while there was no difference in the mortality rate between the two groups (p > 0.99). Using PSM, 98/168 IT patients could be matched with 98/354 non-IT patients to analyze the long-term survival. Both groups were comparable in terms of overall (p = 0.54) and disease-free survival (p = 0.63).
P-233 RADIOTRACER COMBINED WITH TACE IN TREATMENT OF HEPTOCARCINOMA LOCATED IN THE SECOND HEPATIC PORTAL
Hong-Tao Hu *, Hai-Liang Li

Introduction: To explore the efficacy and safety of PFA combined with TACE for the treatment of HCC in the second hepatic portal.

Methods: Between February 2011 and June 2013, 19 consecutive patients with HCC in the second hepatic portal received combination therapy of TACE and RF ablation for at our institution. Nineteen patients had 25 hepatic tumors and 19 tumors located in the second hepatic portal including two patients with PVTT. All of the patients underwent both TACE and RFA under the DSA and CT guidance. The two patients with portal vein tumor thrombosis (PVTT), CT guided 125I-iodine implantation in the PVTT was performed after the first TACE session.

Results: All procedures were performed successfully. There was no mortality and major morbidity due to RFA. Seventeen patients (89.5%) were completely ablated after one sessions of treatment. During follow-up (range 6-52, mean 28 months), Local tumor progression alone developed in 1 of 19 patients (5.3%), new tumors developed in the untreated liver in 8 patients (42.1%), and both local tumor progression and new tumors developed in 1 patient (5.3%). No distant metastasis was found. Six of 19 patients (31.6%) died, 3 because of tumor progression (15.8%), 2 because of liver failure (10.5%), and 1 because of massive hemorrhage of gastrointestinal tract (5.3%). Overall survival rates were 94.7% (18/19) (95% CI, 89.0%-98.8%) at 12 months, 94.7% (18/19) (95% CI, 89.0%-99.8%) at 18 months and 68.4% (13/19) (95% CI, 59.8%-81.8%) at 24 months. The median survival time of all of the 19 patients was 26 months.

Conclusion: Combination therapy of TACE and RFA is a useful therapeutic option for the HCC with the tumor located in the second hepatic portal.


Disclosure of Interest: None Declared

P-234 MANAGEMENT OF SPONTANEOUS HCC RUPTURE FOLLOWING TRANSAARTERIAL CHEMOEMBOLIZATION: EXPERIENCE FROM A TERTIARY CARE CENTRE
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Introduction: Spontaneous rupture of hepatocellular carcinoma (HCC) following transarterial chemoembolization (TACE) is a rare but potentially fatal complication. The aim of the present study was to assess the clinical characteristics, treatment strategies and follow-up outcomes of patients undergoing TACE for HCC.

Methods: A retrospective study was performed on 35 patients who received TACE for treatment of resectable HCC and who developed spontaneous HCC rupture within 1 week from the TACE procedure was recorded.Data on clinical characteristics, treatment strategies and survival time were analyzed.

Results: Among the 35 patients, 8 patients with HCC rupture underwent TACE (16.7%) and 5 patients developed spontaneous tumor rupture after the procedure. Spontaneous rupture was diagnosed using abdominal computed tomography with or without a diagnostic percutaneous biopsy. Of the 16 patients, 15 (93.8%) had symptoms of epigastric pain and/or right upper quadrant pain. Local tumor progression and new tumors developed in 1 patient (2.3%) and 2 patients (1.7%) died of hepatic failure within 3 months after tumor rupture. At the last follow-up, three (18.8%) patients were still alive at 4, 6 and 14 months after tumor rupture.

Conclusion: Spontaneous HCC rupture after TACE is a rare but potentially fatal complication and the patients have a poor prognosis.

Disclosure of Interest: None Declared

References:
Results: In six of the 16 patients extrahepatic lesions with non-physiological high uptake of 18F-FDG were detected. Four of these lesions (bone =3 and lung =1) were confirmed to be HCC metastases by either histology (n=5) or re-examination with ceCT/MRI. One of these patients had received a liver transplant due to HCC and recurrence in the transplanted liver was suspected. The remaining two findings was examined with biopsy and turned out to be benign: Warthin tumor of the parotid gland and oncocytic metaplasia in the nasopharynx. Only one of the four HCC metastases was detected by 18F-FDG PET/CT – a 2 cm large metastasis in the left scapula with destruction of bone cortex.

18F-FDG PET/CT lead to six additional extrahepatic findings (lymph nodes in porta hepatitis = 2, lymph node in relation to the ear = 1, colom polyp with low grade neoplasia = 1, fat necrosis = 1 and poor dental status = 1). One of the two patients with 18F-FDG positive lymph nodes in porta hepatitis have had a needle biopsy performed which did not show HCC.

Conclusion: These preliminary results indicate that 18F-FDG PET/CT have a markedly better sensitivity than 18F-FDG PET/CT for detection of extrahepatic metastases from HCC. Furthermore the number of non-HCC extrahepatic findings by 18F-FDG PET/CT seems to be fairly limited compared to 18F-FDG.

Disclosure of Interest:

References:

Disclosure of Interest: None Declared

P-236 THE ROLE OF SERUM ALPHAFETOPROTEIN DETERMINATION IN HCV-CIRRHOSIS AFTER ANTI-VIRAL TREATMENT

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Introduction: Serum alphafetoprotein (aFP) determination has been removed from recommendation of International Scientific Societies for the non invasive diagnosis of hepatocellular carcinoma (HCC), because of its low sensitivity and specificity. The sensitivity and specificity of aFP were never defined in HCV related cirrhosis as a sustained virological response (SVR) to antiviral treatments. To define sensitivity and specificity of aFP in patients with HCV related cirrhosis according to SVR to antiviral therapy.

Methods: Consecutive patients with HCV related cirrhosis, undergoing antiviral therapy from 2007 to 2013, were enrolled at the end of antiviral treatment. SVR was defined as undetectable serum HCV-RNA at 24th week after treatment. The diagnosis of cirrhosis was either histological or clinically based. All the patients underwent semiautomatic ultrasound (US) and aFP determination. HCC was diagnosed according to AASLD 2010 recommendation. aFP value was tested with commercial kits (Abbott Inc), normal value <7 ng/ml. Patients were classified into three mutually exclusive categories 1) aFP persistently normal (<7 ng/dl) 2) fluctuating levels of aFP 3) persistently elevated aFP levels (>7 ng/dl).

Results: 192 patients, 114 (62%) males, mean age 59 years (range 30-72) were enrolled. SVR was achieved in 98 (51%) patients. De novo HCC developed after antiviral therapy during a mean 6 years follow-up in 6 (6%) SVR patients and in 20 (21%) non-SVR patients (p<0.0001). In non-SVR patients aFP was persistently normal in 28 (30%) patients, fluctuating (3-54 ng/ml) in 15 (16%) and persistently elevated (8-74 ng/ml) in 51 (54%). HCC was diagnosed in 20 (21%) patients, 5 (18%) with persistently normal aFP and in 15 (22%) of the remaining patients (p=0.56); aFP sensitivity, specificity, PPV and NPV were 51%, 74%, 49% and 87%, respectively with an accuracy of 49%. In SVR patients aFP was persistently normal in 85 (87%) patients, fluctuating (3-20 ng/ml) in 3 (3%) and persistently elevated (8-25 ng/ml) in 10 (1%) (p=0.00001). HCC was diagnosed in 3 (3.5%) with persistently normal AFP and in 3 (23%) of the remaining patients (p=0.03). aFP sensitivity, specificity, PPV and NPV were 50%, 89%, 23% and 96%, respectively, with an accuracy of 87% (p=0.008).

Conclusion: In HCV related cirrhotic patients aFP has a different behaviour according to the achievement of SVR. aFP determination may have a role for the surveillance of cirrhotic patients who achieve SVR.

Disclosure of Interest: None Declared

P-237 NEW TECHNOLOGY TO DETECT OF TUMOR-FEEDING BRANCHES AND SIMULATE EMBOLIZATION AREA OF HEPATOCELLLAR CARCINOMA WITH SYNAPSE VINCENT DURING TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

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Introduction: To evaluate the usefulness of transcatheter arterial chemobolization (TACE) guidance software that uses the volume analyzer SYNAPSE VINCENT in detecting tumor-feeding branches and simulating embolization area of hepatocellular carcinoma (HCC).

Methods: The application soft of SYNAPSE VINCENT, liver analysis, were used in chemobolization of 6 patients of 7 HCCs. Detectability of tumor-feeding branches was compared versus that of nonselective digital subtraction angiography (DSA). Embolization area of chemobolization was evaluated by within one week CT findings after TACE.

Results: The maximal diameter of these tumors ranges 10 to 42mm (mean ± SD, 20.9 ± 10.6mm). The average time for detect tumor-feeding branches was 242 seconds. Total time to detect tumor-feeding branches and simulate the embolization area was 384 seconds.

Conclusion: This new technology has possibilities to reduce the amount of radiation exposure and to improve the therapeutic effect of TACE.

Disclosure of Interest: None Declared

P-238 INCIDENCE OF CANCER RELATED FATIGUE AMONG PATIENTS UNDERGOING THERAPY WITH SORAFENIB FOR HEPATOCELLULAR CARCINOMA AND ITS IMPLICATIONS ON THEIR EMOTIONAL WELL BEING IN INDIA

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Introduction: Fatigue is one of the most obstructing challenges among patients receiving anti cancer treatment with an immense impact on their Quality of Life (QOL). Although clinicians across the globe acknowledge the importance of regular assessment of fatigue, however it is not being assessed and documented in clinical practice in India and therefore remains unidentified parameter among oncology practice in this country, also very few studies in the literature exist reporting on Cancer-Related Fatigue (CRF) among Indian population.

Methods: For this study an exploratory design was adopted, using a purposive sampling method, patients (n=23, M=16, F=7) undergoing therapy with Sorafenib at Rajiv Gandhi Cancer Hospital and Research Center, Delhi, India, aged 36-74 years were included. The level of fatigue was assessed using 16-item Multidimensional assessment of Fatigue (MAF) scale and a semi structured in-depth interview schedule. These interviews were recorded, transcribed and analyzed.

Results: Irrespective of age, and education, 87% at the patients reported clinical significant fatigue, of which 57% experience extreme level of fatigue requiring immediate psychological intervention and 30% patients reported moderate level of fatigue, which is also clinically significant. Fear of therapy related side effects (33%), loss of appetite (31%) and fear of pain during chemotherapy by 24% were reported as the top most psychosocial issues by most of the patients followed by logistic issues by 7% and fear of dependency by 5%. Of all the patients, (63%) were aware of their diagnosis, of which only 7% were either fully aware or partially aware about the prognosis (13%).

Conclusion: Fatigue remains one of the most important clinical parameters among majority of Indian patients receiving therapy with Sorafenib for hepatocellular carcinomas irrespective of age and education. While one third of them report fear of therapy related side effects and loss of appetite due to therapy as topmost psychosocial concerns of therapy with Sorafenib, unlike nearly one-fourth also reported apprehension of pain during therapy as a significant psychological parameter. Indian cancer patients should be evaluated for treatable conditions that might contribute in achieving
P-239  IS LOW DOSE PEGINTERFERON ALFA-2A USEFUL IN PREVENTING RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER SURGERY?

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Introduction: Chronic hepatitis C often raises de novo cancer after hepatectomy for hepatocellular carcinoma (HCC). So, the treatment for hepatitis C with a low dose peginterferon alfa-2a(PEG INF) after surgery has a chance of conducting better prognosis.

Methods: From July, 2011 to June, 2014, we operated 176 cases of HCC. 22 cases, combined with hepatitis C and with no recurrence before the therapy, had PEG INF at dosage of 90 μg every two or three weeks. The profiles of the patients are shown in the table. We evaluated their clinical courses.

Results: In 12 cases, hepatitis C virus(HCV) were disappeared and another eight cases have removed HCV by interferon free therapies. Eight cases had recurrences in the liver. Seven of eight had liver cirrhosis and six lesions occurred after acquisitions of undetectable HCV. Four had liver resection, one surgery and RFA, two RFA and one TACE. Seven cases are surviving with no recurrence for 14-40(months).

Conclusion: Eight cases(36%) had recurrence, so, this therapy can not prevent early recurrence or de novo carcinogenesis. However, their clinical courses after the second treatment were good. PEG INF treatment after surgery may prevent second or third recurrence. The recurrent lesions maybe existed before this therapy and the viral disappearance possibly impacts on the clinical course later. Low dose peginterferon alfa-2a after surgery for hepatocellular carcinoma does not prevent the recurrence in early times.


Disclosure of Interest: None Declared

P-240  SYNERGISTIC EFFECT OF CD44 AND TGF-ß1 DURING EPITHELIAL-MESenchyMAL TRANSITION THROUGH AKT/ GSK3ß/B-CATENIN SIGNALING

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Introduction: The character of metastatic cells is strongly correlated to epithelial-mesenchymal transition (EMT) and cell adhesion molecules such as cadherin and CD44. CD44 is a receptor for hyaluronic acid, plays a role in migration, tumor cell metastasis, and invasion. Also, transforming growth factor beta (TGF-ß) signaling acts as the main factor in EMT. Therefore, TGF-ß1 induces the EMT and metastasis in HCC progression. We investigate the correlation between high CD44 and TGF-ß1 during EMT in HCC cell lines.

Methods: We determined the expression of CD44 through FACS. Also, we determined the expression of TGF-ß1 from the supernatant of SNL-354 and SNL-368 by ELISA. To investigate synergy effect of CD44 and TGF-ß1, we induced EMT by TGF-ß1 treatment. Also, we inhibited EMT by shCD44 transfection and TGF-ß1 inhibitors. Morphological changes were evaluated using microscopy and expression of EMT-related proteins detected by western blot. Also, EMT characteristics analyzed with sphere formation and migration assay.

Results: At the FACS analysis, the CD44 was highly expressed in SNL-354 (69.37±4.96%) and SNL-368 (82.69±3.15%) cell lines. TGF-ß1 was only expressed in SNL-368 but not in SNL-354. SNL-368 CD44+ cells showed lower E-cadherin expression and higher N-cadherin expression in expression up-regulation of AKT/GSK3ß/B-catenin pathway. By comparison, SNL-354 CD44+ cells increased expression of N-cadherin but did not increase the expression of E-cadherin, and then AKT/GSK3ß pathway showed down-regulation. But, TGF-ß1-treated SNL-354 cells exhibited morphological changes from an epithelial to a spindle-like mesenchymal morphology and accompanied by loss of E-cadherin and gain of N-cadherin with increased AKT/GSK3ß/B-catenin. Also, TGF-ß1-treated SNL-354 cells enhanced sphere formation and migration. On the other hand, TGF-ß1-inhibited SNL-368 cells showed reduced N-cadherin and AKT/GSK3ß/B-catenin. Also, TGF-ß1 inhibition decreased sphere formation and migration. Moreover, the treatment with both shCD44 and TGF-ß1-inhibitors reduced N-cadherin and AKT/B-catenin pathway and decreased migration in SNL-368 cells.

Conclusion: TGF-ß1 increased the expression of EMT-related proteins with CD44 in SNL-354 cells. TGF-ß inhibitors showed reversed EMT in SNL-368. In addition, co-expression of TGF-ß1 and CD44 were needed for tumor metastasis because it significantly increased sphere formation and migration.


Disclosure of Interest: None Declared

P-241  ANTI-HBE POSITIVITY IS PROTECTIVE FOR HCC DEVELOPMENT IN NAIVE HEPATITIS B VIRAL CIRRHOTIC PATIENTS TREATED WITH LONG-TERM ENTECAVIR MONOTHERAPY

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Introduction: Hepatitis B virus (HBV) DNA replication by potent antiviral agent can reduce fibrosis progression and cancer development in patients with chronic HBV infection. Although HBsAg positive is a significant risk factor for hepatocellular carcinoma (HCC), it is not yet known whether anti-HBE status is independently associated with HCC in HBV-related cirrhotic patients under long-term ETV treatment.

Methods: We performed a retrospective analysis of data from 303 naïve HBV-related cirrhosis patients who underwent 0.5 mg ETV monotherapy for at least 1 year between March 2007 and August 2013. Subjects were categorized into 4 groups according to HBsAg/anti-HBE status: group A (HBsAg positive, anti-HBE negative), B (HBsAg positive, anti-HBE positive), C (HBsAg negative, anti-HBE positive) and D (HBsAg negative, anti-HBE positive) at pretreatment point.

Results: For 303 patients, complete and partial virologic responses, virologic breakthrough rates, and genotypic resistance at 12 months were 85.8%, 8.9%, 5.3%, and 2.0%, respectively. The number of subjects in the subgroup categorized by HBsAg/anti-HBE status were 113 (37.9%, group A), 117 (38.7%, group B), 23 (7.7%, group C), and 40 (13.2%, group D), respectively. During the follow-up period of 37.1 (SD 16.7) months, 2 patients (0.7%) died, 2 (0.7%) received a liver transplant, and 25 (8.3%) developed HCC. Cumulative HCC incidences in group A, B, C, and D were 3.5%, 0%, 10%, and 1.7% at 3-year, 4.7%, 0%, 14.8%, and 2.5% at 5-year, respectively (p=0.028). The multivariate analysis showed that anti-HBE positivity (HR 0.133, 95% CI 0.034-0.524, p=0.004) and achievement of undetectable HBV DNA level (HR 0.95, 95% CI 0.014-0.635, p=0.015) were independent protective factors for developing HCC after adjustment for age and gender in HBsAg negative cirrhotic patients receiving long-term ETV treatment.

Conclusion: Surveillance for HCC development should be performed strictly in naïve hepatitis B related cirrhotic patients who show incomplete virologic response and those without anti-HBE.

Disclosure of Interest: None Declared
P-242
INFLUENCE OF THE ANGIOARCHITECTURE OF THE LIVER TUMORS ON THE SELECTION OF THE MICROSPPHERES DIAMETER

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Introduction: To study the possible applications and uses of various chemodrug-loaded microspheres according to the morphological variants of the tumor angiarchitect.

Methods: We analyzed the results of the morphometric study of three study groups of patients with liver metastases. Among these 10 patients (41%) had metastasized colorectal cancer, 8 pts. (33%) metastases of gastric cancer and esophageal, 6 pts. (26%) had a pancreatic cancer. The tumors diameter ranged from 3 cm to 7 cm. The samples of liver tissue biopsies were fixed in 10% buffered formalin solution (pH 6,8-7), dehydrated in alcohols of increasing concentrations, embedded in paraffin blocks, sectioned, of which a thickness of 3 - 5 microns followed by staining with hematoxylin and eosin. Each biopsy of the liver we determined by the volume fraction of the vessels of portal tracts, which had the tumor embolic agents. Calculation was performed using the automated system, using software VideoTest Morphology 5.0 (Axioskop 40 FL, Carl Zeiss).

Results: Morphological picture of metastatic colorectal cancer was presented by hypervascular masses with a diameter of vessels from 30 to 110 μm from the center to the periphery of the entities with the chaotic arrangement. Metastasis of cancer of the stomach and pancreas had heterogeneous vasculature with areas of hyper- and hypo vasularization, with diameters ranging from 20 to 130 μm. With considering of the masses angiarchitect we theoretically selected the appropriate P-value of the chemodrug microspheres for target chemoembolization (TACE). In view of the morphological pattern, we assumed that the smaller the diameter, the more efficiently will chemotherapeutic and ischemic effects of the procedure. In the presence of zones hypervascularization represented by small arteries to the target occlusion prefer to use is loaded with calibrated microspheres smallest diameter.

Conclusion: The TACE with chemodrug microspheres is one of the methods for the palliative treatment of liver tumors, which allows to stabilize the patient status and improve the quality of life. In theory, the choice of the size of the diameter microspheres should be based on the features of the tumors angiarchitect. The microspheres diameter should choose depending on the morphology and diameter of vascular tumor structure. It is advisable to use a precisely calibrated microspheres of 40μm in accordance with the diameter of the vessels from the tumor center to the periphery localization. Therefore, the clinical effect of this technique of choice depending on angiarchitect before the end is not completely explored, but it will be studied and reported in the future.

Disclosure of Interest: None Declared

P-243
LIVER TRANSPLANT FOR HEPATOCELLULAR CARCINOMA IN QATAR: AN INITIAL EXPERIENCE

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Introduction: Background: Liver transplant is the best available option for early unresectable hepatocellular carcinoma (HCC). Liver transplant program in Qatar started by the end of 2011 and has progressed steadily since then, and here we report our initial experience.

Methods: From December 2011 till present, 15 patients were transplanted, 8 of them had HCC. Diagnosis of HCC was based on dynamic magnetic resonance imaging. Selection of patients was limited to patients within Milan criteria. All patients were adults and received whole liver grafts from brain-dead donors. Patients were divided into 2 groups (HCC versus non-HCC groups) for comparison. Data were summarized as mean ± SD. Survival was calculated using Kaplan-Meir curves, and SPSS software (SPSS inc., Chicago, US, version 22) was used for analysis. P-value <0.05 was considered significant.

Results: Over a period of 4 years, a total of 15 patients were transplanted with a mean follow-up of 1.5 ± 1.3 years. The underlying liver disease was hepatitis C in 11 patients, and 14 patients were males with a mean age of 52.6 ± 7.4 years at time of transplant. The average time on waiting list was 8.3 ± 6.5 months. The average length of stay in the intensive care was 2.1 ± 0.7 days and for hospital stay was 12.5 ± 3.4 days. There was no significant difference between patients who were transplanted due to HCC and those who were transplanted due to non-HCC cause regarding age, sex, stay on the waiting list, average stay in intensive care unit and in the hospital post transplant (P-value >0.5). No reported cases of bile leak, biliary structure, post-operative early or late bleeding, hepatic artery thrombosis, or portal vein thrombosis in both groups. One-year and overall patient survivals after liver transplant are 93% and 87%, respectively. There were no significant difference between both groups regarding survival post-transplant, and no reported cases of HCC recurrence after transplant. Two patients were lost, one patient in HCC group due to massive myopericardial infarction 6 weeks post-transplant and one patient in non-HCC group due to liver metastasis (adenocarcinoma) of unknown origin.

Conclusion: Despite the initial small number, outcome of transplants is excellent in terms of patient survival compared to the international figures, and in terms of no surgical complications, and no recurrence of HCC. Patient selection and surgical team experience are of paramount importance to achieve such outcome.

Disclosure of Interest: None Declared

P-244
PHASE I STUDY TO EVALUATE SAFETY AND ANTI-TUMOR ACTIVITY OF AUTOLOGOUS T CELLS WITH ALPHA-FETO PROTEIN (AFPc332) RECEPTOR IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

Richard Finn1, 2Elliott Norry1, Suhaila Ranganathan3, Andrew Gerry4, Miguel Maroto5, Lini Pandit5, Rafael Amador6, 1UCDA, Johnsens Comprehensive Cancer Center, Los Angeles, 2Adaptimmune LLC, Philadelphia, United States, 3Adaptimmune Ltd, Oxford, United Kingdom

Introduction: AFP is an abundant serum protein in the fetus but is transcriptionally repressed shortly after birth. Reappearance of AFP in the circulation of adults is associated with liver regeneration, hepatocarcin, chronic liver diseases, or malignant growth, and elevation of serum AFP is associated with poor prognosis in HCC. Tissue microarrays suggest the frequency and intensity of immunohistochemistry (IHC) staining to be lower in non-HCC tissue than in HCCs that express AFP. When HCC expresses AFP, it tends to be homogeneous and of high intensity, which is attractive for an immunotherapeutic target. Adaptimmune has developed an enhanced affinity TCR engineered to target HCC. AFPc332 specifically recognizes the HLA-A*02-01 restricted AFP peptide antigen FMNRYEILE. Extensive preclinical safety evaluations have been performed. The proposed study is designed to determine safety and tolerability of AFPc332 in patients with advanced HCC.

Methods: This is a first-in-human study in patients with histologically confirmed HCC not amenable to transplant, resection or loco-regional therapy and failed sorafenib treatment (or couldn’t tolerate or refused sorafenib). Patients must be positive for HLA-A*02:01 allele. Eligibility may be broadened to include HLA-A*02:05, *02:06, or *02:07 for the expansion portion of the study. HLA-A*02:02, HLA-C*0404 and HLA-B*5103 alleles are excluded due to potential alloreactivity of the AFP TCR against these alleles. Patients must have AFP expression by IHC of ≥ 1+ in ≥40% HCC tumor cells, and ≤ 3+ at any level in non-cancerous liver tissue by IHC. Other key eligibility criteria include Child Pugh ≤6, ECOG 0-1 and adequate organ function. Autologous T cells obtained through leukapheresis are positively selected and expanded with CD3/CD28 magnetic beads and transduced with a self-inactivating lentiviral vector expressing an affinity enhanced AFP specific TCR. Patients will be enrolled using a modified 3+3 design and dosed as shown in the table below to evaluate safety, tolerability and dose limiting toxicities (DLT). Up to 30 patients may be enrolled including up to 12 patients at a selected dose. Primary objective is evaluation of the safety, tolerability and cell dose range for future studies and secondary objective is evaluation of anti-tumor activity. Exploratory objectives include evaluations of persistence of AFPc332 over time to be correlated with safety parameters and with antitumor activity, antigen spreading as a mechanism of response, and evaluation of post-treatment biopsies and surrogate tissues for biomarkers of immune response, antitumor activity and resistance.

Results: N/A

Image: N/A

Group | Number of Subjects | AFPc332 T Transduced cells | Cyclophosphamide and Fludarabine doses |
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<td>CY: 500 mg/m²/d x 3d Flu: 20 mg/kg/d x 3d</td>
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Conclusion: N/A

Disclosure of Interest: None Declared

P-245
COST ANALYSIS OF MULTIMODAL TREATMENT IN HEPATOCELLULAR CARCINOMA

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Introduction: Therapeutic procedures for hepatocellular carcinoma include interventional and surgical options and ultimately liver transplantation, with a high impact on total cost of hospitalization.
and medical care. We aim to analyze the cost of these procedures in patients admitted to the Clinic of Internal Medicine of Fundeni Clinical Institute with the diagnosis of hepatocellular carcinoma between January 2014 and January 2015.

Methods: We included 159 patients diagnosed with hepatocellular carcinoma who were consecutively admitted to our Clinic, with a follow-up period of one year (up to January 2016). The patients were classified according to the BCLC classification and treated accordingly. We analyzed the cost of hospitalization for each procedure and we correlated these costs with survival parameters.

Results: Out of 159 patients, 111 underwent a single procedure (8 surgical resections, 59 transarterial chemoembolization (TACE) - 29 patients with conventional TACE and 30 patients with chemomobilization with doxorubicin eluting beads), 15 radiofrequency ablations, 15 systemic chemotherapy and 14 best supportive care. The rest of the patients underwent several procedures, with a better outcome in terms of survival parameters. A total of 5 liver transplants were performed. Analysis of mRECIST assessment found that 8% of patients obtained a complete response, 43% obtained partial response, 47% presented disease progression and 2% were classified as stable disease. We evaluated survival parameters in patients with a single therapeutic procedure and found that surgical resection had a progression free survival of 12 months and an overall survival of 22 months. Conventional TACE had a progression free survival of 6 months and an overall survival of 20 months. DEB-TACE had a progression free survival of 7 months and an overall survival of 11 months. Radiofrequency ablation had a progression free survival of 14 months and overall survival of 22 months. In patients undergoing treatment with sorafenib or the best supportive care there was no disease free survival. Overall survival in these cases was of 9 months for sorafenib and 8 months for supportive care. Cost-effectiveness was expressed as RON/QALY. As such, for surgical resection QALY was of 4.35, with a cost-effectiveness of 3770 RON/QALY. For radiofrequency ablation QALY was of 4.85 with a cost-effectiveness of 1443 RON/QALY. For conventional TACE, QALY was of 3.25 while for DEB TACE it was 3.10, with a cost-effectiveness of 1914 RON/QALY and 3387 RON/QALY respectively. Chemotherapy with sorafenib had a QALY of 0.38, with a cost-effectiveness of 657 RON/QALY.

Conclusion: Liver transplantation was associated with the best outcome. On the short term, radiofrequency ablation and surgical resection were more effective than chemoembolization, but this advantage disappears later in the evolution. The highest QALY was obtained in the group of patients who underwent surgical resection and radiofrequency ablation. Multimodal treatment is the best solution for maintaining patients on the waiting list for liver transplantation.


Disclosure of Interest: None Declared

P-246 USEFULNESS OF THE ALBI GRADE FOR CHILD–PUGH GRADE A PATIENTS TREATED WITH TACE

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Introduction: For patients with hepatocellular carcinoma (HCC), baseline liver function is a pivotal factor associated with prognosis. Recently, a novel scoring system known as the “ALBI grade” was reported1), which enables the stratification of liver function within the same Child–Pugh grade. In the present study, we aimed to clarify the usefulness of the ALBI grade for predicting the prognosis and making treatment decisions for HCC patients who first underwent transarterial chemoembolization (TACE).

Methods: We included 208 patients who were Child–Pugh grade A and were treated with TACE. Baseline liver function was investigated with the Child–Pugh score and ALBI grade, and tumor burden was assessed with up-to-7 criteria (IN and OUT). After the first TACE, additional TACE was performed only when the residual or new viable tumors were identified during the follow-up period (on demand TACE). The overall survival and Child–Pugh grade exacerbation rate (CPER) were analyzed as the clinical outcomes.

Results: In total, the median survival time was 37.1 months, and CPER at 24 months was 74%. Among 116 patients with Child–Pugh score 5, 57 and 59 were classified into ALBI Grade 1 and Grade 2, respectively. Among 90 patients with Child–Pugh score 6, only 2 were classified into ALBI Grade 1. ALBI Grade 1 patients showed a better OS (MST 66 months vs. 35 months, p = 0.067) and a lower CPER at 24 months than Grade 2 patients (50% vs. 91%, p < 0.007). In patients with up-to-7 OUT, CPER at 12 months was significantly higher than in those with up-to-7 IN (22% vs. 9%, p = 0.059). Patients with up-to-7 OUT needed significantly more frequent TACE procedures within 12 months than in those with up-to-7 IN (p = 0.023). In patients with up-to-7 OUT, CPER at 24 months exhibited no significant difference compared with those with up-to-7 IN (89% vs. 77%, p = 0.33). However, ALBI Grade 1 patients had a significantly lower CPER at 24 months compared with ALBI Grade 2 patients after stratification by up-to-7 criteria. Among the up-to-7 OUT patients, CPER at 24 months was 56% and 84% for ALBI Grade 1 and Grade 2 patients, respectively, (p = 0.003). Moreover, among the up-to-7 IN patients, CPER at 24 months was 42% and 81% for ALBI Grade 1 and Grade 2 patients, respectively, (p = 0.006).

Conclusion: The ALBI grade was useful for subclassifying a Child–Pugh score of 5 and assessing the risk of Child–Pugh grade exacerbation for patients treated with TACE. Therefore, in patients with ALBI Grade 2 and up-to-7 OUT, treatment decisions accounting for liver function deceleration should be considered.


Disclosure of Interest: None Declared

P-247 RADIOFREQUENCY ABLATION (RFA) FOR IMMEDIATELY RECURRENT AFTER TRANS CATHETER ARTERIAL CHEMO-EMBOLIZATION (TACE) WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: According to clinical practice guideline for HCC 2013 of the Japan Society of Hepatology, TACE is first recommended for more than three nodules of HCC in patients without poor liver function. Moreover, if repeated TACE would be non-effective, treatment with sorafenib is recommended as a next method. However, response rate of sorafenib is very low, and its suitable introduction timing has not yet been established. Thus, we always try to control HCC by RFA regardless of the number of the nodules. We have validated the effectiveness of our RFA strategy for the immediately recurrence after TACE with more than three HCC nodules.

Methods: From April 2006 to the end of December 2015, 796 patients with HCC were performed RFA at our hospital. Out of them, we have investigated a prognosis and treatment efficiency in 77 patients who had more than three nodules and treated by RFA for immediately recurrence after TACE.

Results: The median number of the lesions is 7 in the 77 patients (M/55/22) who were performed TACE (52 cases were excluded because of uncontrollable lesions). Median survival time (MST) of the 77 patients is 25 months (2.08 years), and the survival rates are as follows; 1 year: 71%, 3 years: 38%, 5 year: 20%.

Conclusion: We have shown that MST of our RFA for the immediately recurrence after TACE is (was) longer than 2 years. (MST of sorafenib) in the SHARP examination was 10.7 months (88.8 years). Poor liver function (Child-B) is strongly related to the inefficacy of sorafenib and maneuver discontinuing taking it due to the side effects. Accordingly, in recent years, only the early introducing sorafenib has been recommended. It is noteworthy that RFA can be performed without lowering QOL of the patient even if whose liver function is poor. Therefore, we propose that RFA prior to even early introduction of sorafenib is recommended for the immediately recurrence after TACE in multiple HCC nodules.

Disclosure of Interest: None Declared

P-248 THERAPEUTIC STRATEGY BASED ON RESCTION FOR LOCALLY ADVANCED HEPATOCELLULAR CARCINOMA OF UICC7 STAGE III IN A CURATIVE INTENT

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Introduction: Some authors, especially in Asian countries, have aggressively resected locally advanced hepatocellular carcinoma (HCC) with extrahepatic major vascular tumor thrombus or large multiple tumors. However, the outcome is still unsatisfactory, and there are controversies in selection of therapeutic modalities and strategy. This paper reviews our experience to resect HCC with UICC7 stage III, and propose the therapeutic strategy in a curative intent.

Methods: From 1999 to 2013, 34 patients with stage IIB were underwent curative hepatic resection. 10 patients were performed downstaging or downsizing chemotherapy followed by hepatic resection (Cx Group) and 24 patients were performed hepatic resection alone (Non-Cx Group). Outcomes of stage IIB among groups were analyzed. Outcomes of Vp3/V4 and Vn2/V3 were analyzed individually.

Results: The patient and tumor characteristics of Cx Group (n=10) and Non-Cx Group (n=24) had no differences (Pv3/V4/Pv2/V3; n=16/6/3/9). The 1, 3, 5 years overall survival rates (OS) of Cx Group and Non-Cx Group was 90%, 70%, 47% and 43%, 15%, 5%, respectively (p=0.0003). The 1, 3 years disease free survival rates (DFS) of Cx Group and Non-Cx Group were 62%, 32% and 21%, respectively (p=0.0054). Among Vp3/V4 patients (n=22), 1, 3, 5 years OS of Cx
Group and Non-Cx Group were 100%, 86%, 68% and 42%, 17%, 0%, respectively (p<0.0017). The 1, 2 years DFS of Cx Group and Non-Cx Group of Vp3/4 were 100%, 53% and 24%, vs respectively (p=0.0095). Among Vp2/3 patients (n=12), the median survival time of Cx Group (n=3) and Non-Cx Group (n=9) were 708 and 689 days with no differences (p=0.9471, p=0.9271).

Conclusion: Even in patients with stage IIB, preoperative chemotherapy improved outcome of Cx Group. Especially, in patients with Vp3/4 patients had excellent outcome even though they were thought to be poor candidates of hepatic resection. The preoperative chemotherapy had no effect in patients with V2/3 and urged to establish new therapeutic strategies. The preoperative chemotherapy for stage IIB improves outcome, especially in patients with Vp3/4. Vp3/4 patients were considered to be “Borderline resectable” and should be avoided readjuvanted chemotherapy.

Disclosure of Interest: None Declared

P-249

**EFFECTIVENESS OF CISPLATIN ELUTING BEADS TACE FOR EARLY / INTERMEDIATE STAGE HCC**

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Introduction: To evaluate the efficacy and safety of transarterial arterial chemoembolization using cisplatin eluting HepaSphere (CEH-TACE) for unresectable hepatocellular carcinoma (HCC) compared with conventional TACE (CTACE).

Methods: We enrolled 19 patients for CEH-TACE and 18 patients for CTACE (CEH TACE / CTACE, male: 12/13, mean age 77.6±7.4 y.o., etiology: HBV/HCV/Hepatitis-associated alcohol/10/2/2/2/4/4; Child Pugh classification: A/B:16/1, cStage:1B/11, 5/13, mean tumor diameter: 38.9±14.5mm / 37.3±16.7mm) between April 2014 and September 2015. CEH-TACE was performed using cisplatin 50mg (CA -call - Nippon Kayaku Co. Japan) -eluting HepaSphere 50-100μm (BioSphere Medical, Inc. USA). As the endpoint of the study, the efficacy and safety of the procedure were evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST) with dynamic contrast-enhanced CT within 3 months post therapy, and Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0, respectively.

Results: TACE was successfully performed in all patients. It was no significant statistical change in response rate and disease control rate (CEHTACE vs CTACE, response rate: 58.0%/66.7%, p=0.737, disease control rate: 84.2%/77.8%, p=1.00). In post-embolization syndrome, fewer was significant statistical change between both group (grade 1-2: 5.26 / 38.9%(p=0.019)), no major adverse events occurred.

Conclusion: CEH-TACE is a safe and effective treatment for unresectable HCC without adverse events.


Disclosure of Interest: None Declared

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**11 YEAR LONGITUDINAL ANALYSIS OF SURVIVAL TRENDS IN SOLITARY UNRESECTABLE HEPATOCELLULAR CARCINOMA**

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Introduction: For patients within Milan criteria [i.e. 3 lesions each less than 3.0 cm or 1 lesion less than 5.0 cm] liver transplantation has become the standard of care. Other intent to cure strategies include energy-based eradication of tumour through percutaneous and surgical ablation (microwave, radiofrequency, cryoablation) with a general understanding that the underlying liver parenchyma has developed metastatic hepatocellular carcinoma (HCC). However, currently no consensus exists for the management of patients with large, solitary unresectable HCC (sunHCC). This is at least in part due to the inherent challenges of surgical resection, the physical limitations of local-regional therapy, the erratic distribution of embolic therapy, and unvalidated data regarding systemic chemotherapy as well as biological therapy. Furthermore, it is not known whether the introduction of sorafenib, drug eluting beads (EBB), stereotactic radiotherapy (SIRT), and radioembolisation (Y90) as compared to chemoembolisation (TACE) has translated into improvement to survival in this population.

Methods: A retrospective chart review over 11 years from a single academic centre was performed. Inclusion criteria included: no previous therapy and sunHCC. Medical records were reviewed to collect demographic data, underlying liver disease, Child-Pugh score (CPS), macrovascular invasion (MI), extrahepatic metastases (EH), treatment, and overall survival (OS).

Results: Data was analyzed with one-way ANOVA, Kruskal-Wallis testing, and multivariable regression. 257 datasets were completed: n=77 palliation, n=15 chemotherapy, n=12 sorafenib, n=17 bland embolization (TAE), n=75 TACE, n=49 DEB, n=3 SBRT. MI, EH, and CPS were found to be strong predictors of OS (p<0.001, 95% CI). Statistical significance was noted between tumor size and OS (p<0.05). A statistically significant difference in OS was found between patients palliated versus treated (p<0.00). TAE, TACE, and SBRT yielded improved outcomes compared to sorafenib and Y90. No statistical difference was demonstrated between TAE, lipiodol TACE, or DEB-TACE. Pre and post sorafenib era yielded no significant difference in OS (mean 221 vs 238d). A trend of improved survival with Y90 vs sorafenib was noted (5152 vs 239d).

Conclusion: In sunHCC, macrovascular invasion, extrahepatic disease, and Child Pugh class were found to be strongly statistically significant predictors of overall survival. Statistically significant decrease in survival was noted when palliation was chosen as compared to other treatment methods.

Disclosure of Interest: None Declared

P-251

**MELATONIN AND SILYMARIN COMBINATION THERAPY OF ADVANCED HEPATOCELLULAR CARCINOMA**

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Introduction: Liver cancer is second-leading cause of cancer-related deaths worldwide, killing >600 000 people annually. Melatonin has complex effects on apoptotic pathways, inhibiting apoptosis in immune cells and neurons but enhancing apoptotic cell death of cancer cells. Inhibits proliferation/ metastasis cancer cells. Silymarin provides cardioprotective activity against ischemia-reperfusion induced myocardial infarction in rats. Silymarin was shown to protect the liver from the cytotoxic effects of anti-tuberculosis drugs by decreasing serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (APL) levels. This effect was related to the anti-oxidant effects of silymarin.

Methods: We undertook a study to investigate the therapeutic potential of orally administered melatonin in patients with hepatocellular carcinoma (HCC). Twenty-three patients received melatonin in doses ranging from 7 mg/m2/day to 700 mg/m2/day in four divided doses and silymarin 10 mg per day.

Results: Two were excluded from analysis. After a median follow-up of 8 weeks, Seven patients had partial responses, six additional patients had stable disease. Sites of response included the liver, and lymph nodes. The median response duration was 36 weeks for the partial responders. There was a suggestion of a dose-response relationship. The toxicity encountered was minimal and consisted primarily of fatigue in 20 of 34 patients. Melatonin also appeared to reduce serum levels of Alpha-fetoprotein (AFP). Also significant decrease were encountered in serum levels of ALP, ALT, AST, GGT and Lactate dehydrogenase (LDH).

Conclusion: We conclude that further study of melatonin and silymarin as a potentially useful agent in advanced HCC is warranted.

Disclosure of Interest: None Declared

P-252

**EFFICACY OF COMBINED THERAPY WITH SORAFENIB AND RADIOTHERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA WITH EXTRAHEPATIC SPREAD OR MACROVASCULAR INVASION**

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Introduction: Sorafenib is recognized as a standard therapy for Barcelona Clinic Liver Cancer stage C (advanced stage) hepatocellular carcinoma (HCC) with extraphepatic spread or macrovascular invasion. However, its treatment efficacy is limited and insufficient. The efficacy of radiotherapy as a local control therapy for extrahepatic metastasis or macrovascular invasion of HCC has been reported. However, because tumors often progress in not only extraphepatic lesions but also intransaphepatic lesions in advanced-stage HCC, it remains unclear whether the addition of radiotherapy as a local therapy to sorafenib improves survival or not. This study investigated the efficacy of combined therapy with sorafenib and radiotherapy to treat advanced HCC with extraphepatic spread or macrovascular invasion.
P-253 LOCAL THERAPY COMBINED WITH SORAFENIB IN THE TREATMENT FOR ADVANCED INITIAL RECURRENT HEPATOCELLULAR CARCINOMA AFTER LIVER RESECTION

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Introduction: To retrospectively evaluate the clinical efficacy of local therapy combined with sorafenib in the treatment of advanced initial recurrent hepatocellular carcinoma (HCC) after liver resection.

Methods: From July 2009 to October 2014, a total of 108 consecutive patients administered with radiofrequency ablation (RFA) combined with sorafenib (RFA-Sorafenib group, n = 55) or transarterial chemoembolization (TACE) combined with sorafenib (TACE-Sorafenib group, n = 53) for advanced initial recurrent HCC after liver resection were enrolled. The treatment-related adverse effects, treatment efficacy of these patients were evaluated and compared between these two groups.

Results: The most common treatment-related adverse events were hand-foot skin reaction (108/108, 100%) and diarrhea (101/108, 93.5%) for all patients. Seventy-eight patients (70/108, 72.2%) were dead due to tumor progression during follow-up. The median OS was 14.0 months for all patients. The 1-, 2-, and 3-year overall survival (OS) rates were 63.8%, 34.3%, and 30.9% for RFA-Sorafenib group, and were 53.3%, 22.8%, and 11.8% for TACE-Sorafenib group, respectively (P = 0.024). Among patients with <3 intrahepatic tumors (n = 50), RFA-Sorafenib group (n = 37) showed better survival outcomes than TACE-Sorafenib group (n = 13) (P = 0.004). Multivariate analysis indicated that AFP distribution (P = 0.036) and treatment group (P = 0.028) were the significant prognostic factors for OS after treatment.

Conclusion: Combined local therapy and sorafenib is an acceptable treatment for patients with advanced initial recurrent HCC after liver resection. RFA-sorafenib is superior to TACE-sorafenib and may improve survivals, especially in patients with <3 intrahepatic lesions.

Disclosure of Interest: None Declared

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Conclusion: This study highlights the importance of keeping in mind that patients with HCC may be used as additional treatment agent in HCC because carcinogenic bacteria can be seen which is located in the Caucasus region, mountains of Georgia, approximately 2400 meters above sea level. A total of 32 patients cell cultures (aged from 28 to 62 years) with locally advanced HCC were studied. Control group was represented by 14 healthy persons hepatocytes cultures (aged from 28 to 72 years). Incubation all the cell culture were in CO₂ incubator at 12 days, medium for the cell culture were used plasma for each own patients. We have studied in all the cells cultures for each separately before and after incubation with “Chinchao Lake Bacteriophage” the expression of genes including in the cell cycle - We tracked the mRNAs and the gene of topoisomerase I and II using the technique of Western-Blot (sensitivity in cytotoxic inhibitors of topoisomerase). Monitoring was conducted on the Cells proliferative activity by others biological methods (ATP-TCA, Western-Blot, PRCRT-POR, Fluorescent Microscopy).

Results: Our results showed that expression of topoisomerase I and II genes were very decreased after influence the specific “Chinchao Lake Bacteriophage” comparison control group Where the bacteriophages have not influence on the healthy cell division.

Conclusion: This research is very important about natural treatment of cancer. In the Nature exist natural anti-cancer agent as: “Cat & mouse”, “wolf & rabbit”, “Bacteria & Antibiotic Produced” etc. This result indicate that this super specific bacteriophages is include while some uncommon pathways in the regulation of expression topoisomerase I and II genes only cancer cells of HCC, and may be used as additional treatment agent in HCC.

Disclosure of Interest: None Declared

P-257 EFFECTS OF IRON CHELATOR, DEFERASIROX, IN HEPATOCELLULAR CARCINOMA IN BASIC AND CLINICAL STUDIES

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Introduction: Iron is essential for cellular metabolism, including DNA synthesis. Although iron chelators are not classified as anticancer drugs, they exert antiproliferative effects in several cancers. We have reported that deferoxamine (DFO) can prevent the development of preneoplastic lesions in mice. The aim of this study is to evaluate the inhibition of DFX against HCC in basic and clinical studies.

Methods: In vitro, the effect of DFX was analyzed using the MTT assay and the activity of caspase-3 in 3 HCC cell lines (HepG2, Hep3B, Huh7). In vivo, we used the mice HCC model using a N-nitrosodiethylamine injection and analyzed the effect of DFX. Six advanced HCC patients who became refractory to chemotherapy were enrolled in the clinical study, which was approved by the Institutional Review Board of our hospital and was registered online (UMIN 000013451). The initial dose of DFX was 10 mg/kg/day and the dose increased by 10 mg/kg/day every week until 30 mg/kg/day. One course of DFX therapy consisted of 28 consecutive days. If a serious clinical toxicity (according to CTCAE v.3.0) occurs, the dose is adjusted.

Results: DFX inhibited the proliferation and induced the activity of caspase-3 in a dose-dependent manner in 3 HCC cell lines. In the mice HCC model, DFX significantly inhibited the development of liver tumors compared with control. In addition, hepatic, transferin receptor 1, and HIF-1α mRNA expression levels in both tumor and non-tumor areas were significantly higher in the DFX group. In clinical study, elevated creatinine occurred in six patients (grade 3 in 1, and grade 2 in 5 patients), and all patients improved with reduction in dose. Anemia occurred in 4 patients (grade 1 in 2, and grade 2 in 2 patients). Throughout first course, all patients required dose reduction and one discontinued one course of the therapy. We assessed the tumor response in five patients except one patient who discontinued; one patient exhibited stable disease, and 4 patients exhibited progression disease. The 1-year survival rate of six patients was 20% (median survival time, 271 days).

Conclusion: We demonstrated the inhibition of DFX against HCC in basic study. However, we did not show the effectiveness of DFX therapy because the dose escalation of DFX cannot be performed due to the toxicities, especially renal dysfunction.

Disclosure of Interest: None Declared

P-258 EPIDEMIOLOGY OF METASTATIC HEPATOCELLULAR CARCINOMA IN A RAPIDLY GROWING COMMUNITY

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Introduction: Our community has grown rapidly over the last few years, population has increased from 1.7 to 2.4 millions between 2011 and 2015. Newly diagnosed cases of hepatocellular carcinoma (HCC) have almost doubled during the same period. The purpose of this study is to investigate characteristics of patients diagnosed with HCC, and to identify predictors of metastatic tumors.

Methods: This study includes patients diagnosed with HCC between 2011 and 2015 in Qatar, either primary liver tumors as well as liver metastases were excluded. Data including patient and tumor characteristics, clinical and laboratory investigations at time of diagnosis and during follow-up were collected from medical records. Univariate analysis was done to identify potential predictors of metastatic HCC using Chi-square test and t-test. Multivariate logistic regression analysis was done to assess independent predictors of metastatic HCC. P-value of <0.05 was considered significant and SPSS software was used for analysis.

Results: A total of 180 patients were diagnosed with HCC, 47 of them (26%) developed metastases. There were 150 male patients, and mean age at time of diagnosis was 58+10.5 years. Follow-up ranged from 0.1 to 4.3 years with a mean of 1.0 ± 1.1 years. Single site metastasis was diagnosed in 10 patients while 37 patients had multiple sites metastases. Metastases included abdominal sites in 24 patients, thoracic in 13, bone in 7 and unusual sites in 3 patients. Potential predictors of metastatic HCC were multi-local HCC, bilobar lesions, macro-vascular invasion, and tumor diameter >5cm. Multivariate regression analysis showed that tumor diameter >5cm is independent predictor of metastatic HCC (OR=3.411, 95%CI= 1.607-7.242) (P=0.001).

Conclusion: Metastatic HCC is rare, it represents 26% of our cohort and tumor >5 cm is associated with high risk of metastasis.

Disclosure of Interest: None Declared
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SIR-Spheres Y-90 microspheres are approved for use in Argentina, Australia, Brazil, the European Union (CE Mark), Switzerland, Turkey, and several countries in Asia for the treatment of unresectable liver tumours. In the US, SIR-Spheres Y-90 resin microspheres have a Pre-Market Approval (PMA) from the FDA and are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

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The three largest ever RCTs investigating selective internal radiation therapy (SIRT) and standard-of-care systemic therapy in unresectable, intermediate to advanced hepatocellular carcinoma (HCC) are enrolled. Two studies comparing SIR-Spheres™ Y-90 resin microspheres with sorafenib, will report by mid-2017. A third study involving combination treatment with both modalities is expected to report in 2018.

To learn more, please attend our Sirtex satellite symposium “SIR-Spheres Y-90 resin microspheres – Shaping the future in primary liver cancer” on Saturday, September 10 2016, 7:30 am at the Fairmont Hotel Vancouver.
Essential Information

Indication: 1. Treatment of hepatocellular carcinoma. 2. Treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. 3. Treatment of patients with locally advanced, inoperable, and metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma refractory to radioactive iodine.

Contraindications: Hypersensitivity to sorafenib or to any of the excipients. Warnings and Precautions: Increased risk of skin reactions and rash. Increased risk of serious adverse reactions including those that may be life-threatening. Increased risk of adverse reactions in patients with hepatocellular carcinoma. Increased risk of bleeding in patients with renal cell carcinoma. Increased risk of arterial bleeding in patients with differentiated thyroid carcinoma. Increased risk of bleeding in patients with squamous cell carcinoma of the lung. Increased risk of bleeding in patients with renal cell carcinoma who are using warfarin concomitantly. Increased risk of bleeding in patients with squamous cell carcinoma of the lung who are using warfarin concomitantly. Increased risk of bleeding in patients with locally advanced, inoperable, and metastatic differentiated thyroid carcinoma who are using warfarin concomitantly.

ADVERSE REACTIONS


WARNINGs and Precautions:

Contraindications:

Hypersensitivity to sorafenib or to any of the excipients.

Indication:

Nexavar® (sorafenib) tablets are indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

For 10 years NEXAVAR® has been extending patient survival1,2, has been unsurpassed in clinical trials as the standard of care3, has partnered with leaders in liver cancer to advance uHCC treatment care, has been a trustworthy and reliable brand for physicians and patients, and has laid the foundational groundwork for the next 10 years of uHCC care.

References: