



EASL

The Home of Hepatology

HCC SUMMIT

HCC SUMMIT PROGRAMME & ABSTRACTS

**2-5 FEBRUARY 2017
GENEVA, SWITZERLAND**

SCIENTIFIC COMMITTEE

Basic Programme: HCC and the hallmarks of cancer

Tom Luedde, *Germany*

Helen Reeves, *United Kingdom*

Clinical Programme: Liver cancer management

Alejandro Forner, *Spain*

Franco Trevisani, *Italy*



Basic Course



Clinical Course



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WELCOME MESSAGE

Dear Colleagues,

The European Association for the Study of the Liver (EASL) is delighted to be your host at the second EASL HCC Summit. Our first summit took place 3 years ago and was a great success, reaching both scientists and clinicians with an interest in liver cancer. This year's programme will be equally as informative and stimulating, covering a broad range of topics presented as high quality presentations by renowned experts.

Our Basic Science programme, 02-03 February, will be centred around 'The Hallmarks of Cancer', including talks from eminent scientists in the field, with a focus on translational advances most relevant to patients with primary liver cancer. This will be followed by the Clinical programme, 04-05 February, showcasing state-of-the-art talks on the most up to date techniques for the management of patients with liver cancer.

Aimed at a broad audience, we have no doubt that there will be something for everyone.

Sincerely,

The Scientific Committee

ORGANISING COMMITTEE

BASIC PROGRAMME



Tom Luedde
Germany



Helen Reeves
United Kingdom

CLINICAL PROGRAMME



Alejandro Forner
Spain



Franco Trevisani
Italy

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ACKNOWLEDGEMENTS

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EXHIBITORS





EASL

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#WorldCancerDay

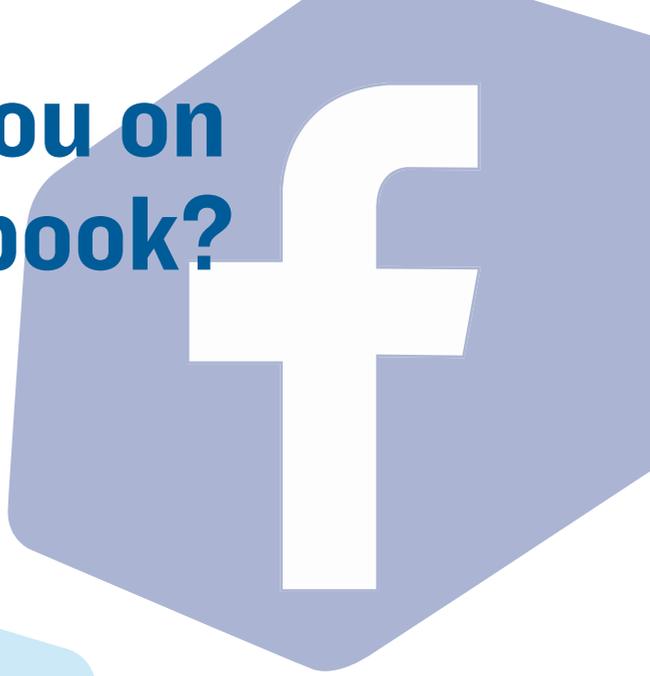
**Visit the EASL booth
to collect your bracelet
and join the fight
against liver cancer**

GENERAL INFORMATION



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Live tweeting!
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GENERAL INFORMATION

CONFERENCE VENUE

Starling Hotel Geneva
Route François-Peyrot 34
1218 le Grand-Saconnex / Genève
Suisse

LANGUAGE

The official language of the conference is English.

CLIMATE

The climate of Geneva is temperate, oceanic (Köppen: Cfb). Winters are cool, usually with light frosts at night and thawing conditions during the day. Precipitation is adequate and is relatively well-distributed throughout the year. Ice storms near Lac Léman are quite normal in the winter. Geneva, in certain years, receives snow in the colder months of the year.

The nearby mountains are subject to substantial snowfall and are suitable for skiing. Many world-renowned ski resorts such as Verbier and Crans-Montana are just over two hours away by car. Mont Salève (1400 m), just across the border in France, dominates the southerly view from the city centre.

NAME BADGES

All participants are kindly requested to wear their name badges throughout the EASL HCC Summit in order to be admitted to the lecture halls and other scheduled activities.

REGISTRATION AND ACCOMMODATION

All participants are invited to register online in order to save time upon their arrival at the conference.

Hotel accommodation for the EASL HCC Summit will be offered to participants during the online registration process. Detailed information, as well as access to the online registration is available on the website. Registered participants are entitled to reduced rates in the conference hotel.

REGISTRATION DESK

The onsite registration desk will be open at the conference venue at the following times:

- Thursday 2 February 2017
08:00 – 18:30
- Friday 3 February 2017
08:00 – 19:00
- Saturday 4 February 2017
08:00 – 19:30
- Sunday 5 February 2017
08:00 – 12:30

CME ACCREDITATION

The “EASL – HCC SUMMIT 2017 (Clinical and Basic scientific programmes)” has accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), <http://www.uems.net/>

The “EASL – HCC SUMMIT 2017 (Clinical and Basic scientific programmes)” is designated for a maximum of (or ‘for up to’) 18 hours of European external CME credits. Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

All attendees will receive an email with a link to a questionnaire at the end of the conference. Upon completion of the questionnaire, attendees should receive their certificates of attendance.

No certificate of attendance will be printed onsite.

Certificates of attendance will only be sent to delegates who attended the conference.

TRANSPORT TO GENEVA

Geneva is a destination which is very well deserved by airlines and high-speed train. The city has one international airport: Geneva International Airport (GVA).

Visit the airport website: <https://www.gva.ch/en/desktopdefault.aspx>

Visit the official national railway (Gare Cornavin) website: <http://www.sbb.ch/en/home.html>

TRANSPORT TO THE VENUE

Access from the airport

Enjoy the free Starling Hotel shuttle service every 15 minutes from / to Geneva airport from 5.10 am to 11.45 pm.

Access by train

From the Geneva Central Railway Station (Gare Cornavin) take the bus n°5 towards “Aéroport/Palexpo” get off at “Grand-Saconnex Place” cross the road and go towards the hotel restaurant La Colombière.

Access by public transport (bus)

From the city centre, take the bus n°5 towards “Aéroport/Palexpo” get off at “Grand-Saconnex Place” cross the road and go towards the hotel restaurant La Colombière.

Free public transportation passes are offered by the city of Geneva during your stay in one of the city hotel.

PARTICIPANTS' LIST

The participants' list will be displayed on-site.

BANKING, SAFETY AND SECURITY

The currency used in Switzerland is the Swiss Franc (CHF). Foreign currency can be exchanged at banks, bureau de change and automatic currency exchange machines. Most of shops, hotels and restaurants are also accepting EURO currency.

Please do not leave bags or suitcases unattended at any time, whether inside or outside the session halls. Hotels strongly recommend that you use their safety deposit boxes for your valuables.

LIABILITY AND INSURANCE

The EASL Office cannot accept liability for personal accidents or loss of or damage to private property of participants. Participants are advised to take out their own personal travel and health insurance for their trip.

CHOLANGIOCYTES IN HEALTH AND DISEASE: FROM BASIC SCIENCE TO NOVEL TREATMENTS

09-11 JUNE, 2017
OSLO, NORWAY

Scientific Organising Committee

Jesus M. Banales, *Spain*

Peter L. Jansen, *Netherlands*

Nicholas F. LaRusso, *United States*

Marco Marzioni, *Italy*

KEY DEADLINES

Abstract submission: 11 MARCH 2017

Early registration: 09 APRIL 2017

SCIENTIFIC PROGRAMME



SCIENTIFIC PROGRAMME

HCC AND THE HALLMARKS OF CANCER: STEPS TOWARDS NOVEL THERAPEUTIC STRATEGIES

THURSDAY 2 FEBRUARY 2017

Welcome and introduction

12.00 – 12.05 Helen Reeves (*United Kingdom*)
Tom Luedde (*Germany*)

OPENING LECTURE

12.05 – 12.30 **The challenge – Bridging the gap between basic science and clinical practice**
Peter Schirmacher (*Germany*)

SESSION I MODELS AND TOOLS FOR IDENTIFICATION AND TRANSLATION OF NOVEL CANDIDATES

12.30 – 14.00 **Chairs: Helen Reeves (*United Kingdom*)
Jessica Zucman Rossi (*France*)**

12.30 – 13.00 **Identifying candidates: ‘Omics’ and next-generation sequencing in HCC**
Jessica Zucman Rossi (*France*)

13.00 – 13.30 **Animal models of HCC: Which models mimic best human biology, pathology and genetics?**
Robert Eferl (*Austria*)

13.30 – 14.00 **Molecular imaging: Principles, progress and application to HCC**
Twan Lammers (*Netherlands*)

14.00 – 14.30 *Coffee break and ePoster session 1*

SESSION 2 SUSTAINED PROLIFERATIVE SIGNALLING AND EVASION OF GROWTH SUPPRESSION

14.30 – 16.30	Chairs: Peter Schirmacher (Germany) Robert Eferl (Austria)
14.30 – 15.00	MAPKinases in hepatocarcinogenesis Erwin Wagner (Spain)
15.00 – 15.30	CAR and beta catenin David Moore (United States)
15.30 – 16.00	The MDM2-p53 pathway in cancer Simone Fulda (Germany)
16.00 – 16.15	ABSTRACT PRESENTATION The disruption of FAK/EZH2 functional interaction induces in vitro and in vivo HCC apoptosis and consequent growth reduction Ilaria Romito (Italy)
16:15 – 16:30	ABSTRACT PRESENTATION Hepatitis C virus induces oncogenic signatures that are not reverted following treatment with DAAs Meital Gal-Tanamy (Israel)
16.30 – 17.00	<i>Coffee break and ePoster session 2</i>

SESSION 3 THE ROLE OF THE INFLAMMATORY MICROENVIRONMENT IN HCC

17.00 – 19.30	Chairs: Robert Thimme (Germany) Frank Tacke (Germany)
17.00 – 17.30	The microenvironment and its contribution to outcome in HCC Xin Wei Wang (United States)
17.30 – 18.00	Granulocytes in liver cancer Derek Mann (United Kingdom)

ABSTRACT PRESENTATION

- 18.00 – 18.15 **Liver NK cells from NLG4^{-/-} mice inhibit progressions of hepatocellular carcinoma of C57BL/6 mice model through decrease in p53 and Akt expressions**
Ahmad Salhab (*Israel*)
-

ABSTRACT PRESENTATION

- 18.15 – 18.30 **Intra-tumour heterogeneity in the regulation of immune-tolerogenic pathways in primary and metastatic hepatocellular carcinoma**
David James Pinato (*United Kingdom*)
-

- 18:30 – 19:00 **Tumour associated antigen responses in HCC**
Robert Thimme (*Germany*)
-

- 19:00 – 19:30 **NK cells and immune driven senescence in HCC**
Tim Greten (*United States*)
-

FRIDAY 3 FEBRUARY 2017

SESSION 4 HALLMARK – ANGIOGENESIS, INVASION AND METASTASES

08.30 – 10.30 **Chairs: Erwin Wagner (Spain)**
Erica Villa (Italy)

08.30 – 09.00 **Prognostic signatures from HCC biopsy**
Erica Villa (Italy)

09.00 – 09.30 **Endothelial cell metabolism and angiogenesis**
Peter Carmeliet (Belgium)

09.30 – 10.00 **TGF beta in HCC progression**
Isabel Fabregat (Spain)

10.00 – 10.15 **ABSTRACT PRESENTATION**
Stromal SULFATASE-2 promotes Human hepatocellular carcinoma cell growth and is a potential novel therapeutic target
Marco Zaki (United Kingdom)

10.15 – 10.30 **ABSTRACT PRESENTATION**
A new in vitro hepatocellular carcinoma model based on human normal and fibrotic 3D extracellular matrix scaffold bio-engineering
Andrea Telese (United Kingdom)

10.30 – 11.00 *Coffee Break and ePoster session 3*

SESSION 5 ENABLING OF REPLICATIVE IMMORTALITY, GENOMIC INSTABILITY AND MUTATION

11.00 – 13.00 **Chairs: Josep Llovet (Spain)**
Lars Zender (Germany)

11.00 – 11.30 **In vivo screening approaches for defining new oncogenic pathways in HCC**
Lars Zender (Germany)

11.30 – 11.45 **ABSTRACT PRESENTATION**
Identification of tumour suppressive and oncogenic microRNAs in gallbladder carcinoma
Stephanie Roessler (Germany)

ABSTRACT PRESENTATION

11.45 – 12.00 **Liver-targeting with the novel nucleotide prodrug MIV-818 designed for the treatment of liver cancers**

Mark Albertella (*Sweden*)

12.00 – 12.30 **Transposable elements and genetic instability**

Ruchi Shukla (*United Kingdom*)

12.30– 13.00 **Molecular classification and drivers of cholangiocarcinoma**

Josep Llovet (*Spain*)

13.00 – 14.00 *ePoster session 4 and lunch break*

14:00 – 14:30 **What makes my liver cancer paper a Cancer Cell Paper?**

Li-Kuo Su (*United States*)

SESSION 6 DEREGULATION OF CELLULAR ENERGETICS

14.30 – 16.30 **Chairs: Peter Jansen (*Netherlands*)
Matias Heikenwalder (*Germany*)**

14.30 – 15.00 **Mechanisms of NASH and NASH-triggered HCC**

Matias Heikenwalder (*Germany*)

15.00 – 15.30 **Obesity, the gut microbiome and liver cancer**

Herbert Tilg (*Austria*)

15.30 – 16.00 **Endoplasmic reticulum proteostasis in hepatocellular carcinoma**

Eric Chevet (*France*)

16.00 – 16.30 **Metabolic receptors in HCC/CCC**

Peter Jansen (*Netherlands*)

16.30 – 17.00 *Coffee break and ePoster session 5*

SESSION 7 CELL DEATH

17.00 – 19.00 **Chairs: Christian Trautwein (Germany)**
Derek Mann (Germany)

17.00 – 17.30 **Regulated cell death pathways in hepatocarcinogenesis**
Tom Luedde (Germany)

17.30 – 18.00 **Cell death response pathways in liver cancer**
Robert Schwabe (United States)

18.00 – 19.00 **Joint translational key note lecture “The hallmarks of cancer in 2016”**
Douglas Hanahan (Switzerland)

19.00 *Cocktail reception for all participants and ePoster sessions 6 & 7*

CLINICAL RESEARCH: LIVER CANCER MANAGEMENT

SATURDAY 4 FEBRUARY 2017

08.20 – 08.30 **OPENING ADDRESS**
Franco Trevisani (*Italy*) and Alejandro Forner (*Spain*)

SESSION 1 THE CHANGING EPIDEMIOLOGY

08.30 – 10.45 **Chairs: Franco Trevisani (*Italy*) and Jordi Bruix (*Spain*)**

08.30 – 09.00 **Epidemiology of HCC: An introduction**
Franco Trevisani (*Italy*)

09.00 – 09.30 **How can we assess the risk of HCC development in alcoholic patients?**
Pierre Nahon (*France*)

09.30 – 10.00 **NAFLD as a risk factor for HCC**
Jean François Dufour (*Switzerland*)

10.00 – 10.30 **Impact of new antiviral treatments on HCC risk**
Michael Manns (*Germany*)

ABSTRACT PRESENTATION
10:30 – 10:45 **Early occurrence of hepatocellular carcinoma (HCC) in patients with HCV cirrhosis treated with direct-acting antivirals (DAAs)**
Vincenza Calvaruso (*Italy*)

10.45 – 11.15 *Coffee break and ePoster session 8*

SESSION 2 DIAGNOSTIC CHALLENGES

11.15 – 13.45 **Chairs: Valerie Vilgrain (*France*) and Massimo Colombo (*Italy*)**

11.15 – 11.45 **Surveillance for HCC: Whom, how, and how often?**
Alejandro Forner (*Spain*)

11.45 – 12.15 **Diagnosis of HCC by imaging: Can we improve its accuracy?**
Carmen Ayuso (*Spain*)

12.15 – 12.45 **Pathology of HCC: Can we improve the diagnostic accuracy?**
Valérie Paradis (*France*)

12.45 – 13.15 **Refinement of staging and prognosis assessment of HCC:
-Pros and cons of the available systems**
Jordi Bruix (*Spain*)
-How to improve the current systems: a glance to the future
Philip Johnson (*United Kingdom*)

13.15 – 13.30 **ABSTRACT PRESENTATION**
**Time course of treatment-emergent adverse events (TEAEs)
in the randomized, controlled phase 3 RESORCE trial of
regorafenib for patients with hepatocellular carcinoma
progressing on sorafenib treatment**
Philippe Merle (*United Kingdom*)

13.30 – 13.45 **ABSTRACT PRESENTATION**
**The concept of therapeutic hierarchy for patients with
hepatocellular carcinoma: a multicenter cohort study**
Alessandro Vitale (*Italy*)

13.45 – 14.45 *ePoster sessions 9 & 10 & 11 and lunch break*

SESSION 3 SURGICAL THERAPY

14.45– 16.45 **Chairs: Vincenzo Mazzaferro (*Italy*) and
Alejandro Forner (*Spain*)**

14.45 – 15.15 **Extending the boundaries for resection**
Daniel Cherqui (*France*)

15.15 – 15.45 **Resection or RFA as first line treatment for early stage HCC?**
Fabio Piscaglia (*Italy*)

15.45 – 16.15 **Resection vs. Liver Transplantation in HCC.**
Pietro Majno (*Switzerland*)

16.15 – 16.45 **Liver transplantation for HCC: Can extending criteria be
applied in clinical practice?**
Vincenzo Mazzaferro (*Italy*)

16.45 – 17.30 *ePoster sessions 12 & 13 and Coffee break*

SESSION 4 LOCOREGIONAL THERAPY

17.30– 19.30 **Chairs: Philippe L. Pereira (Germany) and Carmen Ayuso (Spain)**

17.30 – 18.00 **TACE: Who should be treated, when to stop, how to be done?**
Markus Peck-Radosavljevic (*Austria*)

18.00 – 18.30 **Which is the role of radioembolization in HCC?**
Sherrie Bhoori (*Italy*)

18.30 – 19.00 **Locoregional therapies: Imaging tumour response evaluation in HCC: Room for improvement?**
Valérie Vilgrain (*France*)

19.00 – 19.30 **Can locoregional therapies be combined?**
Philippe L. Pereira (*Germany*)

SUNDAY 5 FEBRUARY 2017

SESSION 5 INTRAHEPATIC CHOLANGIOCARCINOMA – AN EMERGING PROBLEM

08.30 – 10.30 **Chairs: Peter Galle (Germany) and Bruno Sangro (Spain)**

08.30 – 09.00 **Intrahepatic cholangiocarcinoma: the changing epidemiology and diagnosis**
Domenico Alvaro (Italy)

09.00 – 09.30 **Surgical therapy in ICC: Resection and liver transplantation**
Ulf P. Neumann (Germany)

09.30 – 10.00 **The role of locoregional therapies in ICC**
Stephen Pereira (United Kingdom)

10.00 – 10.30 **Systemic therapy**
Arndt Vogel (Germany)

10.30 – 11.30 *Coffee Break and ePoster sessions 14 & 15*

SESSION 6 SYSTEMIC TREATMENTS AND BEYOND IN HCC

11.30 – 13.30 **Chairs: Massimo Colombo (Italy) and Josep Llovet (Spain)**

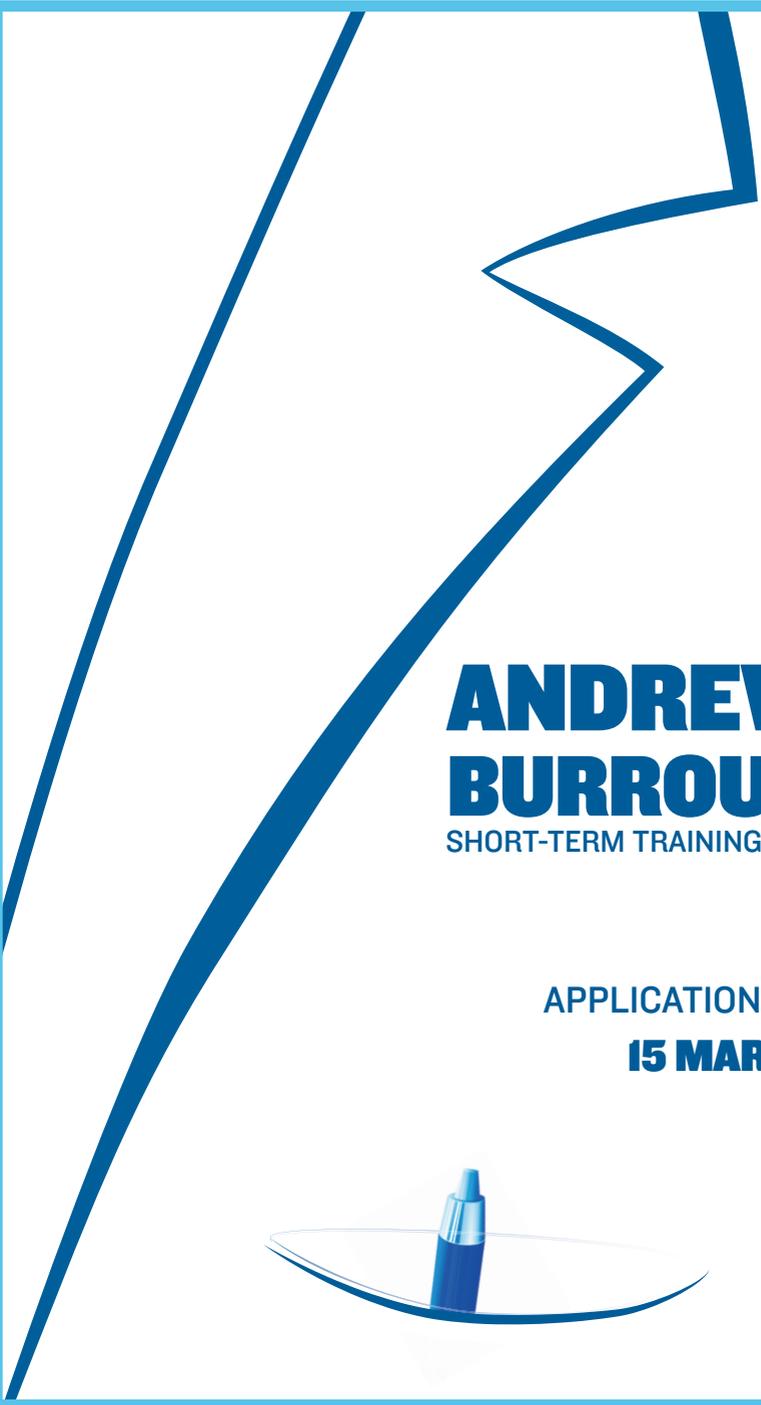
11.30 – 12.00 **Sorafenib in HCC: Is the efficacy predictable?**
Maria Reig (Spain)

12.00 – 12.30 **Second line in HCC – promising new developments**
Peter Galle (Germany)

12.30 – 13.00 **Rationale basis and ongoing trial of immunotherapy**
Bruno Sangro (Spain)

13.00 – 13.30 **Pathway of care of HCC in 2017**
Massimo Colombo (Italy)

13.30 *End of the HCC Summit*



**ANDREW K.
BURROUGHS**
SHORT-TERM TRAINING FELLOWSHIP

APPLICATION ENDS ON:
15 MARCH 2017



ePOSTER PRESENTATIONS



HCC AND THE HALLMARKS OF CANCER: STEPS TOWARDS NOVEL THERAPEUTIC STRATEGIES

DAY 1 – THURSDAY 2 FEBRUARY 2017

Session I

ePoster presentations 14:00 – 14:30

ePOSTER PRESENTATIONS

Screen	Title	Abstract	Presenter
1	Hepatocyte nanodelivery using siRNA c-Jun N-terminal Kinase-2 (siJnk2) for the treatment of chronic liver disease and hepatocellular carcinoma	P01.01-YI	<i>Marius Wotok</i>
2	Dual effects of C3G in the tumorigenic capacity of human hepatocarcinoma cells	P01.02-YI	<i>Celia Sequera</i>
3	Hypoxia-induced STC1 enhances progression of hepatocellular carcinoma	P01.03-YI	<i>Kristy Chan</i>
4	All posters available		
5	Unexpected longevity of the tumor-penetrating effect of iRGD in hepatocellular carcinoma	P01.05	<i>Christian Schmithals</i>
6	Mapping the heterogeneity of circulating neutrophils in Hepatocellular Carcinoma.	P01.06	<i>Caroline Wilson</i>
7	Serine-threonine kinase receptor-associated protein maintains hepatocellular carcinoma cell growth through Wnt/ β -catenin signaling	P01.07-YI	<i>Wenhui Wang</i>
8	Polyphenic trait promotes liver cancer in a model of epigenetic instability	P01.08-YI	<i>Marco Cassano</i>

Screen	Title	Abstract	Presenter
9	Tumour suppressor protein SH2D4A is involved in endosomal trafficking of STAT3 in HCC cells	P01.09-YI	<i>Carolin Ploeger</i>
10	Neuroigin4 over expression on NK cell cause their impairment in patients with cirrhosis and HCC	P01.10-YI	<i>Johnny Amer</i>
11	Distinct features of early and late-stage liver cancer cells correlate with their response to metabolic perturbation	P01.11-YI	<i>Zeribe Nwosu</i>
12	Ubiquitin Carboxy-terminal Hydrolase L1 expression is increased in hepatocellular carcinoma cells and renders those cells more sensitive to ER stress-induced cell death following inhibition.	P01.12-YI	<i>Astrid Vandierendonck</i>

Session 2

ePoster presentations 16:30 – 17:00

Screen	Title	Abstract	Presenter
1	pH regulatory inhibitors as therapeutic strategy to counteract hypoxic/acidic microenvironment and inflammation/immunosuppression in hepatocellular carcinoma.	P02.01-YI	<i>Alessandra Tuccitto</i>
2	All posters available		
3	miR-21 deficiency decreases small intestine permeability after bile duct ligation in mice	P02.03-YI	<i>André Santos</i>
4	Activation of miR-34a contributes to liver and muscle insulin resistance in experimental and human Non-Alcoholic Fatty Liver Disease	P02.04-YI	<i>André Simão</i>
5	LNCRNA H19 Is Increased In Hepatocellular Carcinoma With Underlying Hcv-Related Cirrhosis	P02.05-YI	<i>Ángela Rojas</i>
6	N22 region based dot blot assay: An alternative to PCR for detection of Torque teno virus infection	P02.06-YI	<i>Dhananjay Singh Mankotia</i>
7	The nuclear import factor karyopherin-alpha 2 is linked to stathmin in hepatocellular carcinoma	P02.07-YI	<i>Elisabeth Drucker</i>
8	Protein kinase CK2 is involved in the modulation of malignant phenotype of cholangiocarcinoma cells	P02.08-YI	<i>Giovanni Di Maira</i>

Screen	Title	Abstract	Presenter
9	CHK2 DNA Damage Response Protein Mislocalization Enhances Chromosomal Instability and Human Hepatocellular Carcinoma Progression	P02.09-YI	<i>Guia Cerretelli</i>
10	Targeting of distinct FXR α isoforms by novel bile acid derivatives prevents lipotoxicity in liver cells	P02.10-YI	<i>Hugo Brito</i>
11	Verteporfin potentiates the anti-tumor effect of Sorafenib by inhibiting hepatocellular carcinoma progression through interfering with the autophagic flux	P02.11-YI	<i>Jacopo Gavini</i>
12	Tumour heterogeneity in multi-focal hepatocellular carcinoma: A genomic sequencing study	P02.12-YI	<i>Waleed Fateen</i>

DAY 2 – FRIDAY 3 FEBRUARY 2017

Session 3

ePoster presentations 10:30 – 11:00

ePOSTER PRESENTATIONS

Screen	Title	Abstract	Presenter
1	Micro RNA-195 enhances the development of hepatocellular carcinoma in murine model	P03.01-YI	<i>Lobna Mourad</i>
2	A gene and epigenetic combination therapy for liver cancer treatment	P03.02	<i>Luca Rinaldi</i>
3	Growth hormone modulates the expression of the β -galactoside-binding protein Galectin-1 in the liver	P03.03-YI	<i>Maria Bacigalupo</i>
4	miRNA-21-deficiency reduces liver injury, fibrosis and necroptosis in cholestatic bile duct-ligated mice	P03.04-YI	<i>Marta Afonso</i>
5	Anti-malarial Drug Chloroquine Potentiates Cisplatin-Induced Apoptosis in Hepatocellular Carcinoma by Disrupting Mitochondrial Membrane Potential	P03.05-YI	<i>Nirajan Shrestha</i>
6	miR-21 ablation and obeticholic acid ameliorate NASH in mice	P03.06-YI	<i>Pedro Rodrigues</i>
7	GNS561 a new quinoline derivative inhibits the growth of hepatocellular carcinoma in a cirrhotic rat & human PDX orthotopic mouse models	P03.07	<i>Thomas Decaens</i>
8	The BCL-2 family member BOK promotes DEN-induced hepatocarcinogenesis	P03.08	<i>Thomas Kaufmann</i>
9	Monitoring of intrahepatic and circulating immune system features in patients with HCC by multicolor flow cytometry	P03.09-YI	<i>Zuzana Macek Jilkova</i>
10	Molecular basis of Natural Killer (NK) cell dysfunction in Hepatocellular Carcinoma (HCC)	P03.10-YI	<i>Valeria Regina</i>
11	Kangai 1 C-terminal interacting tetraspanin plays an important role in cholangiocarcinogenesis	P03.11-YI	<i>Khac Cuong Bui</i>
12	All posters available		

Session 4

ePoster presentations 13:30 – 14:00

Screen	Title	Abstract	Presenter
1	Dual inhibition of pERK and pMAPK14 overcomes resistance to sorafenib in hepatitis B virus replicating hepatoma cells	P04.01	<i>Amir Shlomai</i>
2	Ang-2 polymorphisms and clinical outcome in advanced HCC patients receiving sorafenib	P04.02-YI	<i>Andrea Casadei Gardini</i>
3	RIPK1 suppresses a TRAF2-dependent pathway to liver cancer	P04.03-YI	<i>Anne Schneider</i>
4	The Role of Six Transmembrane Epithelial Antigen of the Prostate 2 in Hepatocellular Carcinoma	P04.04-YI	<i>Carla Zeballos</i>
5	Modelling doxorubicin-eluting bead therapy in combination with DNA-damage repair inhibition in human liver cancer	P04.05-YI	<i>Catherine Willoughby</i>
6	Characterization of rarely detectable tumour-associated antigens (TAA)-specific CD8 T cells in HCC patients	P04.06-YI	<i>Catrin Tauber</i>
7	Epidermal Growth Factor Receptor (EGFR) as regulator of liver inflammation during hepatocarcinogenesis	P04.07-YI	<i>Daniel Caballero-Diaz</i>
8	Tumor-initiating Cells as Cellular Drivers of Acquired Resistance During Anti-angiogenic Therapies in Hepatocellular Carcinoma	P04.08-YI	<i>Darko Castven</i>
9	Orthotopic hepatocellular carcinoma mouse model for investigation of tumor-specific CD8 T cell responses	P04.09-YI	<i>Dmitrij Ostroumov</i>



Screen	Title	Abstract	Presenter
10	The Role of B cells in Non-Alcoholic Steatohepatitis (NASH) and NASH-driven Hepatocellular Carcinoma (HCC)	P04.10-YI	<i>Eleni Kotsiliti</i>
11	Potential ultrastructure predicting factors for hepatocellular carcinoma in HCV infected patients	P04.11	<i>Eman El-Ahwany</i>
12	All posters available		

Session 5

ePoster presentations 16:30 – 17:00

Screen	Title	Abstract	Presenter
1	Patient-derived cancer cells resemble the transcriptomic and genomic landscape of diverse human liver cancers	P05.01-YI	<i>Darko Castven</i>
2	Recombinant lymphocytic choriomeningitis virus vectors carrying model antigen elicit tumour directed immune responses, inhibit tumour progression and prolong mouse survival	P05.02-YI	<i>Jessica Wingerath</i>
3	Role of the Transforming Growth Factor beta (TGF-beta) in hepatocellular carcinoma cell metabolism	P05.03-YI	<i>Jitka Soukupova</i>
4	Effect of novel AKT inhibitor ARQ 751 as single agent and its combination with sorafenib on hepatocellular carcinoma in a cirrhotic rat model	P05.04-YI	<i>Kurma Keerthi</i>
5	All posters available		
6	Telomere length in chronic liver diseases secondary to hepatitis C and its association with the severity of liver disease	P05.06-YI	<i>Patricia Almeida</i>
7	Mucosal gut microbiota composition in patients with HCV-related hepatocellular carcinoma	P05.07-YI	<i>Marco Sanduzzi Zamparelli</i>
8	Transcriptional Regulatory Networks in Hepatitis C Virus-induced Hepatocellular Carcinoma	P05.08	<i>Marwa Zahra</i>
9	Elevated levels of circulating osteopontin in patients with cholangiocarcinoma predict poor survival after tumor resection	P05.09-YI	<i>Sven Loosen</i>
10	Preclinical analysis of sangliferin-based cyclophilin inhibitors showing potential for treatment of hepatocellular carcinoma	P05.10	<i>Michele Tavecchio</i>



ePOSTER PRESENTATIONS

Screen	Title	Abstract	Presenter
11	Circulating Tumour Cells to stratify therapy for patients with hepatocellular carcinoma – a focus on DNA-PK	P05.11-YI	<i>Misti McCain</i>
12	All posters available		

Session 6

ePoster presentations 19:00 – 19:30

Screen	Title	Abstract	Presenter
1	Integrated analysis of exosomal microRNA, gene and pathway regulatory networks in fibrosis and hepatocarcinogenesis	P06.01-YI	<i>Robert Cheng</i>
2	LY3039478 a notch gamma-secretase inhibitor blocks cholangiocarcinoma growth in a patient-derived xenograft PDX model	P06.02-YI	<i>Serena Mancarella</i>
3	Importance of genetic variability of HCV in the viral hla ag union and its relationship with the immune response. Rational bases for obtaining a therapeutic vaccine	P06.03	<i>Sergio Manuel Jimenez Ruiz</i>
4	Differential effect of Transforming Growth Factor Beta family members on tumor initiating and invasive properties in primary liver cancer	P06.04	<i>Sharon Pereira</i>
5	All posters available		
6	Up-regulation of C/EBPa by small activating RNA significantly increases post partial hepatectomy survival in DEN induced cirrhotic rats	P06.06	<i>Vikash Reebye</i>
7	AKT inhibitor ARQ 092 and sorafenib additively inhibit progression of hepatocellular carcinoma and improve immune system in cirrhotic rat model	P06.07-YI	<i>Zuzana Macek Jilkova</i>
8	Effect of RECK Gene Polymorphisms on Hepatocellular Carcinoma Susceptibility and Progression in Egyptian patients	P06.08-YI	<i>Ahmed El-Sayed Ahmed El Nakib</i>
9	Thrombin generation test and risk of portal vein thrombosis in patients with liver cirrhosis and hepatocellular carcinoma	P06.09-YI	<i>Alberto Zanetto</i>



Screen	Title	Abstract	Presenter
10	All posters available		
11	Whole-exome sequencing in Brazilian patients with hepatocellular carcinoma	P06.11	<i>Andreza Correa Teixeira</i>
12	All posters available		

Session 7

ePoster presentations 19:30 – 20:00

Screen	Title	Abstract	Presenter
1	Potential diagnostic and prognostic value of lymphocytic mitochondrial DNA deletion in relation to folic acid status in hepatocellular carcinoma	P07.01	<i>Dalia Omran</i>
2	Heterologous immune vaccination induces specific therapeutic CD8 T-cell immune responses against tumor-associated antigen alpha-fetoprotein expressed in hepatocellular carcinoma	P07.02-YI	<i>Steve Duong</i>
3	Case-control study nested in a prospective cohort of microbiome found in cirrhotic patients with and without hepatocellular carcinoma	P07.03	<i>Federico Piñero</i>
4	EpCAM-positive circulating tumor cells as liquid biomarker for early micrometastases and HCC recurrence risk	P07.04-YI	<i>Johann Von Felden</i>
5	All posters available		
6	ASS1 immunohistochemistry identifies unclassified hepatocellular adenoma. Experience of a single French liver center	P07.06	<i>Paulette Bioulac-Sage</i>
7	Peripheral T cell subpopulation In patients with Hepatocellular carcinoma: relation to ablation therapy.	P07.07-YI	<i>Shaker Shaltout</i>
8	All posters available		
9	Impact of natural killer cells receptors gene haplotypes on the development of hepatocarcinoma in cirrhotic patients	P07.09-YI	<i>Simona Onali</i>

Screen	Title	Abstract	Presenter
10	Discovery to first-in-man studies of a multi-peptide-based hepatocellular carcinoma vaccine adjuvanted with CV8102 (RNAAdjuvant – HEPAVAC	P07.10	<i>Luigi Buonaguro</i>
11	Osteopontin promotor gene polymorphism at locus (-443C/T) and development of hepatocellular carcinoma in cirrhotic hepatitis C patients	P07.11	<i>Nermeen Sherif Abdeen</i>
12	All posters available		

CLINICAL RESEARCH: LIVER CANCER MANAGEMENT

DAY 3 – SATURDAY 4 FEBRUARY 2017

Session 8

ePoster presentations 10:45 – 11:15

Screen	Title	Abstract	Presenter
1	Liver transplantation in the hepatocellular carcinoma (HCC) setting: a Single-Center Experience from Brazil	P08.01	<i>Andreza Correa Teixeira</i>
2	Assessment of the difference in liver steatosis, measured by Controlled attenuation parameter, between patients with HCV-related advanced hepatic fibrosis versus HCV-related hepatocellular carcinoma	P08.02-YI	<i>Hend Shousha</i>
3	Comparative Study Between Radiofrequency Ablation Alone And If Combined with Percutaneous Acetic Acid Injection in The Treatment of Hepatocellular Carcinoma	P08.03-YI	<i>Hisham Saad Mohammad</i>
4	Effectiveness of Hepatitis B Vaccine with Various Doses and Types under Rapid Vaccination Schedule among Adults	P08.04-YI	<i>Li Nie</i>
5	Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma and Portal Vein Thrombosis	P08.05-YI	<i>Mohamed Zaitoun</i>
6	The diagnostic and prognostic values of serum PIVKA-II in Thai patients with hepatitis B-related hepatocellular carcinoma	P08.06	<i>Pisit Tangkijvanich</i>
7	Effectiveness of Percutaneous Ethanol Injection in relation to hepatocellular carcinoma size: a single centre experience	P08.07-YI	<i>Rocco Granata</i>
8	Clinical profile of hepatocellular carcinoma in Indian patients	P08.08-YI	<i>Sanchit Budhiraja</i>

Screen	Title	Abstract	Presenter
9	Transarterial Chemoembolization Complications and its Most Common Causes in Patients with Hepatocellular Carcinoma	P08.09-YI	<i>Shahenda Shahin</i>
10	Hepatocellular carcinoma in central Slovakia: cohort from tertiary referral centre	P08.10	<i>Svetlana Adamcova- Selcanova</i>
11	Ultrasound-guided Percutaneous Irreversible Electroporation (IRE) of Hepatocellular Carcinoma (HCC) not suitable for surgery or thermal ablation: initial report on safety and efficacy from a western center	P08.11	<i>Antonio Giorgio</i>
12	Hand-foot-skin reaction of grade two or higher within sixty days as the best response criterion for survival prediction in hepatocellular carcinoma treated by sorafenib	P08.12	<i>Guohong Han</i>

Session 9

ePoster presentations 13:45 – 14:05

Screen	Title	Abstract	Presenter
1	Metronomic capecitabine versus best supportive care as second-line treatment in hepatocellular carcinoma: a retrospective study	P09.01-YI	<i>Andrea Casadei Gardini</i>
2	Evaluation of liver stiffness as a predictor of hepatocellular carcinoma ablation outcome after percutaneous microwave ablation or transarterial chemoembolization: a cohort study	P09.02-YI	<i>Hend Shousha</i>
3	Portal vein infiltration in patients with hepatocellular carcinoma: the impact of correct classification	P09.03	<i>Arndt Weinmann</i>
4	Pathological and radiological findings in early stage hepatocellular carcinoma: a correlative study	P09.04-YI	<i>Letizia Veronese</i>
5	All posters available		
6	Cone beam computed tomography TACE is more effective than traditional technique in BCLC A HCC patients ineligible to surgery	P09.06-YI	<i>Riccardo Patti</i>
7	Determinants of survival and treatment outcome in hepatocellular carcinoma: a single center experience	P09.07-YI	<i>Tim Labeur</i>
8	Obstructive jaundice from Hepatocellular carcinoma is associated with poorer outcomes overall despite successful biliary drainage	P09.08-YI	<i>Vinay Kumar Balachandrakumar</i>
9	Transarterial chemoembolization shows no superiority than bland embolization as the adjuvant therapy after curative hepatectomy for hepatocellular carcinoma: a retrospective cohort study	P09.09	<i>Lei Zhao</i>

Screen	Title	Abstract	Presenter
10	Could blood indices predict the early recurrence of hepatocellular carcinoma after Trans-Arterial Chemoembolization?	P09.10-YI	<i>Ahmed El Nakib</i>
11	Percutaneous Ablation of Advanced HCC after dowstaging with Sorafenib	P09.11	<i>Luciano Tarantino</i>
12	All posters available		

Session 10

ePoster presentations 14:05 – 14:25

Screen	Title	Abstract	Presenter
1	Metformin effects on clinical outcome in advanced HCC patients receiving sorafenib: validation study	P10.01-YI	<i>Andrea Casadei Gardini</i>
2	Laser ablation is superior to TACE in large size hepatocellular carcinoma: a case-control study	P10.02-YI	<i>Silvia Camera</i>
3	The survival benefit of laparoscopic ablation over trans-arterial chemoembolization in patients with hepatocellular carcinoma ineligible for liver resection or percutaneous ablation	P10.03-YI	<i>Alessandra Bertacco</i>
4	Prospective validation of a score to predict hepatocellular carcinoma (HCC) in patients with HCV cirrhosis that takes into account sustained virological response (SVR). Influence of direct-acting antivirals (DAAs)	P10.04-YI	<i>Andres Castaño</i>
5	Comparison between de-novo occurrence and recurrence of hepatocellular carcinoma (HCC) after direct-acting antivirals (DAAs) in cirrhotic patients with hepatitis C: a real-life cohort study	P10.05	<i>Liliana Chemello</i>
6	Clinical outcomes of patients with recurred hepatocellular carcinoma after curative surgical resection: in relation to recurrence time	P10.06	<i>Young-Hwa Chung</i>
7	Factors associated with tumor recurrence after liver transplantation for hepatocellular carcinoma: prospective cohort on 371 patients	P10.07	<i>Thomas Decaens</i>
8	Effectiveness of drug-eluting bead-transarterial chemo-embolization in intermediate stage of hepatocellular carcinoma	P10.08	<i>Akihiro Deguchi</i>
9	False-negative liver ultrasound limits benefits of HCC surveillance	P10.09-YI	<i>Shirin Demma</i>

Screen	Title	Abstract	Presenter
10	Validation of a simple scoring system to predict sorafenib effectiveness in patients with hepatocellular carcinoma	P10.10-YI	<i>Rocco Granata</i>
11	External validation of the ITA.LI.CA prognostic system for patients with hepatocellular carcinoma: a multicenter cohort study	P10.11	<i>Mauro Borzio</i>
12	All posters available		

Session II

ePoster presentations 14:25 – 14:45

Screen	Title	Abstract	Presenter
1	Preliminary data on level of CA 19-9 and its prognostic value in HCC patients treated by conventional TACE regarding HCC recurrence	P11.01-YI	<i>Mostafa Elshenmawy</i>
2	Aggressive behavior of HCV-related hepatocellular carcinoma: Comparative analysis between patients treated or not for HCV using direct acting antivirals	P11.02-YI	<i>Hend Shousha</i>
3	Natural history of hypovascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MR imaging in cirrhotic patients during surveillance program	P11.03-YI	<i>Luca Ielasi</i>
4	Previous and resolved HBV infection is not a risk factor for the development of hepatocellular carcinoma (HCC) in patients with liver cirrhosis due to HCV or alcohol	P11.04	<i>Carlos Rodríguez-Escaja</i>
5	All posters available		
6	Utility of SCCA-IgM levels in the prediction of hepatocellular carcinoma in cirrhotic patients	P11.06-YI	<i>Antonio Gil-Gómez</i>
7	Prediction and prevention of liver failure after extensive liver resections for liver cancer: the role of functional tests	P11.07-YI	<i>Aisha Isaeva</i>
8	Extent of portal invasion in patients with HCC: The more, the worse?	P11.08	<i>Roman Kloeckner</i>
9	Hepatocellular carcinoma recurrence after direct antiviral agent treatment: a european multicentric study	P11.09-YI	<i>Philippe Kolly</i>
10	Combination of Sorafenib with Transarterial Chemoembolization (TACE) Improves Survival as Compared to TACE Alone in Patients with Hepatocellular Carcinoma: A metaanalysis of 17 Studies	P11.10	<i>Ashish Kumar</i>

Screen	Title	Abstract	Presenter
11	Risk of Hepatocellular Carcinoma (HCC) Recurrence in HCV Cirrhotic Patients treated with Direct Acting Antivirals (DAAs)	P11.11	<i>Giuseppe Cabibbo</i>
12	Radiological assessments in patients with hepatocellular carcinoma following transarterial chemoembolization: can initial response independently predict the survival regardless of tumor load?	P11.12	<i>Guohong Han</i>

Session I2

ePoster presentations 16:45 – 17:05

Screen	Title	Abstract	Presenter
1	Metronomic Capecitabine as second-line systemic treatment for hepatocellular carcinoma	P12.01-YI	<i>Francesca Garuti</i>
2	Comparative analysis between patients who developed hepatocellular carcinoma and were treated for HCV using direct acting antivirals: De novo versus recurrence lesions	P12.02-YI	<i>Hend Shousha</i>
3	Liver resection for hepatocellular carcinoma ≥ 5 cm	P12.03-YI	<i>Giovanni Battista Levi Sandri</i>
4	Apolipoproteins Alterations in Hepatitis C Associated Hepatocellular Carcinoma: Could They Serve as A Diagnostic Tool?	P12.04-YI	<i>Heba Omar</i>
5	Microwave ablation of large HCCs by simultaneous multiple antennae insertion: long term follow-up	P12.05	<i>Luciano Tarantino</i>
6	Can hepatic resection be advocated over the transarterial chemoembolization for patients with hepatocellular carcinoma?	P12.06-YI	<i>Hussien Ahmed</i>
7	Platelet-count influences survival in patients with hepatocellular carcinoma	P12.07	<i>Johannes Weiss</i>
8	The functional liver tests (ICG, HBS, 13-metacitin) in liver cancer patients: which is the best?	P12.08-YI	<i>Leonid Petrov</i>
9	Alpha fetoprotein – a useful tool for follow-up of interferon-free treated cirrhotic patients with de novo hepatocellular carcinoma after SVR	P12.09	<i>Liana Gheorghe</i>



ePOSTER PRESENTATIONS

Screen	Title	Abstract	Presenter
10	Prognostic factors for survival of BCLC-C stage hepatocellular carcinoma patients according to previous treatments: a real-life experience	P12.10-YI	<i>Francesca Romana Ponziani</i>
11	Hepatocellular carcinoma recurrence rate in HCV infected patients treated with direct antiviral agents. A single center experience	P12.11-YI	<i>Marco Sanduzzi Zamaparelli</i>
12	All posters available		

Session I3

ePoster presentations 17:05 – 17:25

Screen	Title	Abstract	Presenter
1	Alkaline phosphatase levels can improve prediction for hepatocellular carcinoma in decompensated noncholestatic cirrhotic patients	P13.01-YI	<i>Pathik Parikh</i>
2	Meta-learning analysis to find the best predictive algorithm for prediction of hepatocellular carcinoma outcome in a cohort of 1200 HCV-related patients	P13.02-YI	<i>Hend Shousha</i>
3	Liver resection for hepatocellular carcinoma, are we going to dismiss the traditional approach?	P13.03-YI	<i>Giovanni Battista Levi Sandri</i>
4	Alpha-fetoprotein (AFP) levels before and after sustained virological response with direct-acting antivirals (DAAs) in patients with liver cirrhosis due to hepatitis C virus (HCV)	P13.04-YI	<i>Andres Castaño</i>
5	Combined treatment, Transarterial chemoembolization and Radiofrequency ablation in patients with Advanced HCC	P13.05-YI	<i>Mohamed Zaitoun</i>
6	Treatment-stage migration maximizes survival outcomes in patients with hepatocellular carcinoma treated with sorafenib: an observational study	P13.06-YI	<i>Clarence Yen</i>
7	Drop-out rate due to HCC progression is not affected by HCV eradication with DAAs in patients awaiting liver transplantation	P13.07-YI	<i>Sarah Shalaby</i>
8	How often patients treated with sorafenib for hepatocellular carcinoma might receive suboptimal decisions about treatment duration? An analysis of the interoperator variability and source of errors in tumor response assessment	P13.08-YI	<i>Francesco Tovoli</i>

Screen	Title	Abstract	Presenter
9	Frequency of Complete Pathological Necrosis of HCC in Explanted Livers: Radioembolization with Resin vs Drug Eluting Beads with Doxorubicin	P13.09	<i>Roshan Shrestha</i>
10	External validation of the HCC-MELD score for patients with hepatocellular carcinoma waiting for liver transplantation	P13.10	<i>Alessandro Vitale</i>
11	Metabolic disorders across hepatocellular carcinoma in Italy	P13.11	<i>Maria Guarino</i>
12	All posters available		

DAY 4 – SUNDAY 5 FEBRUARY 2017

Session I4

ePoster presentations 10:30 – 11:00

Screen	Title	Abstract	Presenter
1	Predicting outcome in patients with intermediate or advanced hepatocellular carcinoma receiving sorafenib: influence of the radiologist experience on the prognostic value of the different proposed radiologic criteria of response	P14.01-YI	<i>Francesco Tovoli</i>
2	Non-alcoholic fatty liver as global burden: a changing trend of Liver Transplantation for Hepatocellular carcinoma in Latin America	P14.02	<i>Federico Piñero</i>
3	Liver Stiffness and serum fibrosis biomarker variations after DAAs treatment: predictive role in HCC development in in cirrhotic patients	P14.03-YI	<i>Federico Ravaioi</i>
4	Telomerase activity: a valuable marker of hepatocellular carcinoma development in cirrhotic hepatitis C patients	P14.04-YI	<i>Mariam Zaghloul</i>
5	Drug-eluting bead Transarterial Chemoembolization versus Conventional TACE in the Treatment of Hepatocellular Carcinoma	P14.05-YI	<i>Mohamed Zaitoun</i>
6	Validation of the ALBI grade as a substitute for the Child-Pugh class in the BCLC classification of hepatocellular carcinoma and of the additional value provided by the Neutrophil-to-Lymphocyte Ratio	P14.06-YI	<i>Matteo Colombo</i>
7	Validation of Liver Imaging Reporting and Data System (LI-RADS) Version 2014	P14.07-YI	<i>Anna Pecorelli</i>
8	Recurrent Hepatocellular Carcinoma after Liver Transplantation: Validation of a Pathological Risk Score on Explanted Livers to Predict Recurrence	P14.08	<i>Karim Qumosani</i>

Screen	Title	Abstract	Presenter
9	Validation of the risk prediction models STATE-score and START-strategy to guide TACE treatment in patients with Hepatocellular Carcinoma	P14.09	<i>Aline Mähringer-Kunz</i>
10	The role of Spleen Stiffness measurement as predictor of HCC recurrence after curative resection in cirrhotic patients	P14.10-YI	<i>Giovanni Marasco</i>
11	Is gender a discriminating factor for hepatocellular carcinoma presentation, management and outcome? Results from the Italian Liver Cancer database	P14.11-YI	<i>Barbara Lenzi</i>
12	transarterial chemoembolization combined with sorafenib for intermediate-stage hepatocellular carcinoma: a window of tumor burden for survival benefit	P14.12	<i>Guohong Han</i>

Session I5

ePoster presentations II:00 – II:30

Screen	Title	Abstract	Presenter
1	Long term results of treatment of intermediate HCC in cirrhosis using high-powered microwaves: a prospective, multicenter study	P15.01	<i>Antonio Giorgio</i>
2	Adherence to hepatocellular carcinoma guidelines in field-practice: PROGETTO EPATOCARCINOMA CAMPANIA	P15.02-YI	<i>Maria Guarino</i>
3	Modified ALBI-T Score as a Prognostic Model in The Evaluation of Egyptian Patients with Hepatocellular Carcinoma	P15.03-YI	<i>Omar Elshaarawy</i>
4	Transarterial Chemoembolization Prior to Liver Transplantation in Patients with Hepatocellular Carcinoma – a single-center experience	P15.04-YI	<i>Ana Ostojic</i>
5	All posters available		
6	Transient elastography can predict the development of hepatocellular carcinoma in hepatitis C cirrhotic patients	P15.06	<i>Denise Paranaguá-Vezozzo</i>
7	Risk factors for hepatocellular carcinoma in a large cohort of patients affected by primary sclerosing cholangitis	P15.07-YI	<i>Francesca Saffioti</i>
8	Multi-Operational Selective Computer-Assisted Targeting of Hepatocellular Carcinoma – Preclinical results	P15.08	<i>Pascale Tinguely</i>
9	Is sarcopenia a predictor of outcome in patients with HCC treated with Sorafenib?	P15.09	<i>Francesca Lodato</i>
10	Temporary suspension of sorafenib by adverse effects is associated with longer survival in patients with hepatocellular carcinoma	P15.10-YI	<i>Carlos Rodríguez-Escaja</i>

Screen	Title	Abstract	Presenter
11	Stereotactic image-guidance for percutaneous local ablation of hepatocellular carcinoma	P15.11	<i>Pascale Tinguely</i>
12	Evidence-based two-and-seven criteria based on tumor number and size best help to predict survival of patients with intermediate-stage hepatocellular carcinoma treated with transarterial chemoembolization	P15.12	<i>Guohong Han</i>

INVITED SPEAKERS' ABSTRACTS



THE CHALLENGE – BRIDGING THE GAP BETWEEN BASIC SCIENCE AND CLINICAL PRACTICE

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Excellence in basic liver cancer research has led to forefront knowledge about the mechanisms of liver carcinogenesis, but these achievements have not generated correlating success in regard to systemic treatment and molecular diagnostics. The therapeutic improvements are limited and with minor impact on patient survival; we are still lacking true personalized treatment options and stratifying (molecular) diagnostics. A disappointingly high number of approval trials have failed in recent years and in many centers clinical recognition of liver cancer does not match its frequency and medical needs. Liver cancer – in contrast to other major tumour entities such as lung, breast, and colon cancer – has benefitted less from the revolution of precision oncology, so far.

This is not due to a different tumour biology of liver cancer, as all molecular findings show that oncogenic mechanism elaborated in other tumour entities are well in place in liver cancer and that e.g. number and frequency of actionable targets appears to be comparable; for many tumour biological aspects liver cancer is even a well suited model disease. Recent analyses have elaborated on the specific roadblocks responsible for the dismal situation.

Especially the structural integration of liver cancer treatment and research merits attention. Although liver cancer treatment and especially systemic treatment and the respective translational research are structurally by far not uniformly positioned throughout the world, a common theme with few exceptions is its underrepresentation in (Comprehensive) Cancer Centers or comparable Oncological Structures. Therefore, it appears to be wise to position liver cancer in the middle of (C)CCs. It is obvious that especially CCs are major structures supporting the progress of precision oncology. Ideally they integrate the expertise, diagnostic and treatment options and translational research portfolio of all involved disciplines. Furthermore, CCCs provide the combined expertise and critical mass to implement and sustain essential core structures needed for treatment and translational research progress, such as clinical trial center, biobanking, registries, and dedicated oncology training programs. Another aspect is that experimental molecular diagnostics as well as trial and therapeutic concepts aiming novel targets have to include trans-entity approaches and these are preferentially allocated to CCCs; in order to fully participate from this progress, liver cancer has to be a visible and integrated tumour entity. Another important aspect is that CCCs are simply a superior selling point. They are overall more attractive for substantial external funding than solitary approaches and

are thus much more suitable to acquire add on funding, either from health care financiers, independent funding agencies, or industry.

What can be done beyond that? Modern molecular diagnostic approaches require a critical mass, usually not provided by a single tumour entity. Strategically, it may be beneficiary to even fuse approaches to biliary and hepatocellular carcinoma (and even pancreatic if required), if possible. Interdisciplinary tumour boards offer the potential to partially lift the separation between evidence based treatment, clinical trials, and even experimental therapy, with the help of so-called umbrella concepts, integrating appropriate ELSI solutions, patient registries, trial portfolios and management, molecular diagnostics, and treatment. Thinking beyond this point, also networking of compatible centers will become necessary. Modern morphological and molecular approaches have taught us, that even frequent tumour entities break up into small treatment groups and sub-entities that form the basis for rational, molecularly based clinical trials. Thus in many trials sufficient and rapid recruitment cannot be provided by single centers and require inter-center cooperation. Access to specific tests and highly specialized treatment options may not even be provided in all larger centers. metadatabases/registries and translational research interaction are further incentives for center interaction. Taking (some of) these steps may help to change the course towards more successful clinical trials and translational research as well as improved diagnostic and treatment options in liver cancer.

Disclosure of Interest: P. Schirmacher: Grant/Research Support: Conflict with: Novartis, Roche, AstraZeneca, Chugai, Sanofi Aventis, Consultant/ Advisor: Conflict with: Novartis, AstraZeneca, Pfizer, MSD, BMS, Merck, Amgen, Roche, Sponsored Lectures: National or International: Conflict with: Novartis, AstraZeneca, Pfizer, MSD, BMS, Merck, Amgen, Roche

ANIMAL MODELS OF HCC: WHICH MODELS MIMIC BEST HUMAN BIOLOGY, PATHOLOGY AND GENETICS?

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INVITED SPEAKERS' ABSTRACTS

Hepatocellular carcinoma (HCC) is frequently associated with inflammation and liver cirrhosis. Chronic liver damage, due to viral infections, cholestasis, alcohol abuse, metabolic disorders or other causes leads to infiltration of cytokine-producing inflammatory cells, formation of reactive oxygen species and somatic mutations. Moreover, there is a substantial association between HCC incidence and obesity. Apart from these various etiologies, HCC is also a malignancy of considerable genetic diversity. Whereas other tumour types such as colorectal cancer or pancreatic ductular adenocarcinoma display typical mutations in the Apc tumour suppressor or Kras oncogene, such driver mutations are not common in HCC. However, mutations and epigenetic alterations have been described in genes implicated in telomere stability, the p53 pathway, Wnt/ β -Catenin signaling, chromatin remodeling, Ras/PI3K/mTOR signaling, oxidative stress, JAK/STAT signaling, PDGFR signaling and IGF signaling. A plethora of different HCC mouse models have been developed as tools for basic research and pre-clinical experiments. The models are based on targeted genetic manipulations, treatments with carcinogens and tumour promoters or transplantation of cancer cells. Given the genetic heterogeneity of HCC and its various etiologies, there seems to be no constructive approach to develop a mouse model that recapitulates all aspects of human HCC. Rather, models have to be adapted to integrate relevant features of distinct human HCC subtypes with respect to etiology, histopathology, genetics, cell of origin, impact of the microbiome and the immunologic tumour microenvironment.

Disclosure of Interest: None Declared

MOLECULAR IMAGING AND DRUG TARGETING: PRINCIPLES, PROGRESS AND APPLICATIONS TO HCC

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Diagnostic and therapeutic agents can be targeted to pathological sites, including to hepatocellular carcinomas (HCC). The molecular imaging and drug delivery fields have expanded exponentially in the last 1-2 decades, and they have resulted in novel tools and technologies for more specifically imaging, targeting and treating liver inflammation, fibrosis and cancer. In this talk, I will summarize several recent advances in molecular imaging and drug targeting, and I will show that these materials and methods are highly suitable for improving the diagnosis and treatment of inflammatory liver disorders and HCC.

Disclosure of Interest: None Declared

TUMOUR ASSOCIATED ANTIGEN RESPONSES IN HCC

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with a continuously high mortality. Thus, the development of new therapeutic strategies is crucial to decrease recurrence rates and to improve the overall survival rates of HCC patients. The rationale for immunotherapy is based on the findings of several studies showing specific CD8(+) T-cell responses against various tumour-associated antigens (TAAs) in HCC patients and a clinical benefit of T-cell infiltration in the tumour tissue. In addition, different vaccination strategies have led to induction of TAA-specific immunity and at least some tumour control. The factors responsible for the failure of TAA-specific immune responses to fully control tumour growth and immune evasion are not completely understood. Most likely, several different mechanisms contribute to the failure of the TAA-specific immune responses, e.g. the expression of inhibitory receptors such as PD-1 and CTLA-4 on TAA-specific T cells, the action of suppressive cell populations such as regulatory T cells or myeloid derived suppressor cells or the tolerogenic liver microenvironment. The aim of immune-based therapies is to overcome these mechanisms of T-cell failure and to induce or boost TAA-specific CD8(+) and CD4(+) T-cell responses. Several preclinical and clinical studies of immune-based therapeutic approaches show encouraging results. For example, recent data indicate that immune checkpoint inhibitors may show at least partial response also in HCC. It can be expected that a better understanding of the mechanisms responsible for TAA specific failure and its restoration will lead to the development of novel immune based treatment approaches that are currently being evaluated in preclinical and in early clinical settings. Indeed, immune checkpoint blockade along with adoptive immune cell therapy and vaccine approaches are currently being tested either alone or in combination with other treatments. Here, we provide an overview for the rationale of immunotherapy in HCC, summarise ongoing studies and provide a perspective for immune based approaches in patients with HCC.

Disclosure of Interest: None Declared

PROGNOSTIC SIGNATURES FROM HCC BIOPSY

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Background and Aim: Prognostication of natural history and/or survival in patients with hepatocellular carcinoma (HCC) is a key issue for the management of this condition. Traditional staging systems (based on clinical or imaging findings) fail to take into account the biologic characteristics of HCC while the molecular signatures set up so far were originated from archival samples derived from liver resection, therefore restricting the information gathered to no more than 10% of the totality of HCC. As HCC is an extremely heterogeneous tumour, this raises the question of the widespread applicability of these signatures to the totality of HCC. Second issue, is constituted by the fact that resection-based signatures use samples acquired several months after the initial diagnosis (as surgical intervention is rarely performed immediately after diagnosis), therefore further raising questions about accurate prognostication.

Methods: A cohort of 132 patients with liver cirrhosis on surveillance for HCC was prospectively studied from the time of HCC presentation. Doubling time (DT) was prospectively calculated (2 CTs performed 6 weeks apart, no therapy in between), gene and MiRNA expression, circulating cytokines levels, immunohistochemistry for PD1/PDL1, E-cadherin, CD138 were evaluated. A fraction of the US-guided diagnostic liver biopsy was sufficient to perform micro- and miRNA-arrays analysis as well as IHC. (IRB10/08_CE_UniRer; NCT01657695).

Results: The identified 5-gene hepatic transcriptomic signature (ANGPT2, DLL4, NETO2, ESM1, NR4A1) accurately defined both DT (ROC AUC: 0.961; 95% CI 0.919 to 1.000; $p < 0.0001$) and mortality (HR: 3.987; 95% CI 1.941 to 8.193, $p < 0.0001$). A 13-miRNA signature was significantly related with the transcriptomic one. TGF- β 1 was the only cytokine significantly increased in patients with aggressive HCC ($P = 0.002$). The microenvironment of aggressive HCC was characterized by PD1 (both in TILs and tumoural hepatocytes)/PDL1 (TILs and scant hepatocytes) overexpression, loss of E-cadherin expression, CD138 overexpression.



Conclusions: A thorough characterization of the microenvironment of HCC, which accurately predicts clinical progression and survival, can be obtained by a single US-guided liver biopsy. This complex set of data (gene expression, MiRNA, IHC, cytokines), should be tested in the frame of the new immune checkpoint inhibitors in order to better understand their performance.

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ANGIOGENESIS REVISITED: ROLE AND (THERAPEUTIC) IMPLICATIONS OF ENDOTHELIAL METABOLISM

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The past 40 years of research in the angiogenesis field have focused on identifying genetic signals such as VEGF and Notch, which determine vessel sprouting. However, the role and therapeutic potential of targeting endothelial cell (EC) metabolism have been largely overlooked. We have recently reported that ECs are glycolysis addicted and that glycolysis importantly co-determine vessel sprouting downstream of VEGF and other pro-angiogenic signals. In addition, we documented that ECs are rather unique in utilizing fatty acid-derived carbons for the de novo synthesis of deoxyribonucleotides for DNA synthesis during EC proliferation when vessels sprout. Moreover, targeting (blocking) glycolysis and fatty acid oxidation inhibit pathological angiogenesis and induce tumour vessel normalization (thereby reducing metastasis and improving chemotherapy), suggesting that these metabolic pathways are new targets for anti-angiogenic drug development without evoking systemic side effects. Furthermore, lymphatic ECs differ from other EC subtypes in their metabolic requirements for lymphangiogenesis. Since many of these metabolic targets are pharmacologically druggable, these metabolic pathways represent a new promising target for therapeutic anti-angiogenesis.

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TGF-BETA IN HCC PROGRESSION

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The Transforming growth factor-beta (TGF- β) family regulates cell proliferation, differentiation, migration or death, playing relevant roles in the homeostasis of tissues and organs. Due to the diverse and pleiotropic TGF- β functions, de-regulation of its pathways contributes to human diseases. In the case of the liver, TGF- β signaling participates in all stages of disease progression, from initial liver injury through inflammation and fibrosis, to cirrhosis and cancer. TGF- β inhibits growth and induces apoptosis in hepatocytes, promoting liver differentiation during embryogenesis and physiological liver regeneration. However, high levels of TGF- β , as a consequence of chronic liver damage, produce activation of stellate cells to myofibroblasts and massive hepatocyte cell death, which contributes to the promotion of liver fibrosis and later cirrhosis. During liver tumorigenesis, TGF- β plays a dual role. It may behave as a suppressor factor at early stages, but overactivation of its signalling could later contribute to tumour progression, once cells escape from its cytostatic effects.

As tumour suppressor, TGF- β early induces cell cycle arrest and apoptosis. However, at later times, it activates proliferative and anti-apoptotic signals through transactivation of other pro-mitogenic pathways, such as PDGF or EGF [1]. Downstream signals, such as the PI3K/AKT axis, counteract TGF- β -induced apoptosis, through impairing up-regulation of the NADPH-oxidase NOX4, which is required for ROS production and TGF- β -induced mitochondrial-dependent apoptosis. Liver tumour cells that overcome TGF- β -induced apoptosis respond to this factor undergoing epithelial-mesenchymal transition (EMT), which contributes to increase cell migration and invasion. Interestingly, up-regulation of SNAI-1, the gene that codifies for Snail (a repressor of E-cadherin expression, up-regulated by TGF- β) also mediates anti-apoptotic signals counteracting TGF- β -induced cell death [1]. This dual, and in some aspects controversial, response of liver tumour cells to TGF- β explains the complexity when studying the role of this pathway in liver tumour progression. A classification established according to the TGF- β -gene signature in HCCs showed that a "late" TGF- β -signature (coincident with the expression of EMT-related, anti-apoptotic and invasion-related genes) correlates with increased tumour recurrence as well as a higher invasive phenotype, when compared to the tumours that show an early TGF- β -signature (suppressor genes) [2].

For all these reasons, targeting the TGF- β signaling pathway is being explored to counteract liver disease progression [3]. Encouraging results in clinical trials using TGF- β receptor inhibitors prove that research is moving forth despite the complexity

of the situation. However, the identification of new TGF- β related biomarkers would help to select those patients most likely to benefit from therapy aimed at inhibiting the TGF- β pathway. In this sense, we have recently described different targets of the TGF- β pathway in HCC that would be required for its effects on EMT and stemness, such as the chemokine receptor CXCR4, which facilitates the response to its ligand (CXCL12/SDF-1, produced by the stroma cells), or the stem-related gene CD44, which contributes to increase the tumour initiating capacity of the cells, as well as their migration and invasion. We also recently identified that expression of the NADPH oxidase NOX4, mediator of the suppressor effects of TGF- β , is decreased in a relevant percentage of HCC patients. The identification of new regulators of TGF- β functions will not only permit to identify patients where anti-TGF- β therapy might be adequate, but also the possibility of targeting secondary regulators in order to alter TGF- β response in the liver.

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RETROTRANSPOSONS AND GENETIC INSTABILITY IN HEPATOCELLULAR CARCINOMA

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Hepatocellular carcinoma (HCC) complicates chronic liver disease (CLD) arising from hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol excess and obesity and is the second commonest cause of cancer death worldwide. Due to late detection, >70% have incurable disease at presentation. Hence, there is utmost need to develop more sensitive early stage detection markers for surveillance in those known to be at risk, as well as improved therapeutic options. Retrotransposons, especially LINE1 elements (Long Interspersed Nuclear Elements, L1s), get activated in HCC [1] due to global hypomethylation – a hallmark of cancer development. Active retrotransposons can move around in the genome contributing towards genomic instability and, depending on the location of an active L1 element, may predispose an individual towards cancer development. We have identified specific genomic loci where the presence of a repeat element increases an individual's risk of cancer development. My group is currently exploring L1 protein expression in different chronic liver diseases in the presence and absence of HCC, both in liver tissues as well as blood. Our aim is to develop circulating biomarker tools that predict HCC risk and aid early detection. These include the detection and quantification of L1 promoter methylation in circulating cell free DNA (cfc-DNA) as well as the detection of L1 protein expression in circulating tumour cells (CTCs). CTC detection is on the basis of cell size, DNA content and lack of CD45 expression [2] and is further characterized by immunofluorescent staining with anti-L1-orf1p or anti-L1-orf2p antibodies. Correlations with outcome, including response to treatment, may aid the development of novel prognostic or predictive biomarkers, which aid treatment stratification and/or monitoring.

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Figure

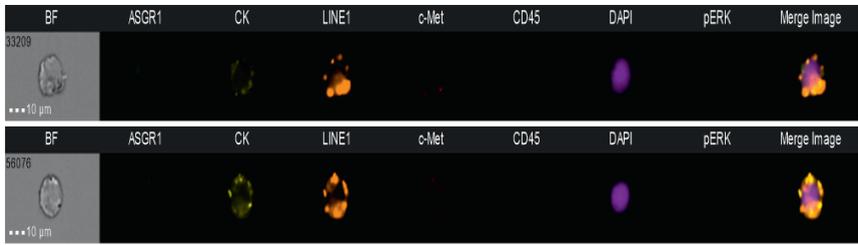


Figure: CTCs in peripheral blood of a HCC patient: Bright-field and immunofluorescent images of 2 CTCs from a single patient, both are positive for L1-orf2p. Exploratory biomarkers (ASGR1, cytokeratin (CK), c-Met and pERK) may aid further associations.

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OBESITY, THE GUT MICROBIOME AND LIVER CANCER

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Obesity and obesity-related disorders such as non-alcoholic fatty liver disease (NAFLD), metabolic syndrome and type 2 diabetes show an increased risk of developing various gastrointestinal cancers. These malignancies include besides others esophageal, gastric, colorectal, pancreatic and hepatocellular carcinoma (HCC). Whereas involved mechanisms remain unclear, chronic inflammation accompanying obesity has evolved in the last years as a potentially important factor. Various pathways might participate including innate immunity, (adipo)-cytokines such as adiponectin or leptin, insulin, insulin-like growth factors, the gut's microbiota and others. Several human metagenome-wide association studies performed in recent years have demonstrated highly significant correlations of certain members of intestinal microbiota with obesity and associated disorders. Dietary factors which are substantially affecting microbial composition, might play here an exceptional important role. Furthermore, evidence is increasing that besides NAFLD many other liver diseases both at early and late stages are accompanied by profound changes in the intestinal microbiome. The relevance of these changes is currently unclear but is assumed that the intestinal microbiota plays a key role in the pathogenesis of chronic liver disorders including the development of HCC.

Whereas clinical studies investigating the intestinal microbiota in liver cirrhosis have demonstrated a convincing "microbial" signature, clinical studies in HCC subjects assessing the intestinal microbiota are still sparse. However, several elegant preclinical studies have suggested that the intestinal microbiota might play a key role in disease process and HCC development. Fermentation of certain prebiotics such as inulin type fructans into short chain fatty acids (e.g. propionate) is able to suppress cancer cell proliferation in the liver highlighting an important interaction between diet, microbiota and cancer. The microbiota affects HCC risk in mice exposed to carcinogen chemicals or hepatitis virus transgenes. TLR4 activation by endotoxins derived from the intestinal microbiota contributes to inflammation-driven HCC tumour promotion whereas tumour initiation was not dependent on the intestinal microbiota. Importantly in this study, HCC promotion was associated by increased proliferative and antiapoptotic signals primarily in resident liver cells. Antibiotic therapy in this model was able to counteract tumour promotion. Diet-induced obesity in mice is accompanied by increased levels of deoxycholic acid (DCA), which is able to cause DNA damage. DCA results in a senescence-associated secretory phenotype in hepatic stellate cells, thereby releasing numerous proinflammatory signals which drive HCC development after exposure to chemical carcinogens. Importantly,

block-ade of DCA or usage of antibiotics prevented HCC development in obese mice. Cer-tain probiotics have been demonstrated to reduce HCC tumour growth significantly, especially by suppressing gut and liver inflammation. Overall, all these studies from the past years suggest that the intestinal microbiota might play a fundamental role in the biology of HCC promotion. More clinical and mechanistic studies further eluci-dating this association are eagerly awaited.

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ENDOPLASMIC RETICULUM PROTEOSTASIS IN HEPATOCELLULAR CARCINOMA

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Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis. HCC is now the third leading cause of cancer deaths worldwide, with over 500,000 people affected and despite intensive efforts, therapy remains limited. Using integrative phosphoproteomics of human tumours, we have shown that protein homeostasis (proteostasis) of the Endoplasmic Reticulum (ER) is altered. Moreover, we identified a signaling network centered on the AAA+ ATPase p97/VCP that controlled adaptation to ER homeostasis imbalance and could play a significant role in the acquisition of malignant traits in HCC. To further document the role of p97/VCP in HCC, we evaluated how its subcellular localization and functional interaction network could mediate protumorigenic functions. First, using a targeted approach we found that p97/VCP tyrosine phosphorylation prompted its nuclear translocation to mediate specific functions in the regulation of gene expression. Interestingly, this process was blunted upon sorafenib treatment. Second, a genome-wide RNAi approach in *C. elegans* revealed that p97/VCP contributed to trigger stress-dependent gene expression through an interaction with another AAA+ ATPase named Ruvb2. These mechanisms were conserved in human HCC-derived cell lines in which the role of Reptin, the ortholog of Ruvb2 is essential. We demonstrate that p97/VCP controls stress-induced gene expression by attenuating select transcription repressor complexes containing Reptin and well-known epigenetic regulators. Altogether, we identify a p97/VCP-dependent evolutionary conserved regulatory circuit controlling transcription upon ER proteostasis imbalance that could impact on the development of HCC as well as tumour sensitivity to current treatments.

Disclosure of Interest: None Declared

FGF19, A DOUBLE-EDGE SWORD AND POSSIBLE CLUE TO THE CANCER RISK IN PRIMARY SCLEROSING CHOLANGITIS AND NON-ALCOHOLIC STEATOHEPATITIS

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Fibroblast growth factor 19 (FGF19) is secreted from the ileum into the portal circulation upon activation of the bile salt receptor FXR. In the liver FGF19 binds to the FGFR4/ β Klotho receptor complex and via ERK/cJUN signalling has a number of metabolic effects including repression of bile salt synthesis. In addition to this physiological function, FGF19 via a STAT3 signalling path, stimulates regeneration upon liver resection and induces liver tumourigenesis in mice upon FGF19 overexpression. FGF19 and FGFR4 are frequently amplified in human hepatocellular carcinoma, cholangiocarcinoma and a range of other tumours indicating a possible role of FGF19 signalling in tumourigenesis (1) (2). Recent evidence indicates that FGF19/FGFR4 via GSK3 β / β -catenin stimulates the epithelial-mesenchymal transition in cultured hepatoma cells, a process that underlies aggressiveness and poor prognosis of HCC and CCA (3). In patients with HCC, FGF19 in the circulation and affected liver are moderately increased (4), and in NAFLD animal models human FGF19 is tumourigenic (Lei Ling, NGM Bio, personal communication). Interestingly, FGF19 is present in high concentrations in normal human bile (5). How exactly FGF19 ends up in bile is not known but it may be produced locally upon exposure of cholangiocytes or gallbladder mucosa to bile salts. It is of interest to note that cholangiocytes and gallbladder epithelial cells express the bile salt transport protein ASBT that mediates the luminal uptake of (small amounts of) bile salts. Mdr2 $^{-/-}$ mice represent an animal model for primary sclerosing cholangitis. Upon overexpression of human FGF19 in the liver of these mice, accelerated tumour formation was seen. A similar 'two hit' situation could be present in PSC patients with locally a high FGF19 production in obstructed areas of the biliary tree. Bile duct injury, exposure to bile salts from bile and local production of FGF19 could create a tumourigenic microenvironment. This would be a drugable scenario. FGF19 engineered to retain metabolic actions but devoid of mitogenic activity (M70, NGM282), has been shown to reduce spontaneous tumour formation in Mdr2 $^{-/-}$ mice (6) indicating that this modified FGF19 might be a tumour-preventing agent in PSC patients by competing with endogenous FGF19 for binding to

FGFR4. In addition, pharmaceutical blockade of FGFR4 signaling via selective inhibitors may be an approach in the treatment of hepatobiliary tumours with autocrine activation of FGFR4 (7).

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REGULATED CELL DEATH PATHWAYS IN HEPATOCARCINOGENESIS

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Hepatocellular death is present in almost all types of human liver disease and is used as a sensitive parameter for the detection of acute and chronic liver disease of viral, toxic, metabolic, or autoimmune origin. Clinical data and animal models suggest that hepatocyte death is the key trigger of liver disease progression, manifested by the subsequent development of inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. For years, the term apoptosis was used synonymously for programmed cell death. Apoptosis is triggered by ligation of death receptors like tumour necrosis factor (TNF) receptor by their cognate ligands and represents a highly synchronized procedure depending on activation of aspartate-specific proteases known as Caspases. Apoptotic death of hepatocytes is a common feature of viral hepatitis, acute liver failure, alcoholic and nonalcoholic steatohepatitis and is associated with fibrosis. However, a growing number of recent studies showed that there are distinct programmed cell death modes other than apoptosis. As such, necroptosis – relying on the kinases Receptor-Interacting Kinase 3 (RIPK3) and RIPK1 – represents a novel form of programmed cell death in development, tissue homeostasis and inflammation. In our work, we have focused on evaluating the functions of RIP Kinase-dependent signaling pathways in liver physiology and pathology. More specifically, data on the roles of RIPK1 and RIPK3 in acute liver injury, NASH and HCC development as well as their interaction with inflammatory signaling pathways will be presented and discussed.

Disclosure of Interest: None Declared

HMGB1 LINKS CHRONIC LIVER INJURY TO HCC DEVELOPMENT

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Cell death is a key driver of inflammation and maladaptive wound healing in the injured liver, thereby fostering the development of a tumour-prone environment. Despite the fact that cell death increases risk for hepatocellular carcinoma (HCC) development in patients and mouse models, the underlying mechanisms remain largely elusive. We investigated the hypothesis that damage-associated molecular patterns (DAMPs) act as a molecular link between hepatocellular death and carcinogenesis, focusing on the high mobility group box 1 (HMGB1), a DAMP with key roles in hepatic wound healing responses. Albumin-Cre induced ablation of HMGB1 inhibited HCC formation in three murine HCC models with chronic cell death but did not significantly alter the development of HCC in models without chronic cell death. HMGB1 may regulate several cell death responses that are regarded as key promoters of cancer, including inflammation, fibrosis, compensatory proliferation. However, we did not observe any significant differences in proliferation, fibrosis or inflammation between HMGB1-deleted mice and their floxed counterparts as assessed in several chronic injury models. Instead, HMGB1-deleted mice displayed a key role in progenitor response as demonstrated by reduced progenitors markers expression in models of chronic liver injury triggered by DDC or MCDE diet, and hepatic Tak1 or Mdr2 knockout. This effect was mediated in a non-autonomous fashion as hepatocyte-specific depletion of HMGB1, induced by AAV8-TBG-Cre, resulted in a similar reduced expression of progenitor markers. The progenitor response was also impaired in RAGEKO mice but not TLR4KO or TLR9KO mice fed with a DDC diet. Moreover, HMGB1-deleted mice displayed reduced progenitor marker expression as well as more mature phenotype in DEN+CCl₄-induced tumours. Based on previous studies showing a key role of progenitor signatures in determining HCC aggressiveness and clinical outcomes, our data suggest that HMGB1 links cell death to the development and progression of HCC by providing signals that may promote a less differentiated and more progenitor-like phenotype. Therefore, HMGB1 may represent a new therapeutic target for the prevention of HCC in patients with chronic liver disease.

Disclosure of Interest: None Declared

HOW CAN WE ASSESS THE RISK OF HCC DEVELOPMENT IN ALCOHOLIC PATIENTS?

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The percentage of hepatocellular carcinoma (HCC) cases attributable to excessive chronic alcohol consumption in Europe is high and, as a whole, is increasing. This trend will be confirmed with the decline in viral-induced HCC expected in forthcoming years in western countries on the heels of more effective viral eradication and control, and by the increase in alcohol consumption observed in developing countries. It is therefore pivotal to identify, among millions of excessive drinkers, those susceptible to developing HCC, i.e. primarily cirrhotic patients, and, among the latter, to select those especially prone to developing liver cancer. Longitudinal studies dealing with the natural history of alcoholic cirrhosis are scarce. Moreover, major selection biases in studies conducted in decompensated patients or based on registry data hamper their interpretation in terms of HCC occurrence, as they mainly report the incidence of other liver-related complications that constitute risks of death competing with liver cancer occurrence in these populations. In these patients, the annual incidence of HCC has been however estimated between 2 and 4%, thus justifying periodic screening. Risk factors for HCC include classical clinical features such as older age, male gender, components of the metabolic syndrome, liver iron overload and severity of underlying cirrhosis. Interestingly, by combining these features, cirrhotic patients can be stratified into various HCC risk classes and thus define a specific phenotype of patients at risk. However, all alcoholic cirrhotic patients are subjected to the same management, namely 6-month periodic HCC screening, with no preventive measures undertaken.

Genetic risk markers of HCC in patients with alcoholic cirrhosis have also been described and might at least in part explain the wide inter-individual susceptibility to HCC in these patients. The study of genetic predisposition to alcohol-related liver cancer aims to identify among patients with alcoholic cirrhosis those particularly exposed to HCC development. Several variants modulating various biological pathways involved in alcoholic hepatocarcinogenesis have been reported as associated with a higher risk of HCC in these patients. These genetic traits can affect ethanol metabolism, oxidative stress, inflammation process, iron or lipid metabolism. Among the latter, a single nucleotide polymorphism (rs738409 C>G) which encodes for an isoleucine to methionine substitution at position 148 in the adiponutrin/patatin-like phospholipase-3 (PNPLA3) protein sequence, as a promoter of intracellular triglyceride accumulation has been tenaciously reported as associated with alcohol-related liver cancer in cirrhotic patients. Initially identified by concordant Genome Wide Association Studies (GWAs) performed in patients with ALD

or NASH, the rs738409 (G) allele was reported to be associated with more pronounced steatosis, advanced fibrosis and higher rates of liver cancer. All studies in this field were conducted in Europe and included homogeneous populations of several thousand of Caucasian patients with cirrhosis, complicated or not by HCC. As a whole, this approach confirmed the influence of PNPLA3 genotypes on liver carcinogenesis in alcoholic Caucasian cirrhotic patients, in whom a two-fold HCC risk was observed for those bearing the G variant.

The challenge is to understand how the combination of several genetic variants with clinical data might refine stratification of alcoholic cirrhotic patients according to different HCC risk classes. These advances will enable implementation of personalized medicine in these patients, i.e. the adaptation of screening and preventive measures, criteria of early diagnosis and the choice of therapeutic procedures based on inter-individual susceptibility. Large prospective cohorts are urgently needed to validate and integrate predisposing genetic traits and phenotypic characteristics into individual HCC risk assessment models.

Disclosure of Interest: None Declared

SURVEILLANCE FOR HCC: WHOM, HOW, AND HOW OFTEN?

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Hepatocellular carcinoma (HCC) is the sixth most frequent cancer and it is the third leading cause of cancer related death. HCC appears mainly in patients with underlying chronic liver disease and it is accepted as one of the most important causes of death in this population. Early detection by surveillance has been suggested as an effective tool for reducing cancer-specific mortality, being semiannual abdominal ultrasound the most accepted strategy in those patients at risk of HCC development. HCC accomplishes the principles for recommending surveillance proposed by the World Health Organization (WHO). In addition, the benefit of HCC surveillance is proven by a randomized-controlled study conducted in China, several prospective or retrospective analyses, and multiple modeling studies. According to the existing scientific evidence, surveillance of HCC should be recommended and widely implemented. Major efforts should be done for improving the diagnostic accuracy of the available screening tools and for better identifying those patients at relevant risk of HCC occurrence in whom surveillance would be cost-effective.

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PATHOLOGY OF HCC: CAN WE IMPROVE THE DIAGNOSTIC ACCURACY?

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According to the international guidelines, diagnosis of hepatocellular carcinoma in cirrhotic patients relies on non invasive imaging features (so called “wash-in” & “wash-out”). Nevertheless, pathological diagnosis remains the gold standard in several settings, cases where imaging has failed, but more importantly in the near future for providing the overall picture of the tumor, in terms of subtyping.

Where we are

1. Diagnostic accuracy for diagnosis early Hepatocellular Carcinoma (eHCC)

Liver carcinogenesis follows a multistep process through the development of preneoplastic nodules arising in a background of cirrhosis. A wide range of preneoplastic nodules, less of 2 cm in diameter, is recognized, from regenerative to low- and high grade dysplastic nodules (1). Differential diagnosis between dysplastic nodules and eHCC relies on a set of architectural and cytological criteria (2). Among them, stromal invasion, has been proposed as the most powerful feature for diagnosing eHCC (3). In addition to morphology, immunophenotypical markers, especially the panel of glutamine synthetase, HSP70 and Glypican 3, improves diagnostic performance, even though on biopsy specimen (4, 5).

2. Diagnostic accuracy of HCC

HCC pathological diagnosis relies on morphologic features including architectural and cytological criteria. Based on these criteria, tumor differentiation of conventional HCC as well as identification of HCC variants can be made, In addition, in the spectrum of primary liver malignancies, hepatocholangiocarcinomas, defined by the presence of both HCC and cholangiocarcinoma areas, represent an increasing challenge for pathologist since non invasive diagnosis by imaging is not performant. Such diagnosis relies on the combination of morphological and immunophenotypical features, mostly based on liver progenitor cell markers (6).

Where we should go

1. Towards a pathomolecular classification

Molecular studies of HCC clearly identified several subgroups of tumors based on their molecular signature, that correlates with clinical characteristics (7, 8). Then, and by analogy with the pathomolecular classification of hepatocellular adenomas, HCC pathological diagnosis may include molecular traits, resulting on a complete picture of the tumor gathering diagnostic and pronostic features.

2. Markers of vascular invasion

Vascular invasion remains one of the main poor prognostic factors. When microvascular invasion (mVI) is present, its identification can only be assessed on the surgical specimen. The development of surrogate markers of mVI is mandatory for improving clinical management of patients. Several potential markers have been proposed without any validation so far (9).

3. Theranostic markers

In addition to surgery, treatment of HCC covers a wide range of modalities, from radiofrequency to trans arterial chemoembolisation (TACE) and more recently targeted therapies. Accordingly, the development of predictive markers of treatment response may be of significant help in the therapeutic strategy (10).

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RESECTION OR THERMAL ABLATION AS FIRST LINE TREATMENT FOR EARLY STAGE HCC?

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Early hepatocellular carcinoma (HCC) in patients with compensated cirrhosis is theoretically amenable to curative treatments (i.e. surgical resection, ablation and transplantation). Liver transplantation can be applied very limitedly due to the shortage of donors, thus the choice in the large majority of cases falls between resection or ablation, a choice which also implies to balance utility vs benefit. In this scenario however, the benefit is related only to the costs generated to the community for either one or the other treatment. A recent meta-analysis showed that in patients which might be equally suitable for both techniques (which comprises no more than half of the population), ablation is more cost-effective in case of very early HCC (<2 cm) or multiple="multiple" tumours (2-3 HCC <3 cm), whereas for HCC >2 cm resection is associated to a well acceptable cost-benefit ratio and could be preferable. In fact, thermal ablation suffers higher rates of local recurrence due to incomplete tumour removal, a risk proportional to tumour size (and secondly connected to difficult locations such as subdiaphragmatic, proximity to intrahepatic vessels or the gallbladder). Conversely, resection provides a higher rate of complete tumour removal at the expenses of higher risk of decompensation and liver failure, which become of major concern in patients with clinically significant portal hypertension (and additionally in the instance of centrally located tumours, which might require extensive parenchymal sacrifice despite small tumours size).

In the ideal candidate, with preserved liver function (Child-Pugh A), no significant comorbidity, no portal hypertension and tumour located in a liver region easily accessible to both thermal ablation and resection, tumour size and economical resources dominate the reasons to choose. Theoretically a sufficiently large randomized controlled trial in this setting would give the final answer to this question, but such a trial will likely never take place for several practical reasons, thus we should base our decision on the current evidence, mainly base on case control series. A recent meta-analysis complemented with a Markov model showed that if the tumour is single <2cm, classifying the patient as BCLC-0, thermal ablation may be preferred as first line therapy since providing the best cost-effectiveness. Conversely if the tumour is bigger than 2 cm surgery is to be considered in first line, especially in all cases of >3cm (since the effectiveness of thermal ablation becomes questionable in comparison to resection). However, the ideal situation only occasionally occurs in real life and quite often many different factors have to be taken into consideration.

For instance, if the forecast of complete tumour ablation with a >5 mm safety margin is uncertain (for poorly visible lesions, difficult locations, etc), then surgery is to be preferred even in very small HCC <2cm (with intraoperative thermal ablation as an option). In the instance of tumours ranging 2 to 3 cm or multiple="multiple" (2 or 3 tumours <3 cm) a multidisciplinary discussion should balance the risks of liver parenchymal sacrifice, risk of post-operative decompensation, perioperative risk due to comorbidities, with the risk of incomplete tumour cure when performing ablation, leading to tailored decisions on the individual patient, whether to offer ablation or resection. Importantly, in the instance of multiple="multiple" tumours, resection and intraoperative ablation can be combined. Portal hypertension is a relative but not an absolute contraindication in this setting and a balance of the prediction of complete tumour removal versus preservation of liver function and of compensated stated of disease is to be made for each potential candidate, leading to the final decision. If liver function or severe portal hypertension contraindicate surgery in tumours >3 cm, a combination of thermal ablation with endovascular embolization is to be considered.

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LOCOREGIONAL THERAPIES: IMAGING TUMOR RESPONSE EVALUATION IN HCC: ROOM FOR IMPROVEMENT?

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Abstract Body: Locoregional treatments are widely used in hepatocellular carcinoma (HCC) at various stages. Radiofrequency or microwave ablations are proposed in early HCC. The reference treatment of intermediate HCC is transarterial chemoembolization (TACE). Selective intraarterial radiation therapy (SIRT, also named radioembolization) is under evaluation in advanced HCC, and combination of percutaneous tumor ablation with TACE is advocated in large HCC. Therefore, there is a crucial need to assess tumor response on imaging. All these treatments share the non-surgical approach but have different mechanisms. While some induce tumor necrosis (tumor ablation and TACE), SIRT has a more complex pathologic process.

The first criteria that have been applied were only based on tumor measurement either bidimensional (WHO) or unidimensional (RECIST). Although these criteria (RECIST) are still widely used in oncology, they have been shown to markedly underestimate tumor necrosis following locoregional treatment of HCC. Indeed they do not take into account the tumor necrosis induced by treatment (1). Thus, both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) have proposed new imaging criteria referred to as the EASL and mRECIST criteria respectively which were designed to improve evaluation of tumor response (2,3). Unlike RECIST 1.1, the EASL and mRECIST classifications of tumor response are based on the analysis of the viable or hypervascular portions of the tumor on contrast-enhanced imaging.

Overall response according to EASL or mRECIST has been shown to be an independent positive prognostic factor and associated with improved survival in patients treated with locoregional therapy. As the mRECIST is easier to use than EASL it represents the reference method for evaluating tumor response during HCC treatment. Yet, mRECIST has limitations: first, it is a 2D method that does not take into consideration the whole tumor; second, it can be only applied to hypervascular HCC.

Besides mRECIST, other approaches have been developed. Among them, the development of 3D quantitative tumor assessment technique based on tumor enhancement seems interesting and is a stronger predictor of survival as compared to diameter-based measurements. Others use functional imaging such as CT perfusion and DCE MRI. Although unicentric studies have shown promising results, no multicentric validation has



been done so far. Diffusion-weighted MR has also been evaluated alone or in combination with tumor enhancement, the latter having better results than classical criteria.

In conclusion, assessment of tumor response after locoregional therapy of HCC is of paramount importance as it may influence major options in patient management such as indication of liver transplantation. They are mostly based today on qualitative assessment of tumor enhancement but there is certainly room for improvement.

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CAN LOCO REGIONAL THERAPIES BE COMBINED?

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Hepatocellular carcinoma (HCC) is the 6th most common cancer and is the third leading cause of cancer-related death worldwide. The main used staging and treatment strategy in Europe is the algorithm from the Barcelona Clinic Liver Cancer group (BCLC) reported different therapeutic approaches depending on the liver function, tumour extent and performance status of the patient. Thus, curative therapies include ablation, resection and transplantation can be offered for patients with early HCC (almost 30% of patients with HCC), whereas palliative transarterial chemoembolisation (TACE) therapies are recommended for patients with large or multiple HCC and good liver function, a macrovascular invasion or a poorer performance status leading to a more palliative approach with multikinase inhibitors (MKi). Surprisingly, clinical effective and in the meanwhile well-established combined approaches such as TACE and ablation are not reported in this algorithm. In several prospective randomised trials, combined transarterial treatments with thermal ablation has demonstrated its superiority in terms of local control and survival comparing with thermal ablation or TACE alone and is therefore reflected in the NCCN and in the German guidelines, but not in the BCLC. Nevertheless, a critical review of these studies shows a deficit in the standardisation of this combined strategy, number of TACE before ablation, art of TACE as well as embolics and drugs are different in all reported studies. Other combined approaches such as TACE with MKi seemed promising but first results were disappointed. Other combined approaches has been performed such as TACE with external radiation, interstitial radiation therapies with ablation, up to now without clear evidences of benefit for the patients with intermediate stages. In this lecture, we will review the different strategies of combined therapies for patients with HCC, their clinical efficacy and the level of evidences of the different studies.

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THE ROLE OF LOCOREGIONAL THERAPIES IN CHOLANGIOCARCINOMA

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Patients with non-resectable cholangiocarcinoma (CC) have a poor outlook with a median survival of 6-11 months and a 5-year survival of less than 5%. Surgery is the only curative treatment but is appropriate in less than 20% of cases, while the remaining 80% of cases require palliation of symptoms in a multidisciplinary context. Although most patients can be palliated promptly by endoscopic or percutaneous placement of one or more biliary stents, the prognosis remains poor. Since the cause of death in CC is commonly due to recurrent biliary obstruction and intrabiliary sepsis rather than metastatic disease, key strategies are local disease control and optimising biliary drainage.

Palliative endoscopic biliary stenting (EBS) has overtaken surgical bypass for malignant biliary obstruction. A Systematic Review and Meta-Analysis (SRMA) found that EBS was associated with lower 30-day mortality and fewer complications.¹Self-Expanding Metal Stents (SEMS) are superior to plastic stents in the palliative setting. Using SEMS for distal extrahepatic or hilar malignant biliary strictures results in significantly longer median patency and lower re-intervention rates when compared to plastic stents. A review identified two RCTs and four retrospective studies comparing unilateral versus bilateral stenting of hilar CC. Although three studies advocated bilateral stenting, both RCTs recommended unilateral stenting.²EUS-guided biliary drainage is an emerging technique for patients who have failed EBS and have contraindications to percutaneous biliary drainage. A stent can be placed anatomically (transpapillary route) or by forming a hepaticogastrostomy. A SRMA (42 studies, n=1192) found this technique to have a 94.7% technical success rate and 91.7% functional success rate but a complication rate of 23.3%.³

A SRMA (6 RCTs, n=327) in 2012 comparing photodynamic therapy (PDT) versus EBS found that PDT was associated with longer OS and improved quality of life, but concluded that the quality of evidence was low.⁴This SRMA did not include a RCT of EBS vs. EBS with PDT that was stopped early due to worse OS in the PDT group (5.6 vs 8.5 months).⁵Evidence for the use of endoscopic Radiofrequency Ablation (RFA) in malignant biliary obstruction is largely restricted to retrospective analyses and small cohort studies. A SRMA (9 studies, n=263) found that RFA resulted in a median stent patency duration of 7.6 months and 2-year OS of 50.4%.⁶Endoscopic brachytherapy has also been used for locally advanced and recurrent CC. A recent retrospective analysis compared survival of patients with unresectable extrahepatic CC receiving conventional

radiotherapy (RT) or RT with brachytherapy.⁷When excluding patients with metastatic disease there was a trend towards improved survival ($p=0.08$). Current guidelines do not advocate brachytherapy.⁸

The techniques described above can be performed percutaneously using interventional radiological techniques. A SRMA of percutaneous RFA for CC (8 observational studies, $n=84$) reported technical success in 80-100% of cases and complete tumour ablation on imaging follow up at 1 month in 66-96%.⁹Current guidelines suggest that RFA may be effective for disease control in small (<3 cm) intrahepatic lesions in non-surgical candidates, but trials are needed to determine the efficacy of RFA in such patients. Several therapies can be delivered via the hepatic artery: Transarterial Chemoembolisation (TACE), Transarterial Chemoinfusion (TACI) and Transarterial Radioembolisation (TARE). A SRMA in 2015 compared the three techniques.¹⁰Median OS was greatest for TACI (22.8 months) followed by TARE (13.9 months) and TACE (12.4 months). Response to therapy was also highest for TACI (TACI 56.9%, TARE 27.4%, TACE 17.3%). However, the rate of grade III/IV complications was also highest for TACI. Importantly, all included studies were either cohort or retrospective studies and most patients probably received systemic therapy before and/or after treatment. Further appropriately designed clinical trials are needed to establish the influence of these and other locoregional treatments on the survival and quality of life of patients with CC.¹¹

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INTRAHEPATIC CHOLANGIOCARCINOMA: THE CHANGING EPIDEMIOLOGY AND DIAGNOSIS

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Abstract Body: The epidemiology of IH-CCA displays enormous geographic differences reflecting the distribution of different risk factors, both environmental and genetic (1-6). While in western countries is still a rare cancer (incidence < 6/100,000), IH-CCA is exceptionally common in different east countries, such as South Korea and North Thailand, where it represents the main primitive liver cancer, linked with liver flukes and/or HBV/HCV infections (1-4). In different countries, a progressive increase of IH-CCA incidence has been reported (doubled in the last 20-25 years) (1). A current matter of debate is whether the registered increasing incidence is biased by misclassification, improved diagnostic tools or better identification, as IH-CCA, of liver cancer of unknown primary site (1). However, the prevailing view is that we are facing a real increase of IH-CCA incidence. Until the end of the past decade, the increased incidence of IH-CCA has been associated with the burden of HCV infection (1) but now, ongoing studies are suggesting HBV occult infection, environmental agents (dioxins, asbestos) and metabolic syndrome as potential risk factors sustaining the continuous increasing incidence of IH-CCA (1, 4). Interestingly, a recent report from USA showed that, while until the end of the past century the curves of incidence and mortality for IH-CCA coincided, in the last 10 years mortality tends to be lower than incidence suggesting a better clinical management (3). IH-CCA shows two main histological sub-types: *mixed-type* arising from small intrahepatic bile ducts and *the mucinous-type* arising from large intrahepatic bile ducts. The *mixed* IH-CCAs display an almost exclusively mass forming (MF) growth pattern and are frequently associated with chronic liver diseases and not preceded by pre-neoplastic lesions. On the other hand, the *mucinous* IH-CCAs are more frequently associated with Primitive Sclerosing Cholangitis and can be preceded by pre-neoplastic lesions. In 20-30 % of cases IH-CCA is associated with chronic liver disease or cirrhosis while in 20-25% of cases, diagnosis of IH-CCA is an incidental finding. However, the majority of IH-CCA cases occurs in the absence of an evident chronic liver disease or other risk factors. In general, the MF type represents the most frequent macroscopic presentation of IH-CCA (> 90%) appearing, at imaging, as a nodule. If MF occurs in context of cirrhotic liver, after exclusion of a metastatic lesion, differential diagnosis with HCC is obligatory (1, 7). In this context, contrast-enhanced MRI studies on IH-CCA patients showed the lack of HCC hallmarks in all cases; however, by TC, this occurs only in large nodules (> 3 cm) since smaller nodules frequently show a pattern similar to HCC

(1, 7). The most frequent imaging patterns displayed by IH-CCA in the cirrhotic liver are a progressive homogeneous contrast uptake until the delayed phase (MRI, CT) or an arterial peripheral-rim enhancement (CT). After excluding HCC in cirrhosis, or in the contest of a nodule in non-cirrhotic liver, biopsy is necessary. According to different guidelines, biopsy should be avoided in case of surgical resectability because of the risk of tumor seeding; however, this lacks of supporting evidence (1, 7). At histology, differential diagnosis of IH-CCA *vs* HCC or metastasis represents an unsolved problem, and no specific marker having been validated. A panel of immunohistochemistry (IHC) markers is required to exclude metastasis, and the cytokeratin profile (CK7+, CK19+, CK20-) in combination with IHC for Hep-Par1 is sufficient to exclude HCC. Recently, the positivity for N-cadherin, the study of Isocitrate Dehydrogenase 1/2 mutations, and the evaluation of albumin expression by *in situ* hybridization have been proposed for IH-CCA differential diagnosis (1, 7).

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ORAL PRESENTATIONS' ABSTRACTS



HEPATITIS C VIRUS INDUCES ONCOGENIC SIGNATURES THAT ARE NOT REVERTED FOLLOWING TREATMENT WITH DAAS

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Introduction: The increasing world prevalence of HCC, involving resistance to conventional chemotherapy, poor prognosis and eventually mortality, place it as a prime target for searching new modes of prevention and treatment. Hepatitis C Virus (HCV) is the most common risk factor for HCC in the US and Europe. Epidemiological studies show that SVR following anti-HCV treatment reduces but not eliminate tumor development and the risk for HCC after treatment with the newly approved DAAs is yet unknown.

Aims: We aimed to evaluate whether HCV infection promote epigenetic alternations that influence host gene expression and oncogenesis and leave an “epigenetic signature” on the host chromatin that is not fully recovered following virus eradication after treatment with DAAs.

Material and Methods: HCV infected and non-infected hepatoma cells were cured using Viekirax and Exviera. The patterns of gene expression and genome-wide histone modification were evaluated in HCV-infected hepatocytes before treatment and following one week and one month of viral eradication by treatment with Viekirax and Exviera.

Results: Strikingly, the mRNA and epigenetic markers levels of most of the tested genes that are implicated in cell proliferation, tumor formation, invasion and metastasis were not or only partially reverted following treatment. This provides an indication for HCV-induced epigenetic signature which may result in oncogenic processes.



Conclusions: Our study unveils a novel mechanism leading to HCV-induced cancer that is implicated in HCV “hit and run” tumorigenesis scenario following HCV eradication. This study may elucidate the cause for the residual risk for HCC following HCV treatment.

Disclosure of Interest: None Declared

THE DISRUPTION OF FAK/EZH2 FUNCTIONAL INTERACTION INDUCES IN VITRO AND IN VIVO HCC APOPTOSIS AND CONSEQUENT GROWTH REDUCTION

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Introduction: Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Several studies report a close association between HCC pathogenesis and sustained activation of proteins that control tissue remodelling, cell adhesion, migration, proliferation and apoptosis, such as focal adhesion kinase (FAK). FAK is a highly conserved non-receptor tyrosine kinase, which mediates cytoskeleton remodelling in correspondence of the focal adhesion points. It is found over-expressed or hyper-phosphorylated in HCC patients suggesting a key role of this protein in the control of cancer cells behavior. However, there are still not molecular explanations for FAK pro-tumorigenic action.

Aims: In this study, we point to investigate the effects of FAK silencing on in vitro and in vivo models of HCC.

Material and Methods: Stable silencing of FAK was performed by transduction with shRNA lentiviral particles in HCC cells. Obtained cells were used to perform in vitro analysis or ingegnerized to be inoculated into the liver of NOD/SCID mice.

Results: We found that FAK depletion in HCC cells reduced in vitro and in vivo tumorigenicity, by inducing G2/M arrest and apoptosis, decreasing anchorage-independent growth, and modulating the expression of several cancer-related genes (189-downregulated and 113 up-regulated in FAK silenced cells compared to control). Interestingly, we found that FAK-dependent genes are involved in the regulation of several cellular processes, highlighting as major molecular functions cell cycle, apoptosis and gene expression. Among these genes, we showed that FAK silencing decreased transcription and nuclear localization of enhancer of zeste homolog 2 (EZH2) and its tri-methylation activity of lysine 27 on histone H3 (H3K27me3). Accordingly, FAK, EZH2 and H3K27me3 were



concomitantly up-regulated in human HCCs compared to non-tumor livers. In vitro experiments demonstrated that FAK affected EZH2 expression and function, at least in part, by modulating p53 and E2F2/3 transcriptional activity.

Conclusions: In summary, we demonstrate that the disruption of FAK/EZH2 functional interaction reduces HCC cell growth by affecting cancer-promoting genes including the pro-oncogene EZH2. Furthermore, we unveil a novel unprecedented FAK/EZH2 crosstalk in HCC cells, thus identifying a new crucial targetable network for anticancer therapies.

Disclosure of Interest: None Declared

LIVER NK CELLS FROM NLG4-/- MICE INHIBIT PROGRESSIONS OF HEPATOCELLULAR CARCINOMA OF C57BL/6 MICE MODEL THROUGH DECREASE IN p53 AND Akt EXPRESSIONS

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Introduction: Cirrhosis is a main risk factor for hepatocellular-carcinoma (HCC) development. However, direct role of NK cell in HCC-progression is not fully understood.

Aims: Therefore we aimed to study the role of neuroligin-4 (NLG4) receptor of NK cells in models of HCC in C57BL/6 mice.

Material and Methods: HCC cell-line (Hep3B) secreted high levels of alpha-feto-protein (α FP) were injected in the back of irradiated C57BL/6 (sub-lethal dose) and liver NK cells from both WT and homozygous NLG4^{-/-} (KO) mice were transplanted at day 5 following HCC injections. Hepatic tumor sizes and serum α FP were then assessed from day 6 till day 14. Liver P53 and Akt expressions by RT were tested at day of sacrifice.

Results: Tumor mass increase in animals with HCC injections and was associated with elevated α FP serum levels in all tested time intervals. Mice receiving the liver NKs from the NLG4^{-/-} animals showed a significant decrease in tumor at days 10, 12 and 14. Liver NKs from the WT animals did not alter tumor progressions. At the day of sacrifice, serum α FP levels maintained were almost not significant in all tested groups as the WT mice showed an elevations in their α FP levels and ended to similar levels of the groups probably attributed to lost effects of irradiations. Liver p53 showed to be significantly high (1.5 fold increase) in the mice groups with HCC alone while almost decreased in mice receiving liver NKs from the NLG4^{-/-} to levels similar to the animals with no HCC. These results were associated with decrease in Akt only in animals receiving liver NKs from the NLG4^{-/-} (p=0.001).



Conclusions: p53 is a more sensitive marker for HCC tumorigenesis than α FP in C57BL/6 mice in advanced stages of tumor. The mechanism of p53-mediated repression of α FP levels may be active during hepatic differentiation and lost in the process of tumorigenesis. NK from NLG4^{-/-} mice showed to decrease tumor through p53 inhibitions and decrease in Akt indicating its associations with pathways decreasing proliferations of HCC and reinforces the importance of NLG4 modulation as a therapeutic target for HCC.

Disclosure of Interest: None Declared

INTRA-TUMOUR HETEROGENEITY IN THE REGULATION OF IMMUNE-TOLEROGENTIC PATHWAYS IN PRIMARY AND METASTATIC HEPATOCELLULAR CARCINOMA

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Introduction: Immune-checkpoint inhibitors targeting the programmed-death (PD) pathway and its ligands (PDLs) have shown preliminary evidence of activity in hepatocellular carcinoma (HCC), with variable response rates. Whilst PD-L1 status is utilised as a stratifying biomarker in clinical trials, evidence from other solid tumours suggests heterogeneity in PD-Ls expression across sampled sites, with implications in the development of immunotherapy.

Material and Methods: We collected archival paraffin embedded samples from 77 patients across 2 institutions: 56 with surgically resected and 21 with intermediate/advanced HCC. In 15 patients, 20 matching metastases were also available. Surgical samples were re-embedded in a tissue microarray including tumour tissue and surrounding cirrhotic background and were analysed for PD-L1 and PD-L2 expression by immunohistochemistry. Following total RNA extraction, we performed targeted transcriptomic analysis by Nanostring technology using a panel of 770 immune-related genes in 12 paired primary and metastatic HCC cores from 6 patients.

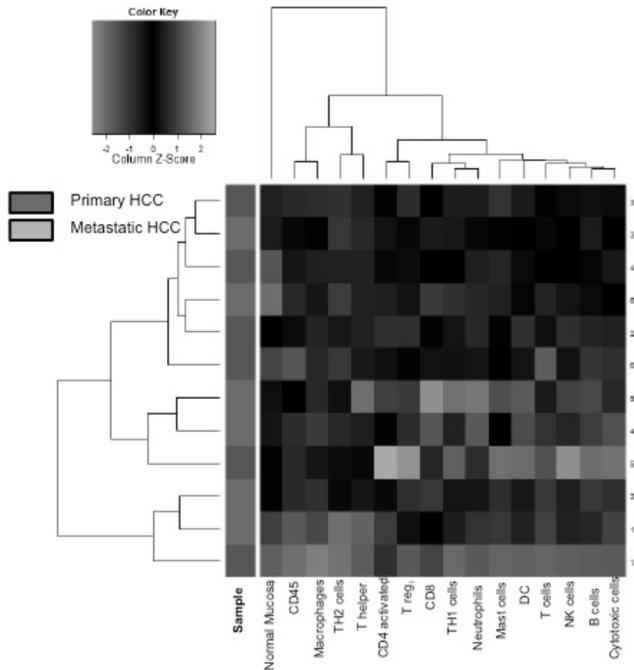
Results: Surgically resected cases were predominantly Child A (51/56, 91%), BCLC stage A (45/56, 80%). In resected tumour cores 11/56 (20%) were PD-L1 and 18/56 (32%) were PD-L2 positive. Surrounding cirrhotic liver revealed PD-L1 in the lymphocytic infiltrate in 8/56 samples (14%), whilst PD-L2 expression was found in the cirrhotic background in 29/56 cases (52%). PD-L2 expression in cirrhotic (p=0.03) but not in tumour cores (p=0.13) correlated with more advanced BCLC stage. In patients with intermediate-

advanced HCC (n=21), the prevalence of tumour PD-Ls expression was 40% (8/21) for both markers. Concordance between PD-L1 positive primary and metastases was 33% and 85% in PD-L1 negative tumours. In contrast, there was universal concordance between in PD-L2 expression between primary and metastatic HCC ($p < 0.001$). Targeted transcriptomic profiling revealed a subset of 40 genes involved in innate and adaptive immunity to be differentially regulated across primary and metastatic disease.

Conclusions: Intra-tumour heterogeneity in the expression of PD-L1 is common in HCC, whilst PD-L2 is homogeneously distributed in primary and metastatic deposits. Unsupervised transcriptomic profiling confirms differential activation of innate and adaptive immune-related pathways in the metastatic dissemination of liver cancer. This has profound implications in the clinical development of immune response biomarkers in HCC.

Figure:

Fig 1: Differential regulation of immune-tolerogenic pathways in primary and metastatic HCC (n=6 each group).



Disclosure of Interest: None Declared

A NEW IN VITRO HEPATOCELLULAR CARCINOMA MODEL BASED ON HUMAN NORMAL AND FIBROTIC 3D EXTRACELLULAR MATRIX SCAFFOLD BIO-ENGINEERING

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Introduction: The liver microenvironment is known to support hepatocellular carcinoma (HCC) development in which a dysregulated extracellular matrix (ECM) is crucial for modulating cancer cell biology. The development of novel platforms able to reproduce the physiopathological conditions is needed for disease modelling and drug testing in order to identify and validate new therapeutic targets.

Aims: This study investigates the role of different ECM and the effect of Transforming Growth Factor- β 1 (TGF β 1) treatment as a major driving force of the Epithelial-to-Mesenchymal (EMT) genetic program in a new 3D in vitro model of HCC.

Material and Methods: Normal and cirrhotic human livers were decellularized and fully characterized. HepG2 cells were seeded in a 2D culture system and in 3D liver scaffolds. After 7 days cells were treated with 5 or 10 ng/ml of TGF β 1 for 48 hours. Histology and immunohistochemistry were performed in order to assess cell morphology and cell distribution within the 3D scaffold. Messenger RNA levels of genes related to differentiation, invasion, TGF β 1 pathway and EMT were measured by employing qRT-PCR. Albumin secretion was quantified with ELISA.

Results: HepG2 cells were able to engraft and repopulate both cirrhotic and non-cirrhotic decellularized liver scaffolds. TGF β 1 treatment was able to change cell morphology and promoted cell migration within the 3D scaffold. Molecular analysis revealed a different gene expression pattern between 2D and 3D models and after TGF β 1 treatment. HepG2 cells treated with 5 and 10 ng/mL of TGF β 1 showed a dose dependent effect on albumin, TGF β 1, MMP9, Integrin- α 6 and E-Cadherin mRNA expression i.e. a partial



de-differentiation. HepG2 cells were more sensitive to 5ng/mL TGF β 1 when cultured in both 3D models, in contrast to cells grown in 2D. More specifically, TGF β 1 induced a dose dependent response in healthy scaffolds which was not observed in the cirrhotic scaffolds. Even though TGF β 1 changed hepatocyte specific gene expression i.e. albumin, the cells cultured in both models lack typical EMT markers such as TWIST, vimentin and N-Cadherin.

Conclusions: This data suggest that acellular liver ECM scaffolds represent a suitable platform for dissecting the biology of liver cancer cells in experimental conditions closer to the natural microenvironment. The various supports and the ECM itself induced different cellular behavior and responses to TGF β 1 treatment.

Disclosure of Interest: None Declared

STROMAL SULFATASE-2 PROMOTES HUMAN HEPATOCELLULAR CARCINOMA CELL GROWTH AND IS A POTENTIAL NOVEL THERAPEUTIC TARGET

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Introduction: Changes in the composition of the tumour microenvironment are central to Hepatocellular carcinoma (HCC) progression. Sulfatase-2 (SULF-2) is an extracellular endosulfatase with two isoforms: membrane bound and secreted. SULF-2 is upregulated in different types of malignancies including HCC.

Aims: Investigation of the biological role of SULF-2 in HCC progression.

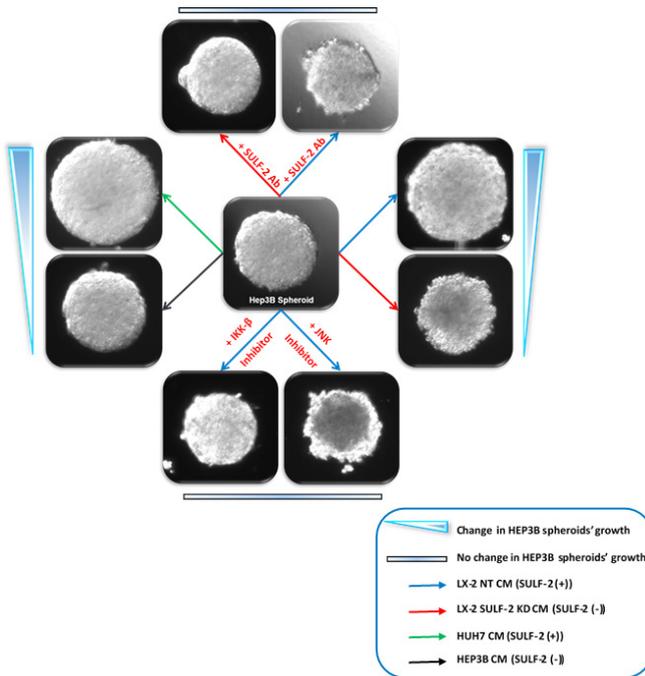
Material and Methods: SULF-2 tissue expression pattern was examined in 51 HCC diagnostic biopsies by immunohistochemistry (IHC). HUH7 HCC, LX-2 stellate (express SULF-2 endogenously) and HEP3B HCC (no endogenous SULF-2 expression) cells were used. Knock down (KD) of endogenous SULF-2 in LX-2 cells was with shRNA. The effect of stromal SULF-2 on tumour cell metabolic activity was measured by MTT assay after indirect co-culture in 2D trans-well inserts. Migration inserts were used to assess the effect of conditioned media (CM) with/without SULF-2 on tumour cell migration. A 3D tumour cell spheroid model was developed to study both direct and indirect (CM) growth promoting effects of stromal or tumour SULF-2. The impact of a SULF-2 monoclonal antibody on spheroid growth was explored.

Results: SULF-2 protein was up regulated in 58% of HCC cases in both the tumour cells (15%) and in the tumour associated stromal cells (52%); Stromal SULF2 expression (scored as absent/scanty; versus widespread/focally intense) was independently associated with poorer prognosis (median survival 15 months versus 41 months; p-value=0.001). Stromal SULF-2 increased metabolic activity of HUH7 and HEP3B cells (p-value =

0.0342 and 0.0035 respectively) and HEP3B cell migration (p-value <0.0001) in vitro. Control SULF-2 expressing LX-2 cells (NT) increased both HEP3B and HUH7 tumour cell growth when directly co-cultured in the 3D spheroid model (p-value <0.0001) compared to LX-2 SULF-2 KD cells. Moreover, growth of tumour spheroids in stromal or tumour cell CM from cells expressing SULF-2 was higher than spheroids cultured in CM from cells with no SULF-2 (p-value <0.0001). The growth stimulatory effect of SULF-2 (+) CM on 3D spheroids was abolished by treatment with a SULF-2 antibody (p-value<0.0001). Finally, SULF-2 exerts its proliferative effect via JNK and IKK-beta pathways.

Conclusions: SULF-2 is a potential predictive marker for HCC progression. Spheroid cultures represent a novel biological system to interrogate stromal-tumour interactions and study the biological effect of SULF-2. We propose that manipulation of matrix derived SULF-2 may have therapeutic benefit.

Figure:



Disclosure of Interest: None Declared

B007

LIVER-TARGETING WITH THE NOVEL NUCLEOTIDE PRODRUG MIV-818 DESIGNED FOR THE TREATMENT OF LIVER CANCERS

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Introduction: Many systemic chemotherapeutics have failed to show efficacy in hepatocellular carcinoma (HCC), often because systemic toxicity prevents efficacious liver levels of the drug from being reached. MIV-818, a nucleotide prodrug of troxacitabine-monophosphate (TRX-MP), has been designed to deliver high levels of the chain-terminating nucleotide troxacitabine-triphosphate (TRX-TP) to the liver after oral dosing while minimizing systemic exposure.

Aims: We compare MIV-818 and troxacitabine using in vitro and in vivo models in order to demonstrate liver targeting.

Material and Methods: LC-MS/MS was used to assess MIV-818 and its metabolites. Effects on tumour growth, inhibition of proliferation (BrdU), and induction of DNA damage (pH2AX) were examined and correlated with TRX-TP exposures in the tumour.

Results: MIV-818 has been optimized for oral administration and liver targeting by maximizing stability in human intestinal S9 fractions, while ensuring rapid metabolism in liver S9 fractions. Oral dosing of 80µmol/kg MIV-818 to rats led to a TRX-TP AUC₀₋₂₄ of 10µM.hr in the liver. In contrast, 80µmol/kg troxacitabine (TRX) dosed i.p. did not yield detectable liver exposure to TRX-TP at any timepoint (LOQ 0.05µM), despite substantially higher systemic exposure to TRX. Compared to the parent nucleoside TRX, MIV-818 has increased potency of inhibition of HCC cell line growth, and increased conversion to its active metabolite TRX-TP in HCC cells. MIV-818 shows strong synergistic anti-proliferative activity with sorafenib in a number of HCC cell lines in vitro. Pronounced tumour growth inhibition of 70% and tumour growth delays of ~11 days were observed in the Hep3B xenograft mouse model after 5 days of dosing and exposures to TRX-TP of 8µM.hr. Quantitative histology demonstrated a 12-fold induction of DNA

damage throughout the tumour sections, consistent with the expected mechanism of action, and with associated inhibition of proliferation, which correlated with tumour TRX-TP exposures.

Conclusions: MIV-818 is a novel TRX-MP prodrug with greatly improved in vitro anti-proliferative activity compared to TRX. Pharmacokinetic studies in rats show that oral dosing of MIV-818 results in a >100-fold increased delivery of the active metabolite, TRX-TP, to the liver compared to an equivalent i.p. dose of TRX. MIV-818 is optimized for the targeted treatment of liver cancers and is in preclinical development ahead of clinical trials in patients with advanced HCC and other liver cancers.

Disclosure of Interest: M. Albertella: Employee: Conflict with: Medivir, K. Tunblad: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir, B. Rizoska: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir, A. Lindvist: Employee: Conflict with: Medivir, S. Juric: Employee: Conflict with: Medivir, F. Öberg: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir, B. Classon: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir, A. Eneroth: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir, J. Öhd: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir, R. Bethell: Stockholder: Conflict with: Medivir, Employee: Conflict with: Medivir

IDENTIFICATION OF TUMOUR SUPPRESSIVE AND ONCOGENIC microRNAs IN GALLBLADDER CARCINOMA

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Introduction: Gallbladder carcinoma (GBC) is a rare cancer entity in Western Europe and the US with an incidence of less than 3/100.000. GBC treatment options are very limited and prognosis of unresectable GBC is poor with 2-year survival rates <10%. Radical surgery is the only potentially curative treatment option and Gemcitabine plus a Platinum-based agent are currently the most effective chemotherapy. Thus, there is a great need for the development of new treatment options, including targeted therapy for GBC.

Material and Methods: To dissect the epigenetic regulation during GBC development, we performed global miRNA profiling of 40 GBC and 8 normal gallbladder tissues. MiRNAs that are associated with survival were functionally analysed by cell proliferation and colony formation assays in two different cholangiocellular carcinoma cell lines. In addition, we performed Affymetrix gene expression microarray analysis of cell lines transfected with miRNA mimics or control.

Results: The miRNA profiles of 40 GBC and 8 normal gallbladder tissues exhibited clear differences with 992 out of 2006 miRNAs being differentially expressed (FDR <0.001). In addition, the GBC cohort showed high heterogeneity and specific survival related subgroups were identified. To select key survival associated miRNA genes, we split our cohort of 40 GBC into two groups based on median survival (18 months). This revealed 8 miRNAs to be down and 16 to be up regulated in the poor outcome group (p<0.05). The most down regulated miRNA was miR-145-5p and the top up regulated miRNA was miR-575. Overexpression of miR-145 led to a significant reduction of cell proliferation and colony formation. In contrary, ectopic expression of miR-575 increased proliferation rate and colony formation capacity. Gene expression profiling of cell lines overexpressing miR-145 revealed activation of the STAT1 signalling pathway in cholangiocellular but not hepatocellular carcinoma cell lines. In addition, ERBB2 which is frequently mutated or amplified in GBC was down regulated upon miR-145 expression. Thus, loss of



miR-145 expression in GBC patients with poor outcome may lead to increased ERBB2/Her2 expression.

Conclusions: MiRNA profiling of a clinicopathological well-characterized German GBC cohort identified pro- and anti-tumorigenic miRNAs. Functional validation confirmed the tumour suppressive function of miR-145 and oncogenic function of miR-575. In addition, miR-145 was found to activate STAT1 signalling and to repress ERBB2/Her2.

Disclosure of Interest: None Declared

THE CONCEPT OF THERAPEUTIC HIERARCHY FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA: A MULTICENTER COHORT STUDY

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Introduction: The ITA.LI.CA prognostic system for patients with hepatocellular carcinoma (HCC) has been recently developed and validated. Strict HCC treatment algorithms (i.e. BCLC or HKLC) are poorly followed in clinical practice.

Aims: We sought to develop and validate ITA.LI.CA indications for treatment guidance in HCC patients.

Material and Methods: Prospective collected databases from 2002 to 2015 in Italy (n=4,627), and Taiwan (validation cohort, n=2,651) were used for the analysis. Multivariable regression models including variables from the ITA.LI.CA prognostic system were used to calculate the propensity score (PS, calculated by logistic regression), and the predicted median survival (MS, calculated by parametric survival model with stabilized inverse probability weight) for each therapy (liver transplantation=LT, liver resection=LR, ablation=ABL, intra-arterial therapy = IAT, Sorafenib=SOR, best supportive care=BSC).

Results: Multivariable logistic regressions showed that the PS of loco-regional therapies (LR, ABL, IAT) was negligible ($PS \leq 1^{\circ}$ quintile) in patients with impaired ITA.LI.CA functional score (Child C, or PST > 2, or Child 8-9 + PST 1-2: only LT or BSC available) or advanced tumor stage (extra-hepatic HCC disease, stage C: only SOR or BSC available). In all other ITA.LI.CA tumor stages (0, A, B1, B2, and B3) with preserved liver function (functional score ≤ 2) survival benefit estimations showed a fixed therapeutic hierarchy



(i.e. LT [MS ≥ 120 months] > LR [MS 24-102 months] > ABL [MS 40-77 months] > IAT [MS 18-64 months] > SOR [MS 15-25 months] > BSC [MS 5-7 months]). All multivariable parametric models proved to give accurate survival estimations (C-index > 0.7). A large proportion of enrolled patients met the ITA.LI.CA criteria (65%), while only 55% and 43% of them met the HKLC and BCLC algorithms respectively. The concept of therapeutic hierarchy within ITA.LI.CA stages was validated also in the Taiwanese cohort.

Conclusions: Based on weighted survival benefit estimations the concept of therapeutic hierarchy was established within each ITA.LI.CA stage in a large Italian population and validated in a large Taiwanese cohort.

Figure:

Figure 1. The concept of therapeutic hierarchy within each ITA.LI.CA stage based on weighted survival benefit estimations.

Variables	0	A	B1	B2	B3	C	Any				
Functional score (FS)	FS ≤ 2 : CTP AB and PST 0; CPT ≤ 7 and PST ≤ 2						FS > 2: CTP C/PST > 2				
Diameter (cm)	< 2	≤ 3	≤ 5	3-5	> 5	3-5	> 5	> 5	Any	Any	Any
N° nodules	1	2-3	1	2-3	1	> 3	2-3	> 3	Any	Any	Any
Vi / meta	no	no	no	no	no	no	no	no	Intra	Extra	Any
Median survival	71	55	46	33	16	14	8				
Therapy	Median survival estimations (months)										
LT	120	120	120	120	28		102				
LR	102	76	64	50	18	15					
ABL	77	61	46	40							
IAT				33							
SOR	64	50	33	25	16	7	5				
BSC											

Abbreviations: FS, functional score; CTP, Child Turcotte Pugh; PST, performance status; Vi, vascular invasion; LT, liver transplantation; LR, liver resection; ABL, ablation; IAT, intra-arterial therapy; SOR, Sorafenib; BSC, best supportive care. LT and ABL in stage B3, and LT, LR, ABL, IAT in stage C were excluded due to negligible propensity score rates. Only LT and BSC reached adequate propensity score values in patients with FS > 2.

Disclosure of Interest: None Declared

TIME COURSE OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs) IN THE RANDOMIZED, CONTROLLED PHASE 3 RESORCE TRIAL OF REGORAFENIB FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA PROGRESSING ON SORAFENIB TREATMENT

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Introduction: The international, randomized, controlled phase 3 RESORCE trial showed that regorafenib improves overall survival in patients with hepatocellular carcinoma (HCC) who had disease progression on sorafenib (HR 0.63; 95% CI 0.50–0.79; one-sided $p < 0.0001$).

Aims: To describe the safety profile of regorafenib in RESORCE including time to onset of clinically relevant TEAEs.

Material and Methods: Adults with BCLC stage B or C HCC who tolerated sorafenib and had radiologic progression during sorafenib, Child-Pugh A liver function, and ECOG PS 0–1 were randomized 2:1 to regorafenib 160 mg/day or placebo on Weeks 1–3 of each 4-week cycle until progression, death, or unacceptable toxicity.

Results: 567 patients were treated (regorafenib=374, placebo=193). Median (IQR) time on treatment was 3.6 months (1.6–7.6) for regorafenib and 1.9 months (1.4–3.9) for placebo. Mean daily dose (SD) was 144 mg (21) for regorafenib and 157 mg (10) for placebo. While grade ≥ 3 TEAEs were reported in 80% (regorafenib) and 59% (placebo) of patients, the majority of most common TEAEs were grade 1 or 2. Rates of worst grade 4 TEAEs were 11% for regorafenib and 7% for placebo; grade 5 TEAEs were higher in placebo (20% vs 13%). Most common grade ≥ 3 TEAEs occurring more often with regorafenib included hypertension (15% vs 5%), hand–foot skin reaction (HFSR; 13% vs 1%), fatigue (9% vs 5%), and diarrhea (3% vs 0%). Median time to onset of these TEAEs was within 4 weeks (Table). The majority of these common TEAEs resolved, except fatigue. Hepatic failure events grade ≥ 3 were more frequent with placebo (6% vs 3%), mainly due to grade 5 events (3% placebo; 1% regorafenib). The rate of permanent discontinuation due to TEAEs was 25% for regorafenib and 19% for placebo, with drug-related TEAEs leading to permanent discontinuation in 10% and 4%, respectively.

TEAEs (CTCAE)	Patients with TEAE all grades/worst grade 3/ worst grade 4		Median time to TEAE onset, days (IQR)		Events recovered or resolved	
	Regorafenib (n=374)	Placebo (n=193)	Regorafenib	Placebo	Regorafenib	Placebo
HFSR	53%/13%/NA	8%/1%/NA	14 (8–22)	15 (4–30)	67%	47%
Diarrhea	41%/3%/0	15%/0/0	26 (10–71)	21 (4–37)	82%	70%
Fatigue	40%/9%/NA	32%/5%/NA	15 (8–43)	28 (15–64)	46%	31%
Hypertension	31%/15%/<1%	6%/5%/0	15 (8–40)	11 (8–33)	62%	60%

IQR, interquartile range; NA, not applicable

Conclusions: In patients with HCC, the safety profile of regorafenib was manageable and consistent with the known safety profile of regorafenib. The majority of common TEAEs occurred early in treatment. There were no unexpected safety findings.

Disclosure of Interest: P. Merle: Grant: Conflict with: Bayer, Onxeo, Consultant: Conflict with: Onxeo, BMS, Bayer, A. Granito: : None Declared, Y.-H. Huang: Grant: Conflict with: Gilead, BMS, G. Bodoky: Consultant: Conflict with: Bayer, Roche, Pfizer, Janssen, Novartis, Lilly, Taiho, Nordic, Sponsored Lectures (National or International):

Conflict with: Bayer, Roche, Novartis, Lilly, Taiho, Nordic, M. Pracht: : None Declared, O. Yokosuka: Grant: Conflict with: Gilead, MSD, Bayer, Tanabe Mitsubishi Pharma, BMS, O. Rosmorduc: Consultant: Conflict with: BMS, Bayer, Transgene, Other: Conflict with: Honoraria from BMS, Bayer and Transgene, V. Breder: Consultant: Conflict with: Merck, BMS, Roche, MSD, Boehringer Ingelheim, AstraZeneca, Bayer, Sponsored Lectures (National or International): Conflict with: Merck, BMS, Roche, MSD, Boehringer Ingelheim, AstraZeneca, Bayer, Other: Conflict with: Travel grants: Boehringer Ingelheim, MSD, R. Gerolami: Consultant: Conflict with: Bayer, Gilead, AbbVie, G. Masi: Consultant: Conflict with: Bayer, Amgen, P. Ross: Sponsored Lectures (National or International): Conflict with: Bayer, Other: Conflict with: Bayer, S. Qin: : None Declared, T. Song: : None Declared, J.-P. Bronowicki: Grant: Conflict with: Bayer, Consultant: Conflict with: Bayer, Sponsored Lectures (National or International): Conflict with: Bayer, I. Ollivier-Hourmand: Grant: Conflict with: Bayer, Lilly, Sponsored Lectures (National or International): Conflict with: Gilead, Bayer, Other: Conflict with: Personal fees (board or travel) from Daiichi, Bayer, Intercept, AbbVie, Boehringer Ingelheim, Gilead, M. Kudo: Grant: Conflict with: Chugai, Otsuka, Takeda, Taiho, Sumitomo Dainippon, Daiichi Sankyo, MSD, Eisai, Bayer, AbbVie, Consultant: Conflict with: Kowa, MSD, BMS, Bayer, Chugai, Taiho, Sponsored Lectures (National or International): Conflict with: Bayer, Eisai, MSD, Ajinomoto, S. Schlieff: Employee: Conflict with: Bayer, S. Fiala-Buskes: Stockholder: Conflict with: Bayer, Employee: Conflict with: Bayer, G. Meinhardt: Stockholder: Conflict with: Bayer, Employee: Conflict with: Bayer, J. Bruix: Consultant: Conflict with: Bayer, Gilead, AbbVie, Kowa, BTG, Arqule, Terumo, BMS, Boehringer Ingelheim, Novartis, OSI, Roche, Onxeo, Sirtex, Eisai, Sponsored Lectures (National or International): Conflict with: Bayer, Sirtex, Terumo

EARLY OCCURRENCE OF HEPATOCELLULAR CARCINOMA (HCC) IN PATIENTS WITH HCV CIRRHOSIS TREATED WITH DIRECT-ACTING ANTIVIRALS (DAAs)

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Introduction: The risk of HCC occurrence during and after DAA based treatment is still debated.

Aims: The aims of this analysis were to evaluate the early HCC occurrence and to analyse the HCC pattern in a large cohort of treated cirrhotic patients.

Material and Methods: We evaluated 2,684 cirrhotic patients (mean age 65.3±10.8 years, 58.4% males, 45.8% naïve to antiviral therapy, 2,364 (88%) Child-Pugh A and 320 (12%) Child-Pugh B) who completed the treatment between March 2015 and October 2016 in 22 centers of RESIST-HCV. Ribavirin was associated to DAAs in 1,354 patients (50.4%), 1,537 patients (57.3%) received DAAs for 12-14 weeks and 1,147 (42.7%) for 24 weeks. Patients received HCC surveillance as indicated by guidelines.

Results: During the observation (mean 34.2 weeks, range 4-72) 55 patients (2.0%) developed HCC. The rate was 1.73% in Child-Pugh A and 4.37% in Child-Pugh B cirrhosis (p=0.004). HCC met Milan criteria in 29 patients (52.7%) while 26 (47.3%) were Milan-out. Seven of 29 patients with Milan-in criteria developed HCC on therapy and 22 out therapy, while 3 of 26 patients with Milan-out criteria developed HCC on therapy and 23 out therapy (p=0.3). The evaluation of SVR was available in 1,628 patients. By intention to treat analysis, 1,435 patients (88.1%) achieved a SVR and 193 (11.9%)

no obtained SVR. The HCC occurrence was 1.88% (27/1,435) in patients with SVR and 5.2% (10/193) in patients without SVR ($p=0.008$).

Conclusions: The occurrence of “de novo” HCC during the first year of observation in our cohort of cirrhotic patients treated with DAAs remained similar to that reported in historical cohorts of untreated patients. The risk of HCC was higher in patients with Child-Pugh B cirrhosis and in patients without SVR. The presentation pattern of HCC was no different on- and out therapy.

Disclosure of Interest: None Declared



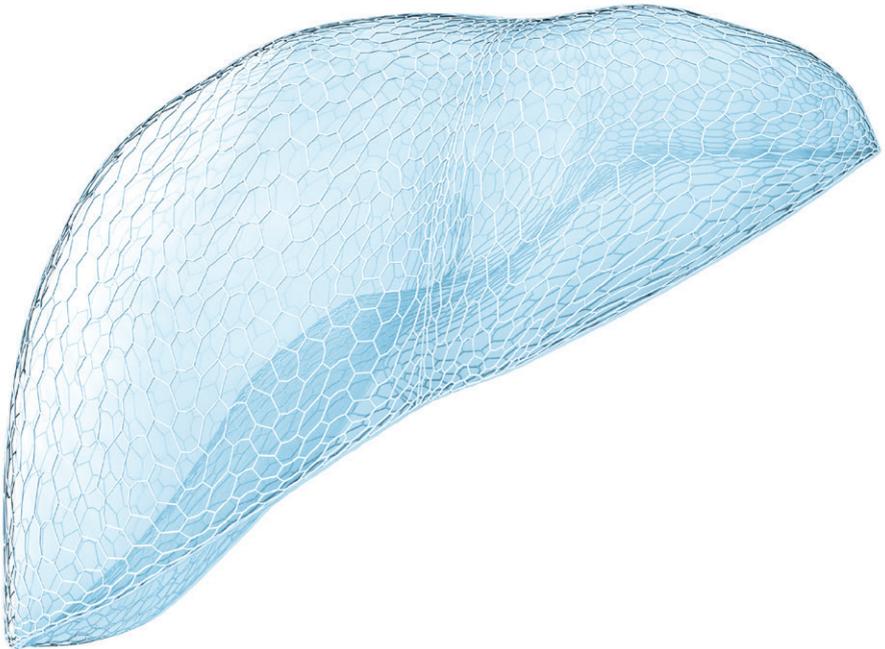
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ePOSTER ABSTRACTS



HEPATOCTYTE NANODELIVERY USING siRNA c-Jun N-TERMINAL KINASE-2 (siJnk2) FOR THE TREATMENT OF CHRONIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

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Introduction: Chronic liver disease (CLD) develops into hepatic fibrosis and end-stage hepatocellular carcinoma (HCC), leading to organ failure and death. HCC is the fifth most common solid cancer which affects one million people per year representing the third cause of cancer mortality worldwide, with limited available therapeutic options. We have previously shown that altered c-Jun N-terminal kinase-2 (Jnk2) signalling regulates cell death and inflammation in an experimental model of CLD.

Aims: In the present study, we aim to evaluate the effects of Jnk2 inhibition specifically in hepatocytes using siRNA nanodelivery, with a focus on HCC development.

Material and Methods: First, we evaluated the specific inhibition of Jnk2 siRNA (siJnk2) in vitro in Hepa 1-6 cells and primary isolated hepatocytes. Moreover, we investigated the efficacy of siRNA delivery in vivo using 8 week old wildtype mice and mice with hepatocyte-specific deletion of Jnk1 (Jnk1 Δ^{hepa}). Next, we determined the in vivo siRNA effects on the Nemo Δ^{hepa} mouse model of CLD at different stages of HCC progression and monitored apoptosis in vivo using fluorescence molecular and micro-computed tomography (FMT, μ CT).

Results: Single dose injection (0.2 mg/kg body weight) revealed a significant reduction of Jnk2 on mRNA and protein levels in wildtype mice after 1 week. Moreover, 4 week siJnk2 treatment had no influence in JNK1 Δ^{hepa} livers. Next, we sought to investigate the effects in an acute model of Nemo Δ^{hepa} mice. Treatment with siJnk2 caused hepatocyte hypertrophy, mitotic catastrophe, karyomegaly, exacerbated cell infiltration, hepatic fibrogenesis and ductular proliferation. These effects were evident by high alkaline

phosphatase levels, cleaved caspase-3 positive cells alongside with increased compensatory proliferation. Furthermore, our data indicated that proinflammatory monocytes massively infiltrate the liver after hepatocyte-specific Jnk2 inhibition. Interestingly, decreased compensatory proliferation, cleaved Caspase-3 protein levels and markers of hepatic stellate cell activation/matrix deposition were observed in a chronic model of NemoΔhepa mice injected over 8 weeks.

Conclusions: siJnk2 therapy successfully depleted the levels of Jnk2 both in vivo and in vitro. Jnk2 knockdown induced significant changes in liver parenchyma and dramatically reduced HCC progression. Thus it might be a suitable therapeutic option. These results open new avenues for precision medicine against CLD with potential translation into the clinic.

Disclosure of Interest: None Declared

DUAL EFFECTS OF C3G IN THE TUMORIGENIC CAPACITY OF HUMAN HEPATOCARCINOMA CELLS

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Introduction: C3G is a guanine nucleotide exchange factor for Rap1 and R-Ras. It is essential for embryonic development and regulates several cellular functions such as cytoskeletal remodelling, differentiation and cell death. However, its role in cancer is controversial acting as either a tumour promoter or suppressor. Our group found that C3G knock-down increased invasion and migration of hepatocarcinoma (HCC) cells through induction of an epithelial-mesenchymal transition (EMT) process. Accordingly, we observed that C3G silenced cells showed higher levels of mesenchymal markers (Vimentin, N-Cadherin) and EMT transcription factors (Snail, Zeb1). All these changes were similar to those elicited by TGF- β , a well-known EMT inducer.

Aims: Based on the pro-invasive effect of C3G knock-down in HCC cells, we wanted to characterize the role of C3G in HCC growth and progression.

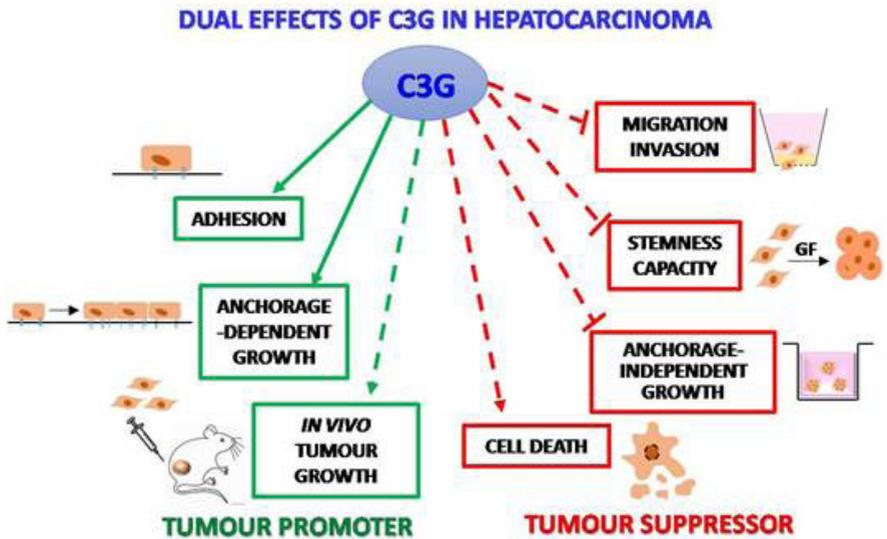
Material and Methods: We evaluated the effect of permanent C3G knock-down on in vitro (anchorage-dependent and independent) and in vivo (xenografts) growth of different HCC cells with a more epithelial or mesenchymal phenotype (Hep3B and HLE). Its effect on adhesion, cell death and stemness capacity was also studied.

Results: C3G knock-down led to a reduced number of foci and a dispersion of the cells within a focus in anchorage-dependent assays. Consistently, adhesion was also decreased, suggesting a lower tumorigenic capacity. In contrast, C3G silencing in Hep3B cells increased the number and size of foci in anchorage independent growth assays, although each focus was composed of less and scattered cells. Additionally, C3G knock-down decreased cell death, which would also promote tumour growth. Accordingly, preliminary studies showed that C3G silenced Hep3B cells form more spheres and increase the expression of some stemness markers. In contrast, in vivo tumour growth in nude mice was reduced in C3G knock-down Hep3B cells. We are currently analyzing cell death, proliferation,

infiltrated fibroblasts and immune cells, as well as vessels within the tumours. In addition, the presence of cancer cells in blood, lungs and bone marrow is under investigation as a way to evaluate their metastatic capacity in vivo.

Conclusions: Our data support a dual function of C3G in HCC. On one side, C3G acts as a tumour promoter by enhancing adhesion, anchorage-dependent growth and in vivo tumour growth. On the other hand, C3G inhibits migration, invasion and anchorage independent growth, reduces the stemness capacity and increases cell death of HCC cells.

Figure:



ePOSTER ABSTRACTS

Disclosure of Interest: None Declared

HYPOXIA-INDUCED STC1 ENHANCES PROGRESSION OF HEPATOCELLULAR CARCINOMA

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Introduction: Hypoxia is a ubiquitous phenomenon in solid cancers including hepatocellular carcinoma (HCC). Hypoxia is closely associated with tumor aggressiveness through promoting metastatic potential and inducing chemoresistance in cancer cells. Thus, exploring the potential functional roles of hypoxia-responsive genes is essential to understand the biology underpinning HCC development. Stanniocalcin 1 (STC1) is identified to be an oncogene and a potential prognostic biomarker in different human solid tumors. Moreover, STC1 is induced by hypoxia or hypoxic mimetics in different cancer cell lines.

Aims: In this study, we postulate that hypoxia-induced STC1 has an oncogenic role in HCC development and aim at investigating the functional significance of STC1 in HCC.

Material and Methods: STC1 expression was evaluated in clinical HCC samples and HCC cell lines using quantitative real-time PCR, immunoblotting and immunofluorescence. Functional roles of STC1 in HCC were examined by transwell migration and matrigel invasion assays using stable STC1 knockdown clones in SMMC-7721 and Huh-7 HCC cell lines as well as stable STC1 overexpression clone in BEL-7402 HCC cell line. Role of STC1 in metastasis was examined with an orthotopic HCC mouse model using stable STC1 knockdown clone in luciferase-labelled MHCC-97L HCC cells. Stable knockdown and overexpression of STC1 cells were established using lentiviral-based approach.

Results: In 125 paired human HCC samples (T) and corresponding non-tumorous liver tissues (NT), STC1 mRNA level was significantly up-regulated in human HCC samples ($p=0.0003$) and its overexpression at transcript level ($T/NT \geq 2$ -fold) was observed in 42% of cases (52/125). In vitro, hypoxia (1% O₂) induced STC1 expression in HCC cells, possibly in a HIF1 alpha-dependent manner. Knockdown of STC1 in both SMMC-7721 and Huh-7 cells inhibited HCC cell invasion and migration capacities under both normoxic (20% O₂) and hypoxic conditions (1% O₂). Forced expression of STC1 in BEL-

7402 cells augmented the metastatic effects. In vivo, tumor growth and lung metastasis were reduced upon silencing of STC1 in MHCC-97L cells.

Conclusions: STC1 is induced by hypoxia in HCC and enhances tumor metastasis.

Disclosure of Interest: None Declared

UNEXPECTED LONGEVITY OF THE TUMOR-PENETRATING EFFECT OF iRGD IN HEPATOCELLULAR CARCINOMA

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Introduction: The novel cyclic RGD peptide, iRGD, containing an RGD motif as well as a cryptic CendR motif, by which it binds to neuropilin-1, has recently been shown to increase the entry of co-injected substances specifically into tumor tissue and thereby the therapeutic efficacy of anti-tumor drugs in diverse mouse models of cancer, including hepatocellular carcinoma (HCC). The duration of the tumor-penetrating effect of iRGD, which is of key importance for a therapeutic application, has been determined in the 4T1 breast carcinoma mouse model was found to be in the same range as the circulation time of the peptide of approx. 30 min.

Aims: Here examined the duration of the tumor-penetrating effect of iRGD in HCC.

Material and Methods: Mice with HCC xenografts and transforming growth factor-alpha (TGF α)/c-myc transgenic mice with endogenously formed HCCs were injected with iRGD or control peptide, followed by determination of the tissue uptake of a contrast agent (Gd-DTPA) by magnetic resonance imaging (MRI) or by dye extraction from tumors/organs.

Results: Gd-DTPA-enhanced MRI of TGF α /c-myc mice with HCC revealed a selective increase of the uptake of the contrast agent into HCC directly after injection of the contrast agent. Surprisingly, this uptake remained elevated 2 and even 4 days after the injection of iRGD. An RGD control peptide had no effect. Similarly, in mice with HepG2 xenografts the increased tumor uptake of the contrast agent was still detectable 24 h after administration of the peptide. The increased tumor uptake of HepG2 tumors was confirmed by the dye extraction method. By contrast, in the 4T1 breast carcinoma mouse

model, the initially increased tumor uptake upon injection of iRGD was absent on the next day.

Conclusions: iRGD elicits a specific and long-lasting increase of the HCC penetrability. The duration of the tumor penetrating effect of iRGD can be determined non-invasively by Gd-DTPA-enhanced MRI.

Disclosure of Interest: None Declared

MAPPING THE HETEROGENEITY OF CIRCULATING NEUTROPHILS IN HEPATOCELLULAR CARCINOMA

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Introduction: Neutrophils are first line defenders against pathogens and until recently, dogma has labelled these cells as short lived and rapidly cleared following infection. However, evidence now clarifies a role for neutrophils as key mediators in promoting cancer progression and metastases. Hepatocellular carcinoma (HCC) is associated with a high neutrophil to lymphocyte ratio that is prognostic of poor survival. Our group has previously shown that neutrophil depletion in a murine HCC model has profound anti-tumour effects. However, as neutrophils are critical for host defence, pan neutrophil depletion is not a viable option for cancer patients already susceptible to infection. Neutrophil polarization in cancer has been classified very simplistically into N1, N2 and myeloid derived suppressor cell (MDSC), describing N1 as anti-tumour and N2/MDSC as pro-tumour. However, distinguishing markers are still poorly defined and this guideline does not provide a tractable option to dissect the functional heterogeneity of neutrophils associated with liver disease and cancer.

Aims: To identify the phenotypic characteristics of neutrophils associated with HCC.

Material and Methods: Neutrophil heterogeneity was assessed by flow cytometry using size (FSC and SSC), a panel of neutrophil markers against cell surface CD66b, CD11b and CD62L and intracellular arginase 1. Neutrophil function was assessed by measuring levels of reactive oxygen species both basally and in response to stimuli. Morphology and nuclear segmentation was assessed by cytospin of peripheral blood and Giemsa staining.

Results: In the 30 patients analysed by flow cytometry and morphology, we have observed a significant increase in the percentage of morphologically distinct hyper-segmented neutrophils in liver cancer patients compared to healthy controls or pre-cancer cirrhotic patients. Importantly, we have also observed functional differences in levels of activation markers CD11b (increased) and CD62L (decreased). Furthermore, we have uncovered a lower level of reactive oxygen species production associated with both basally and in response to stimuli in the form of the chemotactic peptide (FMLP) and platelet activating factor.

Conclusions: This data suggests that there are phenotypic and biologically relevant changes in peripheral blood neutrophils from liver cancer patients. Further characterisation of these cells may enable us to better define the ‘pro-tumour neutrophil’ associated with HCC and develop potential therapeutics to target these cells selectively.

Disclosure of Interest: None Declared

SERINE-THREONINE KINASE RECEPTOR-ASSOCIATED PROTEIN MAINTAINS HEPATOCELLULAR CARCINOMA CELL GROWTH THROUGH Wnt/ β -CATENIN SIGNALING

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Introduction: Serine-threonine kinase receptor-associated protein (STRAP) is upregulated in colon and lung cancers. It was shown that STRAP could promote Wnt/ β -catenin signaling in progression and metastasis of colon cancers.

Aims: However, little is known about the function of STRAP in progression of hepatocellular carcinoma (HCC). Therefore, we have investigated the expression level of STRAP in HCC tissues and studied its role in supporting growth of HCC cell lines.

Material and Methods: Immunohistochemical stainings were performed on paraffin embedded tissue microarrays of HCC patients in comparison with adjacent normal tissues (n=115). Six HCC cell lines were used, three of which carrying oncogenic CTNNB1 mutations and two showing inactivating AXIN1 mutations. CRISPR/Cas9 mediated genome editing was used to completely knockout STRAP function in three cell lines.

Results: STRAP protein level, mainly detected in the cytoplasm, was significantly higher in human HCC tissues compared to adjacent liver tissues (n=115, p<0.0001). Using a β -catenin signaling reporter assay, siRNA mediated knockdown of STRAP clearly suppressed β -catenin signaling activity in both CTNNB1 and AXIN1 mutant cell lines as well as non-mutant Huh7. Based on this, we established CRISPR/Cas9 mediated knockout of STRAP protein in CTNNB1 mutant Huh6, AXIN1 mutant PLC and non-mutant Huh7. Consistently, reduced β -catenin signaling activity was observed in STRAP knockout clones compared with clones retaining expression. Western blot assay showed no effect on total β -catenin protein levels in these STRAP knockout clones but a clear decrease of active β -catenin (unphospho-Ser33/Ser37/Thr41) was observed in Huh6 and PLC clones. The knockout clones also showed a significant cell cycle arrest in the G0/G1 phase or G2/M phase compared to control clones.

Conclusions: Our results suggest that upregulation of STRAP protein provides growth advantage to HCC cells via enhancing Wnt/ β -catenin signaling. These observations suggest STRAP protein as a new target to regulate Wnt/ β -catenin signaling in HCC patients.

Disclosure of Interest: None Declared

POLYPHENIC TRAIT PROMOTES LIVER CANCER IN A MODEL OF EPIGENETIC INSTABILITY

Marco Cassano*¹, Sandra Offner¹, Evarist Planet¹, Alessandra Piersigilli², Suk Min Jang¹, Hugues Henry³, Markus B. Geuking⁴, Kathy D. McCoy⁴, Andrew J. MacPherson⁴, Didier Trono⁵

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Introduction: Hepatocellular carcinoma (HCC) represents the fifth most common form of cancer worldwide and carries a high mortality rate due to lack of effective treatment (Fattovich et al, 2004). Males are eight times more likely to develop HCC than females, an effect largely driven by sex hormones, albeit through still poorly understood mechanisms (Bosch et al. 2004).

Aims: We identified TRIM28 (Tripartite motif containing 28) as a crucial mediator of sexual dimorphism in the liver. Trim28^{hep-/-} mice display gender-specific transcriptional deregulation of bile and steroid metabolism genes encompassed by hepatic adenoma development.

Results: Here we reveal that obesity and ageing precipitate TRIM28-less liver transcriptional perturbations, leading to a state of metabolic infection with highly penetrant male-restricted hepatic carcinogenesis due to the combined impact of aberrant androgen receptor stimulation, biliary acid-disturbances and altered responses to gut microbiota. Correspondingly, we demonstrate that androgen deprivation attenuates tumor burden and severity, and most importantly that raising Trim28^{hep-/-} mice in axenic conditions completely abrogates their abnormal phenotype.

Conclusions: This work reveals how an epigenetically metastable condition can alter organ homeostasis and contribute to establish a cancer-prone state. Our study unveils new evidence linking metabolic disturbances, hormonal imbalances, gut microbiota and cancer. Furthermore, it demonstrates for the first time that the intestinal flora can represent an obligatory factor in the development of liver carcinoma. Future studies conducted in a gnotobiotic environment could help identify strains that contribute prominently

to this tumorigenic phenotype, and our results more generally warrant efforts aimed at characterizing the gut microbiota of patients presenting with states known to predispose to liver cancer, and at exploring the potential of its manipulations for the prevention and treatment of this disease.

Disclosure of Interest: None Declared

TUMOUR SUPPRESSOR PROTEIN SH2D4A IS INVOLVED IN ENDOSOMAL TRAFFICKING OF STAT3 IN HCC CELLS

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Introduction: In our previous study, we showed that chromosome 8p tumour suppressor genes SORBS3 and SH2D4A are physically and functionally linked and inhibit signal transducer and activator of transcription 3 (STAT3)-mediated interleukin-6 (IL-6) signalling in hepatocellular carcinoma (HCC). SH2D4A was found to directly bind STAT3 in the cytoplasm and thereby, reducing STAT3 transcriptional activity upon IL-6 stimulation. Recently, it was published that STAT3 localizes to lipid rafts and endosomal structures and translocates from the cytoplasm to the nucleus via endocytic trafficking. Thus, the aim of the current study was to analyse the role of SH2D4A in endosomal trafficking of STAT3.

Aims: The aim of the current study was to analyse the role of SH2D4A in endosomal trafficking of STAT3.

Material and Methods: Live cell imaging was performed for tracking SH2D4A-STAT3 complexes that were visualized by using bimolecular fluorescence complementation (BiFC). HCC cells were transfected with BiFC constructs, serum starved and stimulated with IL-6. Combination of BiFC assay and staining of lipid rafts and early endosomes were used to track localization of SH2D4A-STAT3 complexes. To study the impact of endocytosis on STAT3 trafficking, pharmacological and low temperature inhibition was applied. Additionally, co-localization was analysed by immunostaining of endosome markers and STAT3.

Results: A direct protein-protein interaction between SH2D4A and STAT3 was confirmed by using BiFC in HuH1 and HLF cells. In untreated cells, BiFC signal visualizing SH2D4A-STAT3 complexes was homogeneously distributed in the cytoplasm. Upon IL-6 treatment the complexes accumulated close to the plasma membrane and translocated in a punctate pattern to the perinuclear region where the signal weakened suggesting a release of STAT3 from the protein-protein interaction enabling nuclear

translocation. Consistently, SH2D4A overexpression resulted in a reduction of nuclear STAT3 protein level.

Conclusions: To conclude, tumour suppressor protein SH2D4A directly interacts with STAT3 and seems to be involved in endosomal trafficking of STAT3.

Disclosure of Interest: None Declared

NEUROLIGIN4 OVER EXPRESSION ON NK CELL CAUSE THEIR IMPAIRMENT IN PATIENTS WITH CIRRHOSIS AND HCC

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Introduction: Natural killer (NK) cells are anti-tumor and anti-fibrotic protectors in the innate immunity. However, impaired NK cell killing reported in cirrhosis and some tumors. We found a novel NK inhibitory receptor, Neuroligin-4 (NLG4) that over expressed on NK cells in patients with advanced fibrosis from different etiologies, and associated with decreased NK cytotoxicity.

Aims: In this study, we aim to explore variations and roles of NLG4 in peripheral blood NK cells from NAFLD/NASH (Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis) patients with or without Hepatocellular Carcinoma (HCC).

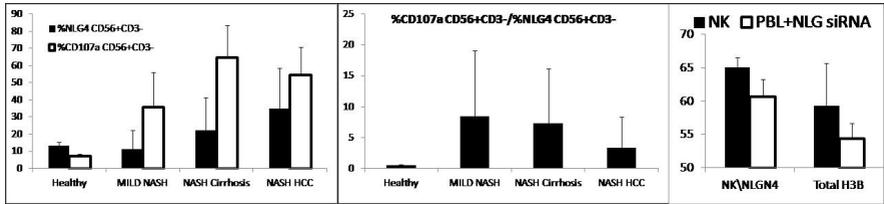
Material and Methods: Peripheral blood lymphocytes isolated from 5 healthy donors, 8 cases with mild NASH determined by F0-F2 (in the Fibroscan or biopsy), 10 NASH cirrhosis patients without HCC and 8 NASH cirrhosis with HCC cases. NLG4 receptor expressions and NK activation marker (CD107, LAMP1) were determined by flow cytometry.

Results: Compared to healthy controls, the NLG4 expressions significantly increased in NK cells from NASH cirrhosis (without and with HCC), suggesting NK impairment. However, HCC cirrhosis cases had higher NLG4 expressions as compared to non-HCC cirrhotic cases. The NK activation marker CD107a increased in mild NASH cases and both cirrhosis groups showed a further increase. Activator ratio (CD107a:NLG4) significantly increased in all sick cases. The mild NASH cases had the highest activation ratio. The NK activation ratio becomes weaker gradually in the cirrhosis groups, with prominent decrease in CD107a in the HCC group. Hep3B (human HCC cell line) highly express the NLG4-ligand β -neuroxin (NLG4 ligand). Co-cultures of Hep3B with human healthy NK cells showed increase Hep3B killing in case of NLG4 siRNA knockdown. Co-cultures of Hep3B with human NK cell line (YTS) or healthy NK cells decreased

their aFP secretions indicating less tumor activity (P<0.001) however, NK cell from HCC patients failed to modulate aFP levels.

Conclusions: The NLG4 is a novel inhibitory NK cell receptor over expressed in advanced fibrosis and HCC, causing NK impairment. CD107a:NLG4 ratio is a better marker for NK killing than CD107a.

Figure:



Disclosure of Interest: None Declared

DISTINCT FEATURES OF EARLY AND LATE-STAGE LIVER CANCER CELLS CORRELATE WITH THEIR RESPONSE TO METABOLIC PERTURBATION

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Introduction: Cancer cells undergo metabolic reprogramming in response to nutritional liabilities or drug-induced stress. This offers an opportunity to interfere with metabolic pathways upon which cancer survival depends.

Aims: In this study, we investigated alterations in liver cancer metabolism, and the prospects of targeting glycolytic pathway.

Material and Methods: We analysed the expression of genes involved in aerobic (Warburg effect) and anaerobic glycolysis across cohorts of hepatocellular carcinoma (HCC) encompassing >500 patients. In addition, Kaplan-Meier survival analysis was performed. In vitro, we treated well (epithelial) and poorly (mesenchymal) differentiated HCC cells with anti-glycolytic agent (2-deoxy-glucose, 2DG), and also modulated glutamine supply. As readouts, we performed assays at functional (e.g. MTT, colony formation, migration), genomic, and biochemical levels.

Results: Clinical HCC have both aerobic and anaerobic glycolytic portraits. Kaplan-Meier survival analysis revealed several glycolytic targets that predict survival outcome in HCC patients, notably HK2, PFKFB1, ALDOA, ALDOB, and PKM. In vitro, we observed that representative epithelial/early stage models (e.g. HUH7) are more anaerobic, showing less sensitivity to glucose starvation or glycolysis inhibition, and do not require extracellular glutamine for proliferation. In contrast, poorly differentiated/late stage models (e.g. HLE) are highly aerobic, reliant on both glucose and glutamine, and have severely impaired functional activities (including migration and proliferation) when both metabolites are withdrawn. Moreover, differentiation status of the HCC cells correlated with intracellular ATP level, lactate output, and pyruvate transporter expression, which were all altered by 2DG, notably in the poorly differentiated cells.

Conclusions: HCC have divergent metabolic features upon which tailored treatment modalities could be designed against the disease at the early and advanced stage.

Disclosure of Interest: None Declared

UBIQUITIN CARBOXY-TERMINAL HYDROLASE L1 EXPRESSION IS INCREASED IN HEPATOCELLULAR CARCINOMA CELLS AND RENDERS THOSE CELLS MORE SENSITIVE TO ER STRESS-INDUCED CELL DEATH FOLLOWING INHIBITION.

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Introduction: The development of hepatocellular carcinoma (HCC) and surrounding micro-environment cause cellular stress. This compromises endoplasmic reticulum (ER)-dependent protein folding and results in ER stress and unfolded protein response (UPR) activation. The UPR aims to restore protein homeostasis or induces cell death via CHOP. Protein degradation is enhanced by UPR-induced proteasome stimulation, a process that is fine-tuned by deubiquitinases (DUBs). DUBs are critical in the regulation of proteins involved in cellular processes and are proposed as potential oncotargets. However, their exact role in HCC development and progression is currently unknown.

Aims: For this study, we investigated the expression of Ubiquitin carboxy-terminal hydrolase L1 (UCHL1), which is known to be involved in proteasome-dependent pathways, in human and experimental HCC and the effect of UCHL1 inhibition by LDN57444 on liver tumour cell survival during ER stress in vitro.

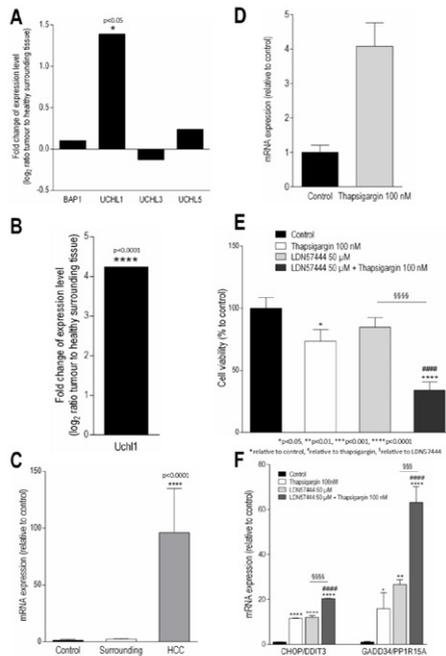
Material and Methods: Micro-array data of human HCCs and corresponding non-neoplastic liver samples (GSE59259) were used for the expression analysis of the UCH-family of DUBs. Micro-array data and RNA samples of diethylnitrosamine (DEN)-induced HCC livers of rats were provided by dr. Fornari (University of Bologna, Italy). The effect of ER stress and UCHL1 inhibition by LDN57444 on the expression of UPR

markers and UCHL1 and cellular viability was analysed in HepG2 cells by using RT-qPCR and MTT assays, respectively.

Results: Micro-array analysis revealed that UCHL1 is the only DUB of the UCH-family to be significantly increased in human HCC^A. This upregulation was confirmed in a DEN-induced HCC rat model^{w,w}, both by micro-array analysis and RT-qPCR^{B,C}. In vitro, the ER stress inducer thapsigargin upregulated the expression of UCHL1 and reduced cell viability^{D,E}. Interestingly, loss of viability was even more pronounced in addition of LDN57444^F. The observed reduced viability might be UPR-mediated since combined treatment of thapsigargin and LDN57444 resulted in enhanced mRNA upregulation of CHOP and its downstream effector GADD34 compared to each mono-treatment^F.

Conclusions: UCHL1 is highly upregulated in both human and experimental HCC. UCHL1 is induced upon ER-stress in HCC cells and renders those cells more sensitive to ER stress-induced cell death following UCHL1 inhibition. Further in vivo studies will have to reveal if UCHL1 inhibition might be an attractive therapeutic strategy for HCCs characterized by ER stress.

Figure:



Disclosure of Interest: None Declared

pH REGULATORY INHIBITORS AS THERAPEUTIC STRATEGY TO COUNTERACT HYPOXIC/ACIDIC MICROENVIRONMENT AND INFLAMMATION/ IMMUNOSUPPRESSION IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) arises in a hypoxic/acidic microenvironment. This condition favours tumour progression and fosters immunosuppression. Tumoural cells survive in this hostile environment overexpressing pH regulatory molecules such as carbonic anhydrase (CA) IX, XII and V-ATPase isoforms, but the relevance of these molecules is poorly defined in HCC.

Aims: To find new therapeutic strategies, we investigated the expression of these molecules in HCC cell lines and patient-derived tumour tissues and analysed their role using specific inhibitors.

Material and Methods: The expression of CAs and V-ATPase subunits were assayed by qRT-PCR, Western Blot and confocal microscopy in HCC cell lines exposed to normoxia (21% O₂) or hypoxia (1% O₂). The effect of pH regulatory inhibitors on HCC cell viability was evaluated by MTT assay. Paired tumoural and adjacent non-tumoural liver tissues (n=57) were analyzed for the expression of pH regulatory molecules by qRT-PCR and by immunohistochemistry (n=23). Human HCC tissue explants were cultured in presence of pH regulatory inhibitors and gene expression was analysed by qRT-PCR.

Results: HCC cell lines displayed a heterogeneous expression pattern of pH regulatory molecules and hypoxia exposure caused a 12-fold increase of CAIX and 4-fold increase of CAXII, while it did not affect the expression of V-ATPase subunits. Ex vivo, HCC specimens showed a focal expression patterns for CAIX and an intense membrane staining was found in discrete tumour nests inside HCC lesions. In normal and non-tumoural tissues CAIX was only detected in the cells of the bile ducts. CAXII, ATP6V0A1 and ATP6V1C1 were expressed selectively by tumoural hepatocytes. The HCC cell viability was highly affected by CAIX and V-ATPase inhibitors, in contrast the effect of CAXII inhibition was less pronounced. HCC tissue explants treated ex vivo with V-ATPase inhibitor showed a modulation of EMT genes such as CDH1, VIM and MYC. Moreover, this treatment was able to interfere with the immune profile of HCC by reducing the expression of the immunosuppressive genes IL6, CCL2, CCL22 and up-regulating the expression of IFNG, involved in protective anti-tumour immunity.

Conclusions: Our data depict an interesting but complex scenario and shows that some pH regulators are selectively over-expressed in HCC microenvironment, likely representing appealing target for direct anti-tumour or immunomodulating therapies in HCC patients.

Disclosure of Interest: None Declared

miR-21 DEFICIENCY DECREASES SMALL INTESTINE PERMEABILITY AFTER BILE DUCT LIGATION IN MICE

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Introduction: The gut-liver axis influences a wide variety of diseases, including hepatocellular carcinoma. Common bile duct ligation (BDL) results in acute cholestatic injury and secondary biliary fibrosis, associated with early increased intestinal permeability and disturbed bile acid homeostasis. We have demonstrated that the oncogenic microRNA-21 (miR-21) is upregulated in the liver following BDL in mice, mediating liver fibrosis.

Aims: We aimed to investigate the role of miR-21 in the response of the small intestine to BDL that may explain miR-21 effects in liver acute liver injury and fibrosis.

Material and Methods: Three-month old C57BL/6 wildtype (WT) and miR-21 whole body knockout (KO) mice were submitted to sham or BDL surgeries. After three days, animals were sacrificed and small intestines carefully removed, washed and preserved. mRNA and protein expression were analysed by qRT-PCR and immunoblotting, respectively. Liver tissue and serum were also collected for biochemical analysis of hepatic damage and fibrosis.

Results: TNF- α and IL-1- β mRNA levels increased in the small intestine of BDL-miR-21 KO mice, compared to WT. Inversely, phosphorylated JNK was reduced. TLR-4 expression was increased in both sham- and BDL-miR-21 KO mice, correlating with Gram-negative bacterial overgrowth. Zona occludens (ZO-1) and occludin mRNA levels were decreased in WT mice after BDL. Strikingly, miR-21 KO reverted mRNA of tight junction proteins to control. BDL miR-21 KO mice showed decreased circulating levels of hepatic enzymes, concomitant with decreased fibrogenic gene expression in the liver, in comparison with WT mice, suggesting that miR-21 contributes to BDL-induced liver injury and fibrosis.

Conclusions: Altogether, our results indicate that miR-21 deficiency associates with decreased small intestine permeability through a ZO-1 and occludin pathway after BDL. As such, miR-21 may inhibit the progression of liver injury associated with cholestasis and fibrosis. (Supported by PTDC/BIM-MEC/089572014)

Disclosure of Interest: None Declared

ACTIVATION OF miR-34a miR CONTRIBUTES TO LIVER AND MUSCLE INSULIN RESISTANCE IN EXPERIMENTAL AND HUMAN NON-ALCOHOLIC FATTY LIVER DISEASE

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Introduction: Non-alcoholic fatty liver disease (NAFLD) pathogenesis associates with lipid accumulation, mitochondrial dysfunction and insulin resistance (IR). Recent evidence supports a functional role for microRNAs (miRNAs/miRs) in regulating mitochondrial impairment and IR during NAFLD pathogenesis. In particular, activation of the miR-34a/sirtuin-1 (SIRT1) pathway correlates with NAFLD severity.

Aims: Our aim was to profile global liver miRNA expression changes occurring in experimental NAFLD and elucidate the role of specific miRNAs, including miR-34a, using in vitro and in vivo disease models.

Material and Methods: Liver and matching skeletal muscle biopsies were obtained from morbid obese NAFLD patients undergoing bariatric surgery. Tissues were also obtained from C57BL6 mice fed control diets and either fast food (FF) diet for 25 weeks, or methionine and choline-deficient (MCD) diet for 2 and 8 weeks. Liver RNA from 8 weeks MCD-fed mice was run in TaqMan MicroRNA arrays. qPCR array data was analysed using the HTqPCR package in Bioconductor. C2C12 muscle cells were incubated with or without palmitic acid (PA). mRNA and protein expression were analysed by qRT-PCR and immunoblotting, respectively. IR was ascertained by assessing the phosphorylation status of insulin signalling proteins.

Results: Mice fed the FF diet developed steatosis, inflammation and IR. MCD-fed mice developed progressive steatohepatitis, liver damage and fibrosis. 25 miRNAs, including miR-34a, were significantly increased in the liver of MCD-fed mice. Inversely, 27 miRs were decreased. miR-34a was also overexpressed in FF-fed mice and in skeletal muscle

of both disease animal models and human NASH. Concomitantly, SIRT1 expression was decreased. Further, PGC-1 α and mitochondrial fusion protein MFN2 were inhibited in MCD-fed mice while, inversely, mitochondrial fission protein Drp1 and the unfolded protein response sensor IRE-1 α were augmented. Finally, incubation of C2C12 muscle cells with PA promoted IR, in part, through activation of the miR-34a/SIRT1 signalling pathway.

Conclusions: Our results show that miRNAs modulated during NAFLD pathogenesis correlate with the development of IR and mitochondrial dysfunction. In particular, miR-34a/SIRT1 induces IR in both liver and muscle cells, constituting an appealing metabolic syndrome prospective target in the NAFLD context. (Supported by PTDC/BIM-MEC/0895/2014, SFRH/BD/104160/2014, FCT, PT and Gilead Sciences International Research Scholars Program 2015).

Disclosure of Interest: None Declared

LNCRNA HI9 IS INCREASED IN HEPATOCELLULAR CARCINOMA WITH UNDERLYING HCV-RELATED CIRRHOSIS

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Introduction: HCV infection induces cirrhosis development, increasing hepatocellular carcinoma (HCC) risk. The non-coding RNA deregulation can result in cancer.

Aims: We aimed to analyse the expression of lncRNA in HCV-cirrhotic and HCV-HCC patients.

Material and Methods: Fourteen patients were included in this study. Liver tissue from cirrhotic patients without (n=7) and adjacent non-tumour tissues from HCC patients (n=7) were obtained from transplant liver candidates at Virgen del Rocío University Hospital after informed consent. Total RNA were isolated by mirVana™ kit (ThermoFisher). RNA were pooled in the 2 groups and 84 lncRNAs were compared by RT2 lncRNA PCR Array Cancer (Qiagen).

Results: Ten patients were infected with HCV genotype 1 and four with genotype 4. 85.7% were men; 54.93 ± 4.93 years old and only two patients were positive at liver transplantation moment.

From 84 lncRNAs studied, five of them showed a higher expression in HCC patients (H19: 2.93, PCAT1: 3.12, AFAP1-AS1: 4.72, CCAT2: 3.07, PTENP1: 3.10 fold induction). Individual expression of these lncRNAs were individually validated one by one. However only H19 was found significantly upregulated in patients with hepatocarcinoma compared to non-HCC (p=0.009). In addition H19 expression was significantly correlated with alpha-fetoprotein levels (r=0.77; n=14; p=0.001).

Conclusions: lncRNA H19 was increased in cirrhotic patients showing HCV-related HCC in comparison with those without it. Thus, H19 could be an interesting lncRNA to predict HCC

Disclosure of Interest: None Declared

N22 REGION BASED DOT BLOT ASSAY: AN ALTERNATIVE TO PCR FOR DETECTION OF TORQUE TENO VIRUS INFECTION

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Introduction: Torque teno virus (TTV) has long been suspected to be one of the causal agents of non-A-G hepatitis. Despite several studies, its pathogenicity, high genomic variability and role in disease causation remains poorly defined. Detection of TTV infection by PCR poses many limitations, including: a) inability to detect cases of past infection/low viral titers, b) lack of a universal primer set to detect all TTV genotypes, c) lack of PCR setup in many diagnostic labs, especially in developing countries. This gives rise to a need for an economical, rapid and reliable method for large-scale screening of TTV in human population. Here, we describe a simple and sensitive dot blot assay which can replace PCR for TTV detection.

Material and Methods: G1-N22 and G2-N22 dot blot assays, based on genotype-1 (G1) and genotype-2 (G2), respectively, were developed using N22 region, a 500 bp conserved part of ORF1 of TTV genome. Sequences were cloned & expressed as 6xHis-tagged proteins, purified using metal affinity chromatography and coated on strips of nitrocellulose membrane (4µg/strip) for use as antigens to detect anti-TTV antibodies. Sera (n=132; 1:1000 dilution) from patients with different liver diseases including acute viral hepatitis (AVH), chronic viral hepatitis (CVH), fulminant hepatic failure (FHF), cirrhosis (CIR) & hepatocellular carcinoma (HCC), as well as healthy controls (HC), were tested using above assays. Results were compared with presence of TTV-DNA using PCR.

Results: N22 region from G1 & G2 were expressed as ~25 kDa proteins and used in dot blot assays. Rate of detection of TTV by G1-N22 and G2-N22 dot blot assays was found comparable to PCR, as shown in Table. All PCR positive cases were also picked by the blot assays; in fact, we achieved slightly higher rates of detection as compared to PCR. Possibly, these additional cases represent cases of past infection or very low viral titers, which may have been missed by PCR. Furthermore, no major differences were observed between G1-N22 and G2-N22 assays, showing lack of genotype-specific antibodies.

Disease group	Number tested	PCR +ve n (%)	G1-N22 blot +ve n (%)	G2-N22 blot +ve n (%)
AVH	20	10 (50)	10 (50)	11 (55)
CVH	25	10 (40)	12 (48)	11 (44)
FHF	12	5 (41.7)	5 (41.7)	6 (50)
HCC	7	3 (42.9)	4 (57.1)	3 (42.9)
CIR	18	8 (44.4)	9 (50)	9 (50)
HC	50	18 (36)	19 (38)	18 (36)

Conclusions: G1-N22 and G2-N22 blot assays can be used as simple alternatives to PCR for screening TTV infection in large population. Further evaluation in a bigger sample size is in progress.

Disclosure of Interest: None Declared

THE NUCLEAR IMPORT FACTOR KARYOPHERIN-ALPHA 2 IS LINKED TO STATHMIN IN HEPATOCELLULAR CARCINOMA

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Introduction: Proteins of the karyopherin superfamily such as importins and exportins represent an important part of the nucleocytoplasmic transport machinery. We could previously show that a subset of nuclear transport factors is deregulated in hepatocellular carcinoma (HCC) including overexpression of karyopherin-alpha 2 (KPNA2). However, the functional role of KPNA2 in HCC remains incompletely understood.

Aims: We aimed to characterize the functional association of KPNA2 and the pro-tumorigenic, microtubule (MT)-destabilizing protein stathmin (STMN1), as indicated by transcriptomic and proteomic approaches outlined below.

Material and Methods: KPNA2 was depleted in HLE cells by using RNAi and changes in global protein abundance were quantified using quantitative mass spectrometry (qMS). Proteins showing the strongest differential expression including stathmin were validated using immunoblotting and qRT-PCR. A transcriptomic data set derived from more than 240 HCC patients was used to calculate the correlation of KPNA2 and STMN1 expression. As both factors have been described to have pro-survival functions, viability assays were performed to analyse the impact of KPNA2 depletion on cell survival in the presence or absence of exogenous STMN1 overexpression. To further dissect the mechanism underlying KPNA2-dependent STMN1 regulation we tested transcription factors potentially involved (e.g. E2F1) by immunofluorescence and cellular fractionation assays.

Results: Our qMS data (~1700 proteins in total) revealed STMN1 among the most downregulated proteins following KPNA2 knockdown. This effect could be validated on protein level and mRNA level not only in HLE but also in HLF cells. Furthermore, we found a strong positive correlation between KPNA2 and STMN1 indicated by a correlation coefficient of $r=0.81$ ($p<10^{-8}$) in human HCC patient samples suggesting

a potential in vivo relevance. Ongoing experiments suggest that the loss of cell viability upon KPNA2 knockdown can be partially rescued by stathmin overexpression. Finally, preliminary data point towards KPNA2-dependent import of E2F1 being required to maintain STMN1 expression.

Conclusions: Our data so far suggest that KPNA2 regulates STMN1 by import of E2F1 and thereby provides a link between nuclear transport and MT-interacting proteins in HCC.

Disclosure of Interest: None Declared

PROTEIN KINASE CK2 IS INVOLVED IN THE MODULATION OF MALIGNANT PHENOTYPE OF CHOLANGIOCARCINOMA CELLS

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Introduction: Cholangiocarcinoma (CCA) is a primary liver cancer arising from cholangiocytes in the biliary tree, characterized by a poor prognosis and deregulation of various signalling cascades and genetic mutations (1,2). The mechanisms underlying the CCA occurrence and progression are largely unknown. CK2 is a ubiquitous serine-threonine protein kinase (3) which contributes to the malignant phenotype in various types of cancer, and its overexpression is associated with unfavourable prognosis (4,5). CK2 may be targeted by different inhibitors, including CX-4945, that is currently being evaluated in clinical trials (6,7).

Aims: The aim of this study is to understand the potential involvement of CK2 in CCA biology.

Material and Methods: Transcriptomic profiling of 104 surgically resected cholangiocarcinoma samples collected from patients in Australia, Europe, and the United States was performed by microarray analysis. Human cholangiocarcinoma cells (HuCCT-1 and CCLP1) were cultured by standard methods. CX4945 was used as a specific CK2 inhibitor. CK2 activity was measured using a CK2-specific peptide substrate. Cell cycle progression was analysed using flow cytometry. Cell migration and cell invasion assays were performed using in vitro scratch method and boyden chamber.

Results: Analysis of transcriptomic profile of human cholangiocarcinoma tissues showed that CK2 subunits expression is significantly increased compared to surrounding matched normal tissues.

Besides CK2 was found to be highly expressed in CCA cell lines. Treatment with CX4945 or CK2 gene silencing decreased cell viability, and activated the apoptotic process.

Moreover CK2 activity was also found to be necessary for cell cycle progression, as exposure of CCA cells to CX4945 affecting cell cycle progression, in particular blocking the G1/S transition. This phenotype was associated with altered expression of key regulators of cell cycle progression such as Cyclin E and p27Kip. Finally, CK2 inhibition affected the protumorigenic properties of CCA cells, blocking cell motility, invasiveness and promotion of epithelial-mesenchymal transition, relevant actions in the progression and metastasis of cholangiocarcinoma.

Conclusions: The findings observed in this study indicate that CK2 plays an important role in the modulation proliferation, cell cycle regulation and metastatic processes in CCA cells. Further investigations are needed in order to better characterize CK2 as new therapeutic target for CCA.

Disclosure of Interest: None Declared

CHK2 DNA DAMAGE RESPONSE PROTEIN MISLOCALIZATION ENHANCES CHROMOSOMAL INSTABILITY AND HUMAN HEPATOCELLULAR CARCINOMA PROGRESSION

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Introduction: High levels of genomic instability correlate with progression in hepatocellular carcinoma (HCC) of which the most common form is chromosomal instability (CIN), resulting in heterogeneity, with drug resistance and immunity escape as a consequence.

Aims: HCC tumorigenesis per se is an important factor of DNA damage sustaining numerical/structural chromosome abnormalities but the underlying causes and mechanisms are unknown.

Material and Methods: An animal model of diethylnitrosamine-induced HCC was employed known to induce DNA damage and elevated mitotic errors. DNA damage response kinase Chk2 localization was determined in two cohorts of human HCC specimens. To assess the functional role of Chk2, gain on- and loss-of-function, mutation analysis with RFP-tagged Chk2 variants, karyotyping, immunofluorescence and live imaging were performed.

Results: Tumours of DEN-treated animals showed nuclear upregulation of Chk2 and phospho-Histone H2A.X known to be expressed in the presence of DNA damage. In vitro, cell divisions caused DNA damage and induced Chk2 overexpression. Chk2 overexpression/phosphorylation-activation and mislocalization occurred within mitotic components of HuS30gen cells but not in HCT116 and Huh7. This coincided with an increased mitotic index which was reversed by knockdown of Chk2. The forkhead-associated (FHA) domain of Chk2 is essential for proper localization to mitotic structures in contrast to the kinase-inactive mutant indicating that the kinase activity is dispensable for Chk2 mislocalization. In addition, Retinoblastoma inactivated by phosphorylation contributed to defective mitoses. We then investigated the level of Chk2 expression in two

cohorts of HCC tissues and we observed a strong cytoplasmic and perinuclear presence in Grade I and Grade II, respectively. In contrast, grade III HCC tissues were marked by a strong and exclusive nuclear Chk2. Furthermore, we analyzed from TCGA-Cancer Genome Atlas the RNA-Seq-based transcriptomes of 188 HCC tissues, 102 with mutated TP53 and 86 with mutated CNNB1. From these groups of HCC, we identified that CHK2 was significantly associated with the group of HCC TP53 mutated characterized by chromosomal instability.

Conclusions: The study reveals a new mechanistic insight in the involvement of Chk2 in the progression of a subgroup of HCCs. These findings propose Chk2 as a putative biomarker to detect CIN in HCC tissues providing a valuable support for diagnosis and therapeutical management of patients.

Disclosure of Interest: None Declared

TARGETING OF DISTINCT FXR α ISOFORMS BY NOVEL BILE ACID DERIVATIVES PREVENTS LIPOTOXICITY IN LIVER CELLS

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Introduction: Farnesoid X receptor (FXR) plays a critical role in maintaining lipid and bile acid (BA) homeostasis. The FXR gene expresses four biologically active variants (FXR α 1-4), which regulate hepatic and lipid metabolism in an isoform-dependent manner.

Aims: Our aim was to screen novel BA derivatives for their potential to selectively activate distinct FXR isoforms and to protect liver cells against free fatty acid (FFA)-induced lipotoxicity.

Material and Methods: Nineteen novel BA derivatives were incubated in HepG2 cells to evaluate modulation of FXR α 1-4 through Dual-Luciferase assay. Selected BA-derivatives were then co-incubated with oleic and palmitic acids for assessment of cellular cytotoxicity and intracellular lipid accumulation. In addition, primary mouse hepatocytes were incubated with BA derivatives for assessment of SHP, SREBP1-c, PPAR α , CYP7 α 1 and VLDLR mRNA levels.

Results: BA derivatives showed differential activation of the FXR α 1-4 isoforms. Seven BA derivatives were stronger activators of both FXR α 1 and α 2, comparing with their natural precursors. Incubation of HepG2 cells with FFAs led to ~25% reduction in cell viability and ~35% increase in cell death, with a dose-dependent accumulation of lipid droplets. Pre-incubation of cells with selected derivatives efficiently prevented FFA-induced cell death and lipid accumulation. Finally, these derivatives strongly induced of SHP, VLDLR and PPAR α mRNA expression. Molecular docking studies confirmed ligand affinity to FXR.

Conclusions: In conclusion, we developed a novel strategy to identify selective agonists of FXR α 1-4 isoforms, while reporting that BA-derivatives with higher FXR 1 and 2 affinity are more effective in affording cytoprotection against lipotoxicity in liver cells.

Disclosure of Interest: None Declared

VERTEPORFIN POTENTIATES THE ANTI-TUMOR EFFECT OF SORAFENIB BY INHIBITING HEPATOCELLULAR CARCINOMA PROGRESSION THROUGH INTERFERING WITH THE AUTOPHAGIC FLUX

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Introduction: Hepatocellular carcinoma (HCC) is one of the most common malignant cancers worldwide and unfortunately, diagnosis often occurs at an advanced stage. Sorafenib (SF) is the only FDA-approved systemic treatment for advanced HCC with limited success and substantial side-effects. It has been shown that HCC exhibits an increased autophagic flux, often correlated to a high resistance to hypoxia, starving conditions and multi-drug resistance development.

Aims: Here we study the effect of the photosensitizer Verteporfin (VP) on HCC growth in a preclinical model without prior light activation, focusing particularly on its mechanism of action either alone or in combination with SF.

Results: Our data suggest that VP markedly reduces tumor growth in a subcutaneous HCC xenograft mouse model, potentiating the effectiveness of SF, by decreasing tumor cell proliferation (Ki67) and impairing tumor angiogenesis (CD31). We found that Verteporfin inhibits Huh7 and HepG2 cell proliferation, interfering with cell-cycle progression by enhancing apoptosis (flow cytometry) and down-regulating the expression of pro-proliferative and differentiation genes (q-PCR). Combining VP with SF led not only to a synergistic (Huh7) and additive (HepG2) reduction of HCC cell line proliferation, but also to an increased inhibition of angiogenesis (tube formation assay). Furthermore VP co-localizes within lysosomes, increasing their number and altering their shape and size (enlargement). Immunoblot analysis showed that VP interferes with the early-stage of the autophagic flux, impairing SF-induced autophagy, which can be activated as a cellular adaptive response mechanism. VP was able to decrease the formation of newly forming autophagosomes (LC3-I), inducing an accumulation of high-molecular weight complexes of proteins (HMW-p62), which finally leads to a proteotoxic effect.

Conclusions: Taken together, these findings suggest that VP, without prior light activation, acts as an early-stage autophagy inhibitor, significantly potentiating the anti-tumor effect of SF in a HCC preclinical model. Treatment of HCC with VP (+/- SF) may be a novel therapeutic strategy for patients with advanced, otherwise inoperable HCC.

Disclosure of Interest: None Declared

TUMOUR HETEROGENEITY IN MULTI-FOCAL HEPATOCELLULAR CARCINOMA: A GENOMIC SEQUENCING STUDY

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Introduction: Hepatocellular carcinoma (HCC) has high mortality and poor prognosis. The majority of patients present with multifocal disease. Tumour morphological heterogeneity is a well recognised microscopic feature of HCC. Corresponding genomic heterogeneity has not been previously elucidated.

Aims: 1- Investigate genomic heterogeneity within the tumour and its correlation to phenotypic histo-pathological features.
2- Characterise the prevalence of heterogeneity between different nodules present within the same liver.

Material and Methods: Whole genome, ultra-low coverage sequencing was performed using Illumina HiSeq2500 (Illumina, San Diego, CA). Sequenced DNA templates were aligned to Hg19 and studied for whole genome copy number variations. Differences in copy number patterns were objectively analysed using Pearson's correlation between normalized ratios (n=27,180 per each sample).

The inter-tumour heterogeneity cohort included DNA extracted from HCV-related HCCs (n=70) found in surgically removed liver specimens (n=19). The intra-tumour heterogeneity cohort included DNA templates (n=52) extracted from distinct areas of microscopically homogenous (n=8) and heterogenous (n=12) HCCs. Each histologically homogenous HCC was annotated into 4 geographically independent quadrants and DNA was isolated from each quadrant. Morphologically heterogeneous HCCs were sampled

from microscopically distinct areas showing variability in either differentiation, cytological or morphological patterns within the same tumour.

Results: Pearson's correlation coefficients of cancers within the same liver ranged between 0.06 and 0.99. DNA extracted from microscopically homogenous HCCs showed a very strong positive linear correlation (r consistently > 0.85 , 35 correlations performed). In contrast, DNA extracted from microscopically heterogenous HCCs showed significantly weaker linear positive correlations ($p=0.01$).

Conclusions: Correlations coefficients of DNA extracted from different HCCs within the same liver indicate that both intra-hepatic metastasis and de-novo carcinogenesis exist. This may justify the possible need for targeted biopsies of every nodule in the liver for genomic sequencing in the context of targeted therapy clinical trials. Further studies are required to identify the dynamics and phylogeny of these lesions.

Genomic intra-tumour heterogeneity did not exist in microscopically homogenous samples. Confirmation of this observation is highly relevant clinically, especially with rising doubts about the role of liver biopsy in HCC.

Disclosure of Interest: W. Fateen: None Declared S. Berri Conflict with: Illumina H. Wood: None Declared J. Wyatt: None Declared M. El-Meteini: None Declared C. Millson: None Declared P. Quirke: None Declared

MICRO RNA-195 ENHANCES THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN MURINE MODEL

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Introduction: MicroRNA-195 is commonly downregulated in different types of cancer, including hepatocellular carcinoma (HCC). MiR-195 plays a significant role in cell cycle control, such as promoting the apoptosis of tumor cells, suppression of proliferation, and inhibition of angiogenesis and metastasis.

Aims: This study aimed to induce hepatocellular carcinoma using novel method in experimental murine model, with the prospect to study molecular pathophysiologic changes accompanying the development of HCC and the effect of miRNA-195 on this process.

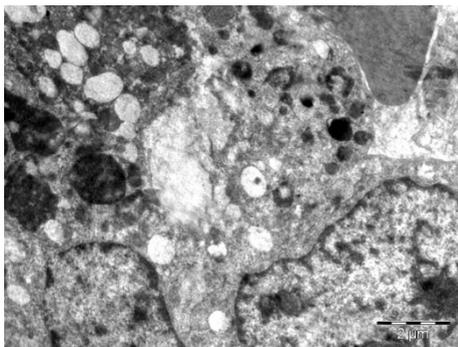
Material and Methods: For this study, three groups of male albino C57BL/6 mice were used as well as one normal control group. HCC was induced in the second and third group by weekly intra-peritoneal injection of diethylnitrosamine (DEN) for 16 weeks. The third group was subjected to intrahepatic injections for 4 weeks with miR-195 vector one week after DEN injection. At the 4th, 8th, and 16th week post DEN treatment the tumor markers alpha-feto protein, the vascular endothelial growth factor, and tumor necrosis factor alpha were assessed in the serum of the different study groups. Hepatic specimens were subjected to Caspase 3 and survivin evaluation using the real-time PCR, as well as ultrastructural pathological examination.

Results: All assessed serological and molecular parameters of miRNA-195 treated third group of mice showed significant increase versus the second treated DEN group $P \leq 0.001$. additionally, ultrastructural criteria of HCC were depicted in the 16th week in the second group versus the 8th week in the third group.

Conclusions: Intra-hepatic injection of miRNA-195 in DEN treated murine model enhances the development of HCC. Thus, further study is important to investigate the effectiveness of anti- miRNA-195 as targeted anti-carcinogenic therapy.

Fig 1: Electron micrograph of an acinus bounded by dysplastic or malignant appearing newly formed hepatocyte. Note: the increase in nuclear cytoplasmic ratio, intracellular accumulation of cytolysosome, lipofuscin granules and increase cytoplasmic proteinaceous material.

Figure:



Disclosure of Interest: None Declared

A GENE AND EPIGENETIC COMBINATION THERAPY FOR LIVER CANCER TREATMENT

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Introduction: Genetic and epigenetic mechanisms are the baseline of cancer initiation, progression and prognosis.

Liver cancer can be the result of viral infections, metabolic disorder, genetic variation/mutation and epigenetic deregulation. Among those phenomena evidence of oncosuppressor gene silencing like p53 and TRAIL represent the major class of liver cancer patients

Aims: Aim of the project is the re-activation of silenced apoptotic pathway in liver cancer models, plasmidic gene delivery and epigenetic treatment.

Material and Methods: HepG2 ATCC were selected for all the experiments. Lipofectamine 2000 (Invitrogen) was used for pEGFP-TRAIL and pEGFP-p53 (Addgene plasmids) and the respective control were selected and propagated in LB broth in order to obtain the necessary amount. Plasmid were purified with Invitrogen PureLink (Thermo) kit. GFP (Green Fluorescent Protein) was acquired via FACS exalibur DB analysis. MS.275 (HDACi calss I) was acquired from selleckchem.

Results: Cell cycle analysis was achieved on HepG2 cells transfected with TRAIL-GFP and pEGFP-p53 recombinant protein. Results were analysed with Cell-Quest and ModIFit software. Data shown the re-expression of selected recombinant proteins in over than 30% cells post 24h from transfection. The transfected cells were treated post 24h with MS-275 for other 8h and the cells were collected. The total protein extract was analysed by western blot and the apoptosis pathways were evaluated via caspase activation proteins. In details we detect the relative bands for capase 8 and caspase 9 full lengths and activated form in transfected cells and post MS-275 treatment.

Conclusions: Results showed the possibility to restore the expression of pro-apoptotic gene TRAIL and p53 in a liver cancer model HepG2. Moreover, the treatment with epigenetic modulators MS-275 enhanced the pro-apoptotic effect mediated by the re-expression of those silenced genes.

Disclosure of Interest: None Declared

GROWTH HORMONE MODULATES THE EXPRESSION OF THE β -GALACTOSIDE-BINDING PROTEIN GALECTIN-1 IN THE LIVER

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Introduction: Growth hormone (GH) expression is associated with poor survival of hepatocellular carcinoma (HCC) patients. Transgenic mice overexpressing GH (GHTg) of 2-4 months old display a preneoplastic pathology similar to that present in humans at high risk of developing hepatic cancer, and old animals (11-14 months) frequently develop liver tumors. Galectin-1 (Gal1) is overexpressed in HCC patients, and is associated with low survival and poor prognosis. We reported that Gal1 overexpression in human HCC cells promotes tumor growth and metastasis in nude mice. Recently, a novel role of Gal1 in liver lipid accumulation after an hepatectomy was described.

Aims: In this study we analyzed Gal1 expression in response to GH using in vivo and in vitro models.

Material and Methods: Gal1 expression was analyzed by immunoblotting, real time PCR and immunohistochemistry in the liver of GHTg mice (contain the bovine GH gene fused to control sequences of the rat phosphoenolpyruvate carboxykinase gene), and Swiss-Webster 3 week (w) old mice treated with GH (6 μ g GH/ g body weight/ day) by implantation of osmotic pumps (continuous treatment) or by two daily injections (intermittent treatment) during 5 w. Human HCC HepG2 cells were treated with GH (1 μ g/ml) with or without the translation inhibitor cicloheximide (Cx, 10 μ M). Cells were scrapped and processed for immunoblotting at the indicated time.

Results: Gal1 mRNA and protein expression levels were drastically upregulated in the liver of GHTg mice of 2 w (\bar{Q} , $\sigma_n=8$ $p<0.01$), 4 w (\bar{Q} , $\sigma_n=5$ $p<0.01$), 2-4 months ($\bar{Q}_n=8$, $\sigma_n=9$ $p<0.001$) and 11-14 months ($\bar{Q}_n=13$, $\sigma_n=8$ $p<0.001$). Hepatic tumors of old GHTg mice showed increased Gal1 expression respect to non-tumoral zone in both sexes

($p < 0.01$, $n = 21$). These results were confirmed by immunohistochemistry. GH treatment with osmotic pumps showed a tendency towards an increase in Gal1 expression ($\text{♀} n = 9$ $154 \pm 23\%$, $\text{♂} n = 9$ $120 \pm 18\%$) while GH injection showed no effect ($\text{♀} n = 6$ $88 \pm 28\%$, $\text{♂} n = 6$ $98 \pm 8\%$). Also, 30 min-treatment with GH increased Gal1 expression in HepG2 cells ($n = 8$ $166 \pm 28\%$ $p < 0,05$), this effect was inhibited in the presence of Cx ($n = 4$ $104 \pm 2\%$). No effect on Gal1 expression was observed after 24 h treatment.

Conclusions: Our results demonstrate that GH positively modulates Gal1 expression in the liver. It could be speculated that both proteins could act synergistically in HCC development and progression.

Disclosure of Interest: None Declared

miR-21-DEFICIENCY REDUCES LIVER INJURY, FIBROSIS AND NECROPTOSIS IN CHOLESTATIC BILE DUCT-LIGATED MICE

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Introduction: Hepatocellular death, inflammation and fibrosis are key factors in the pathogenesis and progression of cholestatic liver disease. We have recently shown that in the common bile duct ligation (BDL) murine model, targeting of necroptosis ameliorates hepatic necroinflammation. Curiously, microRNA 21 (miR-21) is oncogenic, modulates necroptosis, and is upregulated in hepatocellular carcinoma.

Aims: We aimed to evaluate the role of miR-21 in mediating deleterious processes associated with cholestatic liver injury and disease.

Material and Methods: C57BL/6N wild-type (WT) or miR-21 knockout (KO) mice were subjected to BDL or sham surgeries (n=7-10 per group), with biochemical analysis of hepatic damage, fibrosis, necroptosis and bile acid metabolism after either 3 (acute injury) or 14 (chronic injury) days.

Results: Liver miR-21 expression increased in BDL WT mice at both 3 and 14 days. Remarkably, BDL miR-21 KO mice displayed decreased circulating levels of hepatic enzymes, concomitantly with decreased fibrogenic gene expression in the liver at both time-points, in comparison with WT mice, suggesting that miR-21 contributes to BDL-induced liver injury and fibrosis. Curiously, sham miR-21 KO mice displayed higher levels of phospho-mixed lineage kinase domain-like protein (p-MLKL) when compared with WT mice. Still, miR-21-deficiency protected from BDL-induced activation of necroptosis, as seen by impaired receptor-interacting protein 3 (RIP3) and p-MLKL upregulation (p<0.05). In addition, BDL-induced heme oxygenase expression and iron accumulation, which we have previously found increased in BDL RIP3-deficient mice, were impaired at 3 days post-BDL. c-Jun N-terminal kinase (JNK) phosphorylation, implicated in both liver necroptosis and BDL-associated fibrogenesis, was also inhibited in BDL miR-21 KO

mice. Finally, miR-21 KO mice displayed an adaptive response in the expression of nuclear receptor- and bile acid uptake-, synthesis-, detoxification-, and secretion-associated genes, accompanied by decreased serum levels of bile acids in both sham and BDL mice.

Conclusions: In conclusion, miR-21 ablation ameliorates liver damage, fibrosis and cholestasis in BDL mice. Of note, decreased acute necroptosis in miR-21 KO BDL mice is not associated with off-target effects seen after RIP3 KO and, as such, inhibition of miR-21 could arise as a promising approach to treat cholestatic liver disease. Supported by PTDC/BIM-MEC/0895/2014, SFRH/BD/91119/2012, FCT, Portugal.

Disclosure of Interest: None Declared

ANTI-MALARIAL DRUG CHLOROQUINE POTENTIATES CISPLATIN-INDUCED APOPTOSIS IN HEPATOCELLULAR CARCINOMA BY DISRUPTING MITOCHONDRIAL MEMBRANE POTENTIAL

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Introduction: Hepatocellular carcinoma (HCC) is one of the commonest cancers worldwide. Surgical resection and liver transplantation remain the potential options for the treatment of HCC. However, due to unresectable disease at presentation and shortage of donor livers, there is ongoing search of alternative approaches. Currently, chemoresistance is the major clinical issue for oncologist for cancer treatment. Chloroquine (CQ), an autophagy inhibitor, is most widely used anti-malarial drug. Recently, it has being studied as combinational therapy in concomitant with chemotherapeutic agents to overcome chemoresistance of various cancers.

Aims: The purpose of the study is to evaluate the efficacy of combinational therapy of CQ and cisplatin in HCC. In addition, the present study aims to explore the mechanism of chemoresistance in HCC and role of CQ to overcome it.

Material and Methods: Cell proliferation and apoptosis were evaluated by MTT assay and flow cytometry in HepG2 cells in vitro. Colony formation assay was performed to measure long-term cell viability after the co-treatment of CQ and cisplatin. Fluorescent dye was used to monitor mitochondrial membrane potential (MMP). The protein expression of autophagy and apoptosis-related genes were evaluated by western blotting.

Results: Autophagy was upregulated in HepG2 cells following the treatment of cisplatin. Cisplatin suppressed cell proliferation and enhanced cell death in HCC. Concomitant treatment of CQ and cisplatin was more potent in suppressing cell proliferation and enhancing apoptosis. In addition, combinational therapy upregulated the apoptotic genes such as cleaved caspase-3 and cleaved-PARP. Furthermore, BAX, a key component of mitochondrial stress-induced apoptosis, was upregulated following concomitant therapy.

Similarly, combined treatment of CQ and cisplatin caused more MMP loss in comparison to monotherapy. Interestingly, the upregulated autophagy due to cisplatin treatment was decreased following combinational therapy with autophagy inhibitor.

Conclusions: In conclusion, anti-malarial drug chloroquine potentiates cell death induced by cisplatin and overcome chemoresistance in HCC in vitro, possibly through autophagy inhibition and disruption of MMP.

Disclosure of Interest: None Declared

miR-21 ABLATION AND OBETICHOLIC ACID AMELIORATE NASH IN MICE

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Introduction: microRNAs were recently suggested to participate in non-alcoholic fatty liver disease progression (NAFLD). Moreover, nuclear receptors, namely peroxisome proliferator-activated receptors (PPARs) and the farnesoid X receptor (FXR) are currently under scrutiny as modulators of lipid and glucose metabolism in non-alcoholic steatohepatitis (NASH).

Aims: We aimed to elucidate the role of the miR-21/PPAR α pathway in liver/muscle tissues of mice NASH models and ascertain the therapeutic potential of miR-21 ablation alone or in combination with FXR agonist obeticholic acid (OCA).

Material and Methods: Wild-type (WT) and miR-21 KO mice were fed a chow (n=10) or methionine and choline-deficient (MCD; n=10) diets for 2 and 8 weeks. Alternatively, mice were fed either chow (n=12) or fast food diet (FF; n=12) for 25 weeks. Six animals from each group had their diet supplemented with OCA 10 mg/kg/day (Intercept Pharmaceuticals, Inc.). Human biopsies were obtained from morbid obese NAFLD patients (n=28). Liver/muscle samples were processed for histological analysis and assessment of miR-21, pro-inflammatory/pro-fibrogenic cytokines, PPAR α and metabolic relevant genes and for insulin resistance mediators, by qRT-PCR and immunoblotting. A Taqman[®] Array was performed to measure the expression of lipid regulated genes.

Results: WT mice fed with the MCD diet developed steatohepatitis and fibrosis, displaying increased levels of lipoapoptosis and serum ALT. In contrast, miR-21 KO mice displayed a significant decrease in steatosis severity, cell death and liver damage, inflammation and did not develop fibrosis. Also, WT FF-fed mice developed hepatomegaly, macrovesicular steatosis, inflammatory infiltrates and increased oxidative stress. miR-21 levels were

increased in WT FF-fed mice, in both liver and muscle, concomitantly with decreased expression of PPAR α . Importantly, miR-21 ablation in combination with OCA stoutly reduced steatosis severity and inflammation, preventing oxidative stress and restoring metabolic pathways, reinstated insulin sensitivity in the liver and muscle. Finally, miR-21/PPAR α axis was found increased in liver/muscle samples of NAFLD patients, as well as in serum samples.

Conclusions: In conclusion, miR-21 abrogation, together with FXR activation by OCA, significantly improves metabolic parameters in NASH and avoids disease progression, highlighting the therapeutic potential of multi-targeting therapies for NAFLD and the metabolic syndrome. (Supported by PTDC/BIM-MEC/0895/2014, SFRH/BD/88212/2012, FCT, PT).

Disclosure of Interest: None Declared

GNS561 A NEW QUINOLINE DERIVATIVE INHIBITS THE GROWTH OF HEPATOCELLULAR CARCINOMA IN A CIRRHOTIC RAT & HUMAN PDX ORTHOTOPIC MOUSE MODELS

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Introduction: Quinoline derivatives are novel class of oral small molecules inducing inhibition of autophagy, apoptosis, and cell cycle modulation.

Aims: The aim of these studies was to assess tolerance and efficacy of a new quinolone derivative GNS561.

Material and Methods: In vitro experiments were realized with viability, apoptosis and migration in tumor cells in HCC cell lines and primary tumor. Drug tolerance and plasma and liver pharmacokinetic were evaluated after single and repeated dosing in mice and rat. GNS561 and sorafenib efficacy in vivo were evaluated in a PDX orthotopic BALB/c-nu mouse model and in a diethylnitrosamine (DEN)-induced HCC cirrhotic rat model. In rat tumor progression was followed by MRI, pathological analysis, immunohistochemistry and PCR analysis after 6 weeks of treatment.

Results: GNS561 shows potent anti-proliferative activity when assayed against a panel of human tumor cell lines and notably against a panel of HCC patient primry tumors even in those with sorafenib resistance (Mean EC50 3 μ M vs 11 μ M for sorafenib). GNS561 is highly selectively trapped in the liver. Plasma and liver PK in mice and rats after single and repeated doses confirm this selectivity with good tolerance and oral bioavailability. In PDX mouse model, tumor growth was significantly reduced by GNS561 with a dose-response manner, this tumor regression was associated with AFP level decreases by 72% with GNS561 (p=0.002) and 54% with sorafenib (p=0.046) compared to control. In rat

model, mean number of tumors was significantly lower in GNS561 (n=50.6), in sorafenib (n=65.1) and in combination group of GNS561+sorafenib (n=40.6), when compared to control (n=100.4; p=0.002, p=0.029 and p=0.0002). Tumor decrease measured by MRI was associated with a significantly reduced proliferation of tumor cells particularly in GNS561 group (70%) and combination (84%) compared to control, whereas the effect of sorafenib alone on proliferation was modest (30%). Moreover, fibrosis area was reduced in GNS561 group compared to control (p=0.04) and in combination group compared to control (p=0.001) and sorafenib group (p=0.015).

Conclusions: GNS561 is a liver selective drug with good tolerance and promising efficacy in different HCC animal models. GNS561 was more efficient than sorafenib to control tumor growth in preclinical models. Based on its safe toxicity profile and potent activity in rodent models, GNS561 is now aimed to further reach clinical development in patients with HCC in 2017.

Disclosure of Interest: F. Bassissi: Employee: Conflict with: Genoscience Pharma, Z. Macek Jilkova: : None Declared, S. Brun: Employee: Conflict with: Genoscience Pharma, J. Courcambeck: Employee: Conflict with: Genoscience Pharma, J. Tracz: Employee: Conflict with: Genoscience Pharma, K. Kurma: : None Declared, G. Roth: : None Declared, C. Khaldi: : None Declared, C. Chaimbault: Employee: Conflict with: Genoscience Pharma, B. Quentin: Employee: Conflict with: Genoscience Pharma, E. Asseraf: Employee: Conflict with: Genoscience Pharma, A. Beret: Employee: Conflict with: Genoscience Pharma, E. Raymond: Employee: Conflict with: Genoscience Pharma, P. Halfon: Employee: Conflict with: Genoscience Pharma, T. Decaens: : None Declared

THE BCL-2 FAMILY MEMBER BOK PROMOTES DEN-INDUCED HEPATOCARCINOGENESIS

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Introduction: The BCL-2 family member BOK shares sequence homology with pro-apoptotic BAX and BAK, which are critical for the activation of the intrinsic apoptotic pathway. BOK is constitutively expressed at the protein level throughout the gastrointestinal tract but its pathophysiological roles are poorly understood.

Aims: Since several members of the BCL-2 family are critically involved in the regulation of hepatocellular apoptosis and carcinogenesis we aimed to establish how loss of BOK affects chemical induced hepatocarcinogenesis in mice.

Material and Methods: 15-day-old WT and Bok-deficient mice were injected with a single dose of diethylnitrosamine (DEN) and sacrificed 9 months after to assess tumor formation and histopathology. The role of BOK in acute liver damage and pathophysiological response to DEN was evaluated in short-term experiments as well as in cell culture models.

Results: Short-term exposure to DEN lead to transcriptional upregulation of Bok in the liver, correlating with hepatocellular apoptosis. As a consequence, Bok-deficient mice were significantly protected from DEN-induced acute liver damage and associated inflammation. Longterm, DEN treated Bok-deficient mice developed fewer and smaller tumors than WT controls. Gene expression profiling revealed that loss of BOK results in upregulation of genes involved in cell cycle arrest. Bok-deficient HCC tumors displayed increased expression levels of the cyclin kinase inhibitors p19^{INK4D} and p21^{cip1} compared to WT controls. Accordingly, the proliferative index was significantly decreased in HCC from Bok-deficient animals (as well as in BOK deficient human carcinoma cell lines) compared to BOK proficient controls.

Conclusions: We conclude that BOK is upregulated by DEN and contributes to DEN induced hepatocellular apoptosis. As a consequence, Bok-deficient mice are partially protected from hepatocarcinogenesis, overall indicating that BOK promotes chemical induced HCC. In addition, our data point towards a novel role of BOK in the regulation of cellular proliferation.

Disclosure of Interest: None Declared

MONITORING OF INTRAHEPATIC AND CIRCULATING IMMUNE SYSTEM FEATURES IN PATIENTS WITH HCC BY MULTICOLOR FLOW CYTOMETRY

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Introduction: During development of hepatocellular carcinoma (HCC), an effective antitumor immune surveillance in liver microenvironment is impaired. Thus, enhancement of antitumor immune responses by immune checkpoint modifications is a promising treatment strategy. However, the network of inhibitory and stimulatory checkpoint molecules is very complex and extensive studies need to be carried out to clarify the co-expression of various checkpoint molecules such as PD-1, CTLA-4, TIM-3, LAG-3, OX40 or 4-1BB and their compensatory changes induced by different treatments.

Aims: The aim of our project is to investigate intrahepatic and circulating immune system in advanced-stage HCC patients i) before treatment by performing direct immunomonitoring on fresh liver biopsies and fresh whole blood, ii) to follow the immunological changes induced during treatment by blood analyses 1 and 3 months after start of treatment and iii) finally to evaluate again intrahepatic and circulating immune system in case of tumor progression.

Material and Methods: To date, 13 HCC patients are included in this study. Fresh liver biopsies from tumor and from non-tumor tissue are immediately mechanically homogenized and stained for FACS analyses. Similarly, whole fresh blood is stained. Following markers are included: Tube 1 – CD45, CD3, CD56, CD16, CD15, CD19, CD8, CD335, CD107, CD69, CD274 (PD-L1) and CD279 (PD-1); Tube 2 – CD45, CD3, CD56, CD16, CD15, CD19, CD8, CD137 (4-1 BB), CTLA-4, LAG-3, CD134 (OX40), TIM-3. Samples are measured using BD-LSRII flow cytometer, data are collected with BD FACS Diva 6.3.1 and analyzed by FCS Express V6 software.

Results: The panel of antibodies for tube 1 and tube 2 was successfully used on fresh liver tumor and non-tumor biopsies and on fresh blood samples of HCC patients. We

constantly observe differences in checkpoint molecule expressions on intrahepatic immune cells compared to peripheral immune cells. For instance, frequency of PD-1⁺ intrahepatic T lymphocytes is much higher compared to peripheral T cells ($p < 0.0001$) and PD-1 is mainly expressed by CD8⁺ T lymphocytes in the tumor tissue. Correlation between immunosuppressive network and clinical outcome together with immunomodulatory effects of different therapies will be presented during meeting.

Conclusions: This study helps to understand the complexity of the inhibitory receptor network that regulates immune system to generate an immunosuppressive microenvironment of HCC and represents an opportunity to derive predictive factors for response to treatment.

Disclosure of Interest: None Declared

MOLECULAR BASIS OF NATURAL KILLER (NK) CELL DYSFUNCTION IN HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: Hepatocellular carcinoma (HCC) is a complex disease with poor prognosis. Natural Killer (NK) cells play a central role in cell-mediated immune response to cancer. In previous studies number and function of NK-cells have been shown to be positively correlated with HCC outcome. Intra-tumor and circulating NK cells have been shown to be functionally impaired and this may contribute to HCC progression and dismal survival.

Aims: A better understanding of the molecular basis underlying NK-cell function in HCC, may inform on target molecules and cellular pathways to be restored in immunotherapeutic approaches potentiating NK cell response in HCC.

Material and Methods: NK cells (CD56+CD3-) were derived by fluorescence-activated cell sorting (FACSaria II) from peripheral blood of 7 patients with Hepatitis C virus (HCV)-related liver cirrhosis, as control, and 11 patients with early stage HCC and HCV-related liver cirrhosis. Gene expression profile was performed by Agilent gene expression microarrays. Differentially expressed genes were defined by GeneSpring and MetaCore for pathway enrichment analysis.

Results: Five-hundred and twenty-three genes were differentially expressed. MetaCore pathway analysis allowed the identification of three most relevant pathways: cytoskeleton remodeling, nociceptin expression and immune system, role of the transcription factor AP1 in the regulation of cellular metabolism. Enrichment analysis allowed to identify genes downregulated in NK-cells from HCC patients: actin, vinculin and filamin in the first pathway, nociceptin and prepronociceptin in the second, and genes constituting the transcription factor AP1 in the third.

Conclusions: These results may explain a lack of immune surveillance by NK-cells in patients with HCC, in fact formation of a mature, cytolytic synapse between NK cell and target tumor cell may be impaired because of insufficient cytoskeleton assembly and organization. In addition, downregulation of AP1 could lead to a reduced NK-cell activation and differentiation.

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KANGAI 1 C-TERMINAL INTERACTING TETRASPANIN PLAYS AN IMPORTANT ROLE IN CHOLANGIOCARCINOGENESIS

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Introduction: Cholangiocarcinoma (CC) is the second most common primary hepatic malignancy. Worldwide incidence and mortality rates are rising, but systemic treatments are limited. Kangai 1 C-terminal interacting tetraspanin (KITENIN), a member of the tetraspanin family, is expressed in different tumors, is important for tumor progression and metastasis. However, the role of KITENIN in cholangiocarcinogenesis is not clear yet.

Aims: Here, we analyse the function of KITENIN in human cell lines (SZ-1, TFK-1), human CC tissues and in an engineered mouse model (Alb-Cre/KRAS^{G12D}/p53^{L/L}) of CC.

Material and Methods: Expression of KITENIN was determined by immunohistochemistry, immunofluorescence and Western Blot. We analysed the effect by small interfering RNA against KITENIN on cell proliferation and mobility by using proliferation-, migration- and invasion-assays. Western Blot was applied to measure the expression of epithelial-mesenchymal transition (EMT) markers.

Results: KITENIN is highly expressed in human CC cell lines (n=2), human CC (n=14) and murine CC (n=5). Silencing of KITENIN effectively reduced proliferation, migration and invasion in both intra- and extra-hepatic human CCC cells (p<0.05). Down-regulation of KITENIN impaired the expression of EMT markers (N-cadherin, Vimentin, Slug and Snail).

Conclusions: Our data demonstrate that KITENIN plays an important role for cholangiocarcinogenesis. KITENIN might become a new and potential therapeutic target against human CC.

Disclosure of Interest: None Declared

DUAL INHIBITION OF pERK AND pMAPK14 OVERCOMES RESISTANCE TO SORAFENIB IN HEPATITIS B VIRUS REPLICATING HEPATOMA CELLS

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Introduction: Hepatitis B virus (HBV) is a small DNA virus that targets the liver and is a major driver for end-stage liver disease and liver cancer. Clinical data suggest that patients with HBV-associated hepatocellular carcinoma (HCC) might have a less favorable outcome with sorafenib treatment, the only molecularly targeted anti HCC drug available today. Therefore, HBV might antagonize the multi-kinase inhibitor sorafenib.

Aims: In this study we aimed to investigate whether HBV is implicated in resistance to sorafenib in hepatoma cell model system and its mechanism of action. Given that a main target of sorafenib is the RAF-MEK-ERK pathway, we further explored for potential alternative pathways that might be evoked by HBV and that can pharmacologically be targeted in order to overcome HBV-associated resistance to sorafenib.

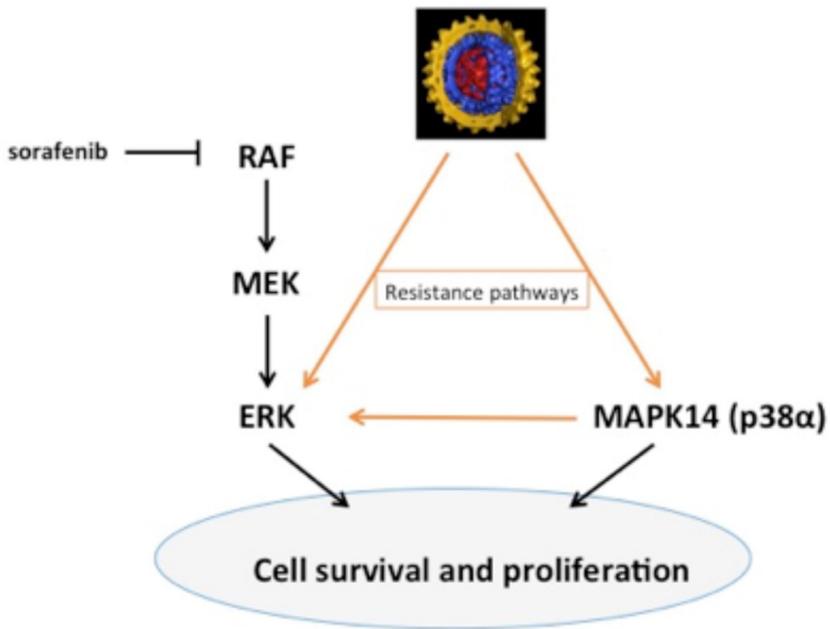
Material and Methods: We used hepatoma cell line with integrated HBV genome and as a control we used the same cell line in which HBV expression was knocked-out by the CRISPR/cas9 system. Pro-apoptotic effect of sorafenib on cells was assessed by cell viability analysis. The effect of HBV on relevant pro-oncogenic pathways was assessed by western blot analysis and by gene specific knockdown with shRNA. Hepatoma cells over-expressing HBx was used to study the potential effect of X protein in mediating sorafenib resistance and possibly HBV oncogenesis.

Results: Here we show that hepatoma cells with replicating HBV are less susceptible to sorafenib pro-apoptotic effect as compared to HBV-null cells. The presence of HBV results in pErk activation and is associated with HBV X protein (HBx)-mediated induction of pMAPK14, a protein kinase that was recently shown to be over-expressed in hepatoma samples from patients with resistance to sorafenib treatment. Pharmacological inhibition or knockdown of Mapk14 result in an increase in the therapeutic efficacy of sorafenib in

HBV replicating hepatoma cells and dual inhibition of pERK and pMAPK14 completely alleviates resistance to sorafenib in these cells.

Conclusions: HBV confers resistance to sorafenib treatment by activating the downstream pERK, possibly by up-regulation of pMAPK14 in HBV-associated HCC cells. Our study suggests that the addition of pERK and pMAPK14 inhibitors to sorafenib treatment may have an additive effect over sorafenib mono therapy, especially among patients with HBV-associated liver cancer.

Figure:



ePOSTER ABSTRACTS

Disclosure of Interest: None Declared

Ang-2 POLYMORPHISMS AND CLINICAL OUTCOME IN ADVANCED HCC PATIENTS RECEIVING SORAFENIB

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Introduction: Sorafenib, an oral multikinase inhibitor, represents the standard care for advanced hepatocellular carcinoma.

Angiopoietin-2 (Ang-2) is a crucial angiogenic factor. By binding to its receptor Tie2, Ang-2 cooperates with the VEGF pathway to maintain normal physiological functions. In the presence of VEGF, Ang-2 destabilizes blood vessels and promotes vascular sprouting. In cancers, Ang-2 is linked to not only angiogenesis but also invasive and metastatic phenotypes. Although sorafenib exerts no significant activity against Tie2, the predictive value of Ang-2 has been explored in 2 studies.

Llovet et al conducted a large biomarker study based on SHARP study. The authors found that a high baseline plasma Ang-2 level was an independent factor for poorer OS but not for reduced sorafenib efficacy. Conversely, in a small retrospective study, a high serum Ang-2 level was associated with a lower DCR and poorer PFS. The actual role of Ang-2 in predicting sorafenib efficacy warrants further investigations.

Polymorphism analysis seems to have more advantages than protein or gene expression analysis. Gene expression analysis is performed on biological material collected at a specific time in the natural history of the disease. It is also subject to the influence of a number of laboratory biases. Conversely, polymorphism analysis can be performed at any time during the course of the disease, is not substantially influenced by laboratory biases and is less expensive.

Aims: In our study we analysed the role of ANG-2 polymorphisms in relation to clinical outcome in patients with hepatocellular carcinoma treated with sorafenib.

Material and Methods: We analyzed 135 patients with hepatocellular carcinoma treated with sorafenib. Peripheral blood samples or FFPE tumor tissues were available for DNA

extraction and genotyping analysis. Nine Ang-2 polymorphisms were analyzed by direct sequencing or Real Time PCR method.

Results: With regard to Ang4 rs55633437 was observed that patients carrying the allele GG were associated with a better PFS and OS. The variants GG were associated with a median OS of 16.9 months vs 6.5 months of variants GT and TT ($p = 0.016$). The variants GT and TT were associated with a median PFS of 2.94 months vs 4.67 months of variants GG ($p = 0.03$). These data were confirmed by multivariate analysis.

Conclusions: ANG-2 polymorphisms could represent prognostic markers in patients with advanced hepatocellular carcinoma treated with sorafenib.

Disclosure of Interest: None Declared

RIPKI SUPPRESSES A TRAF2-DEPENDENT PATHWAY TO LIVER CANCER

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Introduction: Cell death is a driver for the progression of chronic liver diseases towards hepatocellular carcinoma (HCC), suggesting that targeting of cell-death mediators might be an option for chemoprevention of liver cancer. Receptor-interacting-protein-kinase-1 (RIPK1) represents an essential signaling-node in mediating cell death and might have kinase-dependent and independent functions in cancer development, but the function of RIPK1 for human hepatocarcinogenesis has remained unclear.

Material and Methods: To examine the hepatic function of RIPK1, we crossed floxed RIPK1 mice with mice expressing cre-recombinase under an albumin promoter with α -fetoprotein enhancer to generate mice with a conditional deletion of Ripk1 in liver parenchymal cells (LPC, RIPK1^{LPC-KO}). For induction of liver injury, RIPK1^{LPC-KO} mice were injected with lipopolysaccharide and liver injury was monitored by measuring serum transaminases and caspase-3 activity. Moreover, molecular mechanisms were analysed by immunohistochemical stainings (IHC), electrophoretic mobility shift assay and Western-blot. For additional genetic analysis, RIPK1^{LPC-KO} mice were intercrossed with Caspase-8- or TRAF2-floxed mice to generate double mutant mice. Finally, IHC-staining of human HCC-samples was performed and assessed using the immunoreactive (IR)-score.

Results: Ablation of Ripk1 in LPC did not cause a spontaneous phenotype, but led to tumor necrosis factor (TNF)-dependent hepatocyte apoptosis and liver injury without affecting inducible NF κ B activation. Loss of Ripk1 induced the TNF-dependent proteasomal degradation of the E3-ligase TRAF2 in a kinase-independent manner, thereby directly activating the apoptosis mediator Caspase-8. Combined ablation of Ripk1 and Traf2 led to the development of spontaneous HCC. The cancer phenotype was caused

by the simultaneous direct activation of Caspase-8 and inhibition of NF- κ B, proving that RIPK1 and TRAF2 have redundant functions in NF- κ B activation. In line with the mouse data, low RIPK1 and TRAF2 expression in human HCCs was associated with an unfavorable prognosis.

Conclusions: A kinase-independent function of RIPK1 controls a novel, TRAF2-dependent checkpoint in murine and human HCC development and RIPK1 and TRAF2 expression levels predict the prognosis of human liver cancer. A better understanding of the kinase-dependent and independent RIPK1 functions might lead to novel chemoprevention and treatment options in patients with chronic liver disease and HCC.

Disclosure of Interest: None Declared

THE ROLE OF SIX TRANSMEMBRANE EPITHELIAL ANTIGEN OF THE PROSTATE 2 IN HEPATOCELLULAR CARCINOMA

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Introduction: The incidence of hepatocellular carcinoma (HCC) in Hispanics in the United States is three times higher than non-Hispanic whites, and even higher in South Texas (STX) Hispanics. Knowledge regarding genetic alterations in Hispanics is sparse due to a lack of Hispanics with HCC in The Cancer Genome Atlas (TCGA). Our group sequenced paired normal and tumor HCC samples from STX Hispanics, which highlighted a gene over-expressed in tumors of Hispanics, called the Six Transmembrane Epithelial Antigen of the Prostate 2 (STEAP2). STEAP2 is a metalloreductase of iron and copper and is thought to increase iron and reactive oxygen species in the liver, which can promote inflammation and cirrhosis, suggesting an oncogenic role in HCC, especially in the setting of obesity.

Aims: We aim to prove that overexpression of STEAP2 will promote malignant property in HCC cells resulting in enhanced proliferation, survival, invasiveness, and eventually tumorigenicity, especially in obese hosts.

Material and Methods: Hispanic paired HCC and adjacent normal tissues were collected for RNA sequencing and establishment of Hispanic HCC cell lines. STEAP2 RNA and protein expression levels in Hispanic and Caucasian samples were evaluated by RT-PCR, Western blot, and immunohistochemistry. Knockdown of STEAP2 in HCC cell lines was done to examine the effects on iron levels, oxidative stress, proliferation, invasiveness, apoptosis and cell cycle in vitro.

Results: Analysis of RNA sequencing data (Hispanic vs. TCGA) demonstrated the overexpression of STEAP2 in HCC tumors in Hispanic patients, which were validated by RT-PCR and Western blot (WB) data. Lipid peroxidation product, 4-hydroxynonal, and copper levels were higher in HCC tumor vs. adjacent tissue. Iron levels were higher

in adjacent tissue vs. tumor tissue in Hispanics. Knockdown of STEAP2 in the SNU398 HCC cells decreased proliferation and migration, while in HUH7 HCC cells STEAP2 knockdown only decreased migration.

Conclusions: STEAP2 is specifically overexpressed in HCC tumors in Hispanics in comparison to HCC tumors in non-Hispanic whites and appears to play a malignant-promoting role in HCC cells. Further studies on the role of STEAP2 as a novel tumor promoter in HCC and its mechanisms, by which it promotes carcinogenesis, are underway. The proposed studies will likely yield mechanistic insights into the molecular mechanisms that drive HCC development and progression in South Texas Hispanics and potential therapeutic targets.

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MODELLING DOXORUBICIN-ELUTING BEAD THERAPY IN COMBINATION WITH DNA-DAMAGE REPAIR INHIBITION IN HUMAN LIVER CANCER

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Introduction: Transarterial chemoembolisation (TACE) is widely used in the treatment of hepatocellular carcinoma (HCC). However, TACE is only curative for a small percentage of patients, and investigational approaches to improve treatment efficacy are limited by the requirement for large animal models. Studies in HCC patients have shown that increased expression of DNA-dependent protein kinase (DNA-PK), a key DNA repair enzyme, correlates with advanced tumour grade, resistance to TACE and shorter survival (1,2).

Aims: We have developed a murine model of drug-eluting bead therapy and explored selective inhibition of DNA-PK to enhance DNA-damaging therapies in the treatment of HCC.

Material and Methods: A model of localised and sustained chemotherapy was established via intra-tumoural injection of doxorubicin-loaded DC M1 beads into CD1 nude mice bearing Huh7 xenografts, and used to explore potential therapeutic combinations *in vivo*. We combined a novel, selective DNA-PK inhibitor with either free doxorubicin or doxorubicin-loaded beads in DNA-PK overexpressing human HCC cell lines *in vitro*, and quantified DNA-PK activity by Ser2056 phosphorylation status, DNA damage by γ H2AX levels, and cell survival using clonogenic assays.

Results: *In vivo*, unloaded beads had no effect on tumour growth compared to non-treated controls (time for tumour volumes to quadruple (RTV4) = 7.8 vs 7.5 days, $P > 0.5$, Mann-Whitney), whereas doxorubicin beads alone had a modest effect (RTV4 = 11.1 vs 7.8 days, $P < 0.005$). The DNA-PK inhibitor dose-dependently prevented DNA-PK activation in HCC cell lines, and significantly increased and sustained DNA damage in response to doxorubicin. Inhibiting DNA-PK also sensitised DNA-PK overexpressing HCC cell lines to doxorubicin in survival assays by ≥ 5 -fold. In the Huh7 xenograft

model, twice-daily oral administration of the DNA-PK inhibitor (30 mg/kg) significantly reduced tumour growth compared to doxorubicin beads alone (RTV4 = 17.8 vs 11.1 days, $P < 0.01$) without adverse effects or significant changes in body weight.

Conclusions: DNA-PK inhibition significantly augmented the anti-tumour activity of locoregional chemotherapy in a murine model. These data highlight the potential utility of modelling localised doxorubicin treatment in human liver tumour xenografts, and support the concept of inhibiting aberrant DNA repair pathways to improve the efficacy of DNA-damaging therapies in patients with HCC.

1. Cornell et al. (2015) Clin Cancer Res. 21: 925
2. Evert et al. (2013) Br J Cancer. 109: 2654

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CHARACTERIZATION OF RARELY DETECTABLE TUMOUR-ASSOCIATED ANTIGENS (TAA)-SPECIFIC CD8 T CELLS IN HCC PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is the second-leading cause of cancer-related deaths worldwide. Incidence and mortality are growing since diagnosis is often established in an advanced stage of disease and only a limited number of therapeutic approaches are available. Therefore, new therapies for HCC are urgently needed. Importantly, CD8 T-cell responses targeting tumour-associated antigens (TAA) beneficially influence patients' survival, thus, immunotherapy based on TAA-specific CD8 T cells seems to be a promising novel therapeutic approach. However, TAA-specific CD8 T-cell responses are often functionally impaired in HCC and the underlying mechanisms of this dysfunction remain elusive.

Aims: In this study, we therefore aimed to characterize TAA-specific CD8 T cells in detail by using a peptide/MHC class I-tetramer-based enrichment strategy to determine the mechanisms of the functional impairment and the immunotherapeutic potential.

Material and Methods: Circulating TAA-specific CD8 T cells of HCC patients (n=16), patients with liver cirrhosis (n=7) and healthy donors (HD; n=10-14) were phenotypically characterized by multicolour flow cytometry. For this peptide/HLA-A*02-tetramers loaded with NY-ESO-1₁₅₇₋₁₆₅ and MAGE-A3₂₇₁₋₂₇₉ or peptide/HLA-A*03-tetramers loaded with Glypican-3₅₁₉₋₅₂₈ and MAGE-A1₉₆₋₁₀₄ were used.

Results: Our data revealed that the frequency of circulating TAA-specific CD8 T cells was significantly reduced in HCC patients compared to HD. Of note, similar to HCC patients, TAA-specific CD8 T cells were also detectable in diminished frequencies in patients with liver cirrhosis that is a frequent precancerous condition in HCC. Interestingly, the frequency of CD8 T cells targeting MAGE-derived epitopes dominated the CD8 T-cell repertoire specific for the tested TAA in all analyzed cohorts. Importantly, in HCC patients a subset of MAGE-specific CD8 T cells displayed a naïve-like phenotype indicating

inefficient recruitment to the effector T-cell pool. However, antigen-experienced MAGE-specific CD8 T cells in HCC patients showed an Eomes⁺T-bet^{hi} profile characteristic for functionally proficient effector T cells. This suggests a minor contribution of T-cell exhaustion to impaired MAGE-specific CD8 T-cell responses in the peripheral blood of HCC patients.

Conclusions: In sum, our results indicate that inefficient recruitment to the effector T-cell pool contributes to reduced frequencies of circulating TAA-specific CD8 T cells and thus to impairment of TAA-specific CD8 T-cell responses in HCC.

Disclosure of Interest: None Declared

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AS REGULATOR OF LIVER INFLAMMATION DURING HEPATOCARCINOGENESIS

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Introduction: Hepatocellular Carcinoma (HCC) is the most frequent liver cancer with an increasing incidence. During hepatocarcinogenesis there is overactivation of proliferation/survival signals. EGFR pathway plays essential roles during liver development and regeneration, but its specific role during liver tumorigenesis is not completely understood

Material and Methods: To unravel the role of the EGFR tyrosine kinase dependent functions in hepatocarcinogenesis, our group generated a novel transgenic mouse model expressing a hepatocyte specific truncated form of the human EGFR, which lacks its catalytic activity and acts as negative-dominant mutant (Δ EGFR). Mice were treated with diethyl-nitrosamine (DEN) to induce liver tumorigenesis. mRNA expression was analyzed by Real Time PCR. Proliferation was analyzed by Ki67 immunohistochemistry. Inflammation was analyzed by F4/80 immunostaining. In vitro analyses were performed in hepatocytes isolated from these animals and in the human HCC cell line Hep3B (where EGFR expression was targeted knock-down by shRNA technology)

Results: Δ EGFR mice showed a delay in the appearance of tumors, not strictly associated to decrease in proliferation once tumor is formed, but delay in the appearance of pre-neoplastic nodules. Interestingly, attenuation of the inflammatory process, associated to DEN-induced hepatocarcinogenesis, was observed. Our results indicate: 1) differences in the expression of Il-6 and Tnf- α in the tumor surrounding tissue; 2) higher Ccl2 expression in tumoral areas; and 3) differential Cxcl1 and Cxcr4/Cxcl12 axis expression in both non-tumoral and tumoral areas. In vitro experiments revealed that after EGFR activation, hepatocytes from Wild Type mice up-regulated Il-6, Tnf- α , Ccl2 and Cxcl1, but Δ EGFR hepatocytes did not. In the same line of evidence, Hep3B cells showed higher levels of CCL2, CXCL8 (human homolog Cxcl1) and CXCR4, a response that was not observed in Hep3B shEGFR cells.

Conclusions: Our data suggest that the catalytic activity of the EGFR in hepatocytes could play an important role during initial phases of hepatocarcinogenesis as regulator of liver inflammation. Further analysis must be required to elucidate how EGFR intracellular signaling regulates the expression of these cytokines and chemokines.

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Disclosure of Interest: None Declared

TUMOR-INITIATING CELLS AS CELLULAR DRIVERS OF ACQUIRED RESISTANCE DURING ANTI-ANGIOGENIC THERAPIES IN HEPATOCELLULAR CARCINOMA

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Introduction: Effective treatment strategy for advanced HCC is inhibition of neo-angiogenesis. However, development of chemoresistance is observed in the majority of patients. Compelling evidence suggest that tumor initiating cells (TICs) may contribute to the acquisition of resistance in many solid tumors, but their exact role in this process for HCC remains to be defined.

Aims: We evaluate importance of TICs in development of resistance and relapse formation after exposure to different anti-angiogenic therapies in HCC and define the concomitant adaptive molecular changes.

Material and Methods: Five HCC cell lines and one primary HCC isolate were exposed to sorafenib and sunitinib for total of 14 days. 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, such as EpCAM, CD133 and ABCG2, were assessed by qRT-PCR and flow cytometry. Whole transcriptome analyses were performed at different time points.

Results: Both treatment regimens effectively reduced oncogenic properties in all investigated HCC cells. Sustained anti-proliferative effect after treatments was observed in one cell line. In three other hepatoma lines initial treatment effect was subsequently followed by rapid re-growth thereby mimicking responses observed in patients. Two cell lines showed differential response to applied drugs, showing anti-proliferative effects to sorafenib, while relapse formation occurred after sunitinib treatments. While anti-oncogenic effects in sensitive cells were associated with significant reduction in sphere

forming capacity, TIC marker EpCAM as well as SP cells, resistant cells showed transient increased in TIC properties. Importantly, acquired resistance to both drugs uniformly developed in cell lines suggesting that common molecular mechanisms might be operative. Adaptive molecular changes involved signaling pathways associated to cell survival and proliferation (RAS, AKT, MYC) and angiogenesis (VEGFR, PDGFR). Also, resistant cells showed compensatory upregulation of key oncogenic molecules such as EGFR as well as multidrug resistance ABC transporters.

Conclusions: 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-oncogenic compensatory signaling pathways might be an effective therapeutic strategy to overcome resistance in HCC.

Disclosure of Interest: None Declared

ORTHOTOPIC HEPATOCELLULAR CARCINOMA MOUSE MODEL FOR INVESTIGATION OF TUMOR-SPECIFIC CD8 T CELL RESPONSES

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Introduction: Hepatocellular carcinoma (HCC) is a major health hazard and the second leading cause of cancer-related death worldwide, with a 5-year survival rate of 10% and increasing incidence.

Development of immunotherapies against liver cancer should consider the functional impairment of tumor-infiltrating lymphocytes (TILs), particularly CD8 T cells that show increased expression of co-inhibitory receptors on their surface and reduced cytokine production.

Aims: The aim was to develop an orthotopic HCC mouse model to investigate the transcriptomic changes in tumor-exhausted specific CD8 T cells.

Material and Methods: Generation of hepatic tumors *in vivo* was achieved using the “Sleeping beauty” (SB) transposon system. Liver hepatocyte transfection was conducted by hydrodynamic injection with plasmids encoding transposon-flanked oncogenes and genomic integration by SB transposase. Tumor formation was induced by plasmid combination of oncogenic NRAS (G12V), myristoylated AKT (myr-AKT) and a short hairpin against the mRNA of p53 (shRp53) to block the p53 apoptotic pathway. For the subsequent analysis of CD8 T cell responses the model antigen ovalbumin (OVA) was linked to oncogenic NRAS (G12V). The anti-tumor response was investigated by using adoptive transfer of OVA-specific CD8 T cells (OT-I). Isolation of specific CD8 T cells from liver tumors was carried out by flow cytometry sorting, followed by RNA isolation and transcriptome microarray analysis.

Results: Phenotype of OVA-specific CD8 T cells exhibited increased surface expression of coinhibitory receptors PD-1, TIM3, LAG3, 2B4, accompanied by low interferon

gamma and tumor necrosis factor alpha production and reduced degranulation capacity. The orthotopic liver cancer mouse model allowed the generation of whole transcriptome data from tumorexhausted specific CD8 T cells and revealed altered expressions of various genes involved in T cell trafficking, effector function, proliferation and apoptosis.

Conclusions: The generation of this liver cancer model in combination with the data of CD8 T cell transcriptome allowed us the identification of new molecular targets involved in T cell exhaustion.

Disclosure of Interest: None Declared

THE ROLE OF B CELLS IN NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND NASH-DRIVEN HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: Hepatocellular carcinoma(HCC) is the most common primary liver malignancy and second cause of cancer related death in humans. Obesity leads to metabolic syndrome, type 2 diabetes, steatosis and steatohepatitis, making HCC the fastest growing cancer in the U.S.A. and Europe. In a long-term choline-deficient high-fat diet(CD-HFD) mouse model we demonstrated that CD8+T and NKT cells interact with hepatocytes to induce NASH and eventually NASH-to-HCC transition. Recently, B cells are considered to be important players in innate and adaptive immune responses associated with metabolic diseases. From our published studies it has become apparent that the lymphocytes are crucial for NASH and NASH-induced HCC, however the exact role of B cells remains unclear. We hypothesized that B cells are important for CD8+ T cells activation either in the liver or in the periphery such as the lamina propria of the gastrointestinal tract.

Aims: Our aim is to decipher the role of B cells in the development of NASH and subsequent HCC and to highlight potential new therapeutic avenues.

Material and Methods: Long term CD-HFD diet was given to mice lacking mature B cells(JH^{-/-}) and mice that are lacking mature B cells apart from the IgA B cells in the lamina propria(μ MT). Mice were analysed through immunohistochemistry(IHC), flow cytometry(FACS) and other biochemical methods (e.g. western blot, qRT-PCR, ELISA).

Results: 61 CD-HFD JH^{-/-} mice showed lack of steatosis, liver inflammation and fibrosis. The CD-HFD JH^{-/-} livers contrary to CD-HFD C57BL/6 lacked an increase in activated CD8⁺ and NKT cells when compared with ND C57BL/6. Metabolic analyses with an intraperitoneal glucose tolerance test (IPGTT) revealed a normal glucose response in CD-HFD JH^{-/-} mice, contrary to CD-HFD C57BL/6. CD-HFD JH^{-/-} mice do not develop NASH or dietary HCC whereas in the CD-HFD C57BL/6 the tumor incidence is approximately 25%. 40 CD-HFD μ MT mice were analyzed. Their livers were steatotic and inflamed although they were not fibrotic. IHC revealed immune infiltration and activation in the liver whereas liver FACS analysis showed increase in CD8⁺ and NKT activation, similar to CD-HFD C57BL/6. Metabolic analyses with an IPGTT revealed an impaired glucose response in CD-HFD μ MT mice similar to CD-HFD C57BL/6 and contrary to ND C57BL/6. HCC developed, albeit with low frequency.

Conclusions: Our data suggest that gastrointestinal B cells contribute to hepatic and metabolomic changes under long-term CD-HFD leading to NASH and low level of NASH-to-HCC development.

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Disclosure of Interest: None Declared

POTENTIAL ULTRASTRUCTURE PREDICTING FACTORS FOR HEPATOCELLULAR CARCINOMA IN HCV INFECTED PATIENTS

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Introduction: Hepatitis C virus represents one of the rising cause of hepatocellular carcinoma (HCC). Although the early diagnosis of HCC is vital for successful curative treatment, the majority of lesions are diagnosed at irredeemable phase.

Aims: This work deals with a comparative ultrastructural study of experimentally gradually induced HCC, surgically resected HCC, and potential premalignant lesions from HCV-infected patients, with the prospect to detect cellular criteria denoting premalignant transformation.

Material and Methods: The materials of this study consisted of 63 liver biopsies processed for conventional electron microscopic examination. They include twenty liver core biopsies showing regenerative or cirrhotic nodules; twenty-eight specimens from the surgically resected HCC and the corresponding tumor free surgical margin from HCV infected patients; twelve liver samples from group of mice subjected to the gradual induction of HCC by weekly intra-peritoneal injection of Dimethylnitrosamine and sacrificed at the interval of four, eight, 16 weeks; and, three liver samples from a normal control group of mice.

Results: This work reports new ultrastructure observations which may be of value in predicting HCC and identifying the appropriate patient for surveillance. Among them, the detection of star shape enucleated cytoplasmic masses detached from progenitor cells or hepatocytes, frequent detection of bile ductules in between hepatocyte trabeculae,

Hering canal and hepatic stellate cells (HSCs) ; increase intercellular tight junctions; the frequent elucidation of hepatic progenitor cells and dividing intermediate hepatocytes; and different hepatocytes electron density.

Conclusions: This study has supported the speculation of the malignant potentiality of liver stem/progenitor cell and the impact of HSCs on this process.

Disclosure of Interest: None Declared

PATIENT-DERIVED CANCER CELLS RESEMBLE THE TRANSCRIPTOMIC AND GENOMIC LANDSCAPE OF DIVERSE HUMAN LIVER CANCERS

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Introduction: Primary liver cancers (PLCs) rank among the most lethal solid cancers worldwide due to a lack of effective biomarkers for early detection and limited treatment options in advanced stages. While cell lines have been of significant impact for cancer research over the last decades, development of in vitro models that closely recapitulate phenotypic and molecular diversity of the primary cancers is urgently needed to improve the outcome of patients.

Aims: Here we evaluate whether long-term cultures of patient-derived cell lines recapitulate phenotypic and molecular diversity of the primary cancers and if individualized therapeutic approach could be performed based on presence of specific actionable mutations.

Material and Methods: Long-term culture of 9 patient derived cancer cell lines of hepatocellular, cholangiocellular and metastatic origin were established using defined culture conditions. Morphological, histological and genomic characteristics of obtained cell lines and xenograft tumors were analyzed and compared to original tumors. Further, time course analyses of transcriptomic and genetic changes were performed using next-generation sequencing (NGS). Key oncogenic alterations were further identified by targeted NGS.

Results: The newly patient-derived cell lines fully resembled morphological features of the primary cancers in vitro and in vivo. Further, genomic alterations as well as transcriptome profiles of the lines showed high concordance with the primary tumors and remained stable for at least 30 passages. Integrative analyses identified key oncogenic alterations (e.g. TP53, KRAS, CTNNB1) characteristic for the primary cancers as well as several actionable mutations (e.g. MET, cKIT, JAK3) potentially amenable for individualized therapeutic approaches. Specific targeting of MET in the cell lines containing MET-mutation confirmed a superior response and sustained sensitivity to MET-inhibition in comparison to non-mutated control cells.

Conclusions: Together, our integrative analysis demonstrates that the use of newly established cell lines represents a sophisticated model to discover relevant molecular subgroups and to test drug sensitivity in precision medicine approaches.

Disclosure of Interest: None Declared

RECOMBINANT LYMPHOCYTIC CHORIOMENINGITIS VIRUS VECTORS CARRYING MODEL ANTIGEN ELICIT TUMOUR DIRECTED IMMUNE RESPONSES, INHIBIT TUMOUR PROGRESSION AND PROLONG MOUSE SURVIVAL

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Introduction: Tumours are one of the main causes of death worldwide. Immune therapy using immune checkpoint blockade has been proven to elongate survival of tumour patients. Still, an efficient therapy to stop tumour progression without disastrous side effects is still missing. Replication-deficient recombinant lymphocytic choriomeningitis virus vectors (rLCMV) carrying an antigen of interest have been shown to induce potent specific CD8 T cell immune responses in vivo with low vector directed immunity.

Aims: The aim of the project is to show if rLCMV can be used as a therapeutic approach to treat hepatocellular carcinoma (HCC).

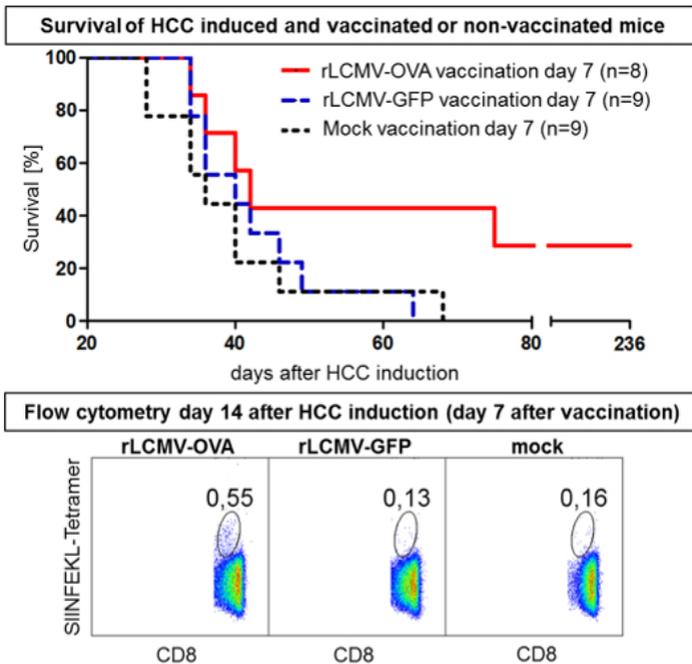
Material and Methods: Female C57BL/6J mice (6-8 wk.) were used for all experiments. rLCMV-vaccinations with 2×10^5 focus forming units (ffu) were injected intravenously. OVA-expressing HCC was generated by hydrodynamic injection (HDI) with transposon-flanked plasmids encoding ovalbumin (OVA) linked to NRasG12V, myrAkt1 and shRp53. Immune responses against the OVA-related peptide SIINFEKL were detected by flow cytometry using tetramer or intracellular cytokine staining. All results were generated under a Research Agreement with Hookipa Biotech, which provided the material.

Results: A single vaccination with rLCMV-OVA prior to HDI prevented the development of OVA-expressing HCC. The SIINFEKL-specific immune response was boosted by the HDI, indicated by the frequency of specific CD8 T cells and their phenotype (PD1, CD127, KLRG1, CD27). In contrast, for therapy of established tumours the beginning of treatment played a critical role. rLCMV-OVA injection 14 days after HDI failed to inhibit progression of tumours. However, a therapy which started 7 days after HDI was

able to prolong the survival of several mice (see figure). The magnitude of the tumour-specific immune response varied between individual mice and correlated with survival. The specific immune response of surviving mice was long-lived and functional, indicated by the expression of different cytokines by memory CD8 T cells. The control vector rLCMV-GFP (green fluorescent protein) failed to induce protective immune response against HCC-OVA.

Conclusions: rLCMV is a safe replication-deficient vector. Vaccinations lead to efficacious protective immune responses which are specific against antigen of interest. In mouse tumour models treatment with rLCMV encoding a tumour specific antigen resulted in delayed tumour progression and prolonged survival of mice. Therefore, rLCMV is a promising tool for future therapy of HCC.

Figure:



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ROLE OF THE TRANSFORMING GROWTH FACTOR BETA (TGF-BETA) IN HEPATOCELLULAR CARCINOMA CELL METABOLISM

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Introduction: TGF-beta plays a pro-tumorigenic role in liver tumors due to its capacity to induce epithelial-mesenchymal transition (EMT). Mesenchymal phenotype in hepatocellular carcinoma (HCC) is associated with high invasive capacity and resistance to conventional therapies. Whether a metabolic reprogramming takes place concomitant with the process of EMT, especially in HCC, has not been yet fully elucidated.

Aims: Here we aim to explore whether TGF-beta has a role in metabolic reprogramming by its ability to induce EMT in HCC cells.

Material and Methods: Cell metabolic status was determined in HCC cells by analysis of oxygen consumption, lactate production, glucose consumption and response to metabolic inhibitors. Metabolite levels were analyzed by metabolomics. Expression of genes involved in the glycolytic and tricarboxylic acid cycle pathway by Real-Time PCR.

Results: Mesenchymal HCC cell lines with high TGF-beta autocrine expression presented a more glycolytic phenotype than the epithelial HCC cells with low autocrine TGF-beta expression. Correspondingly, mesenchymal HCC cells were more sensitive to glycolytic inhibitors, such as 2-deoxyglucose and less sensitive to mitochondrial inhibitors, such as metformin. Moreover, mesenchymal cells presented a higher glutamine addiction and higher expression of glutamine metabolism-related genes, such as glutaminase 1 (GLS1) and glutamine transporters.

A stable TGF-beta Receptor I knock-down in mesenchymal SNU449 cells down-regulated the expression of mesenchymal genes and provoked a switch to a more oxidative phenotype, coincident with down regulation of GLS1 and glutamine transporters. On the other hand, chronic treatment with TGF-beta in the epithelial PLC/PRF5 cell line, induced up-regulation of mesenchymal genes, decreased oxidative metabolism and increased the expression of GLS1.

Conclusions: Autocrine activation of the TGF-beta pathway in mesenchymal HCC cells favors glycolysis to obtain energy and generates addiction to glutamine for cell growth. Glycolytic inhibitors, such as 2-deoxyglucose, and inhibitors of glutamine metabolism could be of benefit in HCC with mesenchymal characteristics. Contrary, inhibitors of OXPHOS, such as metformin, would be useful in HCC with epithelial characteristics.

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EFFECT OF NOVEL AKT INHIBITOR ARQ 751 AS SINGLE AGENT AND ITS COMBINATION WITH SORAFENIB ON HEPATOCELLULAR CARCINOMA IN A CIRRHOTIC RAT MODEL

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Introduction: AKT pathway is activated in almost half of HCC cases. Moreover, longer exposure to sorafenib, classical treatment of advanced liver cancer, often over-activates AKT pathway, leading to HCC resistance to sorafenib treatment. In our study, we investigated the efficacy of a novel allosteric AKT inhibitor ARQ 751, a second generation AKT inhibitor alone and combination with sorafenib.

Aims: To identify specific adverse effects that could be related to the background of cirrhosis, we used diethylnitrosamine (DEN)-induced cirrhotic rat model which faithfully reproduce human scenario of advanced HCC.

Material and Methods: 28 rats were treated weekly with intra-peritoneal injections of DEN during 14 weeks to obtain cirrhosis with fully developed HCC. After that, rats were randomized into 4 groups (n=7/group): control untreated, sorafenib, ARQ 751 or combination of sorafenib+ARQ 751. Animals were treated for 6 weeks, and tumor progression was followed by three MRI. Pathological analysis (tumor size and number) and immunohistochemistry was analysed in a double blind manner.

Results: Tumor progression in rat liver was significantly reduced with treatment of ARQ 751 as single agent (91.5%) compared to the control group (158.8%), but the greatest effect on tumor progression rate was observed in combination group (49.4%) compared to the control, ARQ 751 or sorafenib group (105.7%). Tumor size was significantly reduced in both ARQ 751 group (4.3 mm) and combination group (3.3 mm) compared to the control group (10 mm) or sorafenib group (6.5 mm). Similarly, mean number of tumors was significantly lower in ARQ 751 group (n=36.6) and combination group

(n=18.2) when compared to the control group (n=100.4) or sorafenib group (n=65.1). The decrease in tumor size was associated with a significant reduction in the proliferation of tumor cells (Ki67 staining) in either combination group or ARQ 751 group after compared to the control or sorafenib group. The results from Sirius red staining showed a decrease in fibrosis of animals treated with ARQ 751 alone or combination of ARQ 751 with sorafenib, in comparison to the control group. The observations on apoptosis, vessel normalization and liver immune system will be presented at the meeting.

Conclusions: Treatment of ARQ 751, a second generation AKT as single agent and combination with sorafenib exerted strong suppression in tumor progression and improved liver fibrosis. These results provide a strong rationale for testing ARQ 751 in clinical settings.

Disclosure of Interest: K. Keerthi : None Declared, Z. Macek Jilkova : None Declared, G. Roth : None Declared, G. Abbadessa: Employee: Conflict with: ArQule Inc, Y. Yu: Employee: Conflict with: ArQule Inc, P. Marche : None Declared, T. Decaens : None Declared.

TELOMERE LENGTH IN CHRONIC LIVER DISEASES SECONDARY TO HEPATITIS C AND ITS ASSOCIATION WITH THE SEVERITY OF LIVER DISEASE

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Introduction: Accelerated telomere loss has been proposed as a factor leading to end-stage organ failure in chronic diseases of high cellular turnover such as liver cirrhosis. Patients with the same risk factors, some develop rapidly for cirrhosis and hepatocellular carcinoma and others have a benign course. In the telomere diseases, mutations in telomerase genes responsible for telomere maintenance and repair lead to organ dysfunction, including bone marrow failure, liver cirrhosis, and pulmonary fibrosis, as well as to an increased risk of cancer.

Aims: To determine whether telomere length and telomerase gene mutations are associated to chronic liver diseases secondary to hepatitis C.

Material and Methods: We performed a retrospective analysis of liver biopsies and peripheral blood leukocytes from 96 HCV patients, and from 96 peripheral blood leukocytes from control subjects without liver disease. The liver biopsies were classified per severity of fibrosis (METAVIR classification). The genetic material was extracted per the protocol of Blood and Tissue DNA Extraction (Qiagen). Telomere length was measured by quantitative polymerase chain reaction (qPCR [RP1]). Genetic screening for mutational analysis (TERT and TERC) was obtained with a Polymerase Chain Reaction test. For statistical analysis was done by linear regression (Minitab 17 software) and Student's t-test (Prism Graph). $P < 0.05$ was considered to indicate a statistically significant difference.

Results: The mean age of HCV patients and control subjects were 48.6 (± 11.2) and 55 (± 7.9) years, respectively. Most HCV patients were male (75%). METAVIR classification showed: F1/2: 73% and F3/F4: 27%. The mean of telomere length of HCV patients with

METAVIR F1/F2, F3/F4 and control subjects were 4.97 Kb (± 1.0), 5.28Kb (± 0.95) and 4.97Kb (± 0.88), respectively. Therefore no significant association between telomere length and severity of liver disease was detected with these data ($p=0.78$). Mutation in the telomerase gene was found in one HCV patient (R979W). This mutation was described in patients with dyskeratosis congenita, associated with telomere dysfunction. Some polymorphisms were found only in HCV patients, TERT G677G/A699A in Exon 5 in genetics sequencing done so far.

Conclusions: These data suggest that the telomere length in HCV patients does not appear to have a role in the severity of liver fibrosis. Our preliminary data regarding telomerase mutations does not allow us to draw conclusion about their participation in liver fibrosis.

Disclosure of Interest: None Declared

MUCOSAL GUT MICROBIOTA COMPOSITION IN PATIENTS WITH HCV-RELATED HEPATOCELLULAR CARCINOMA

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Introduction: The outcome of HCV infection is not uniform, suggesting that multiple additional genetic and environmental factors can influence its progression to hepatocellular carcinoma (HCC). An alteration of gut microbiota has been reported in many human diseases including cirrhosis and its complications. Recent studies have also demonstrated that gut microbiota can promote chemically induced hepatocarcinogenesis in animal models.

Aims: Aim of this study was to characterize ileal and colonic mucosal gut microbiota of patients with HCV-related HCC.

Material and Methods: Healthy controls and patients with HCV infection were recruited among those who underwent colonoscopy for colorectal cancer screening. In all subjects multiple biopsies in the ileum and sigma were performed. We excluded patients with macroscopic or microscopic intestinal mucosal alteration, and on antibiotics, antivirals, lactulose, probiotics, proton-pump inhibitors and steroids in the last 2 months. The mucosal microbiota was quantified by a 2-step PCR-based protocol, following the Illumina 16S Metagenomic sequencing library preparation guidelines.

Results: The study population consisted of 13 healthy controls (HC) and 29 HCV positive patients of whom 6 with chronic hepatitis (CHC), 9 with cirrhosis (CIR) and 14

with HCC. A progressive reduction of Bacteroidetes and Firmicutes and a progressive increase of Proteobacteria at phylum level was observed from CHC to CIR and HCC. Within the Bacteroidetes phylum, the *Bacteroides vulgatus* progressively decreased in the ileum; within the Firmicutes phylum the *Prevotella copri* progressively decreased in both ileum and sigma; within the Proteobacteria phylum the *Escherichia coli* and *Shigella boydii* progressively increased in both ileum and sigma. Finally HCC patients in comparison to CIR patients showed in both sites higher levels of *Acidovorax LW1*, *Sutterella wadsworthensis*, *Streptococcus termophilus*, *Lysobacter termophilus* and *Streptococcus salivarius* and lower levels of *Haemophilus parahaemolyticus*.

Conclusions: The mucosal gut microbiota composition progressively changed from patients with CHC to CIR and HCC providing biological plausibility for a role of gut microbes in the progression of HCV-related liver disease. Nevertheless, further studies to elucidate the causality or consequence of these variations are warranted.

Disclosure of Interest: None Declared

P05.08

TRANSCRIPTIONAL REGULATORY NETWORKS IN HEPATITIS C VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

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Introduction: HCV epidemic affects an estimated 160 million individuals worldwide.

Aims: Understanding the transcriptional regulatory elements that influence the progression of liver disease in the presence of HCV infection is thereby crucial for diagnostic and therapeutic purposes.

Material and Methods: In this study, 124 microarray samples were assessed in order to determine differentially expressed genes for 4 tissue types/conditions (normal, cirrhosis, cirrhosis HCC, and HCC). Differentially expressed genes were assessed for their functional clustering and annotated with their potential transcription factors and miRNAs; transcriptional regulatory networks were constructed for visualization.

Results: In this study 12 transcription factors were found to have high expression patterns amongst all 6 pairwise comparisons and these transcription factors also highlight the conditions of the liver as it progresses through angiogenesis, hepatic steatosis, and the induction of cancer. Each liver condition was found to have its own signature miRNA expression pattern; yet it was observed in the 6 pairwise comparisons 14 miRNAs were found to have high expression patterns in all 6 pairwise comparisons.

Conclusions: Based on the findings of this study (and a systematic analysis of many studies) it can be concluded there are specific transcription factors regulating the condition of the liver transitionally; while the downregulation of miRNAs' expression through each stage stresses the imbalance that occurs in cellular homeostasis. Therefore, in order to stop the progression of HCV induced HCC there must be interference in the transcriptional regulation that disrupts cellular homeostasis.

Disclosure of Interest: None Declared

ELEVATED LEVELS OF CIRCULATING OSTEOPONTIN IN PATIENTS WITH CHOLANGIOCARCINOMA PREDICT POOR SURVIVAL AFTER TUMOR RESECTION

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Introduction: Cholangiocarcinoma (CCA) represents a primary hepatic malignancy with a global rise in incidence and a still very high mortality. Surgical treatment has remained the only potentially curative treatment option, but it is still unclear which patients benefit most from extended liver surgery, highlighting the need for new preoperative stratification strategies. Osteopontin is a secreted extracellular glyco-phosphoprotein that has been associated with inflammation, metabolic disorders and cancer.

Aims: We examined the potential of circulating osteopontin levels as a diagnostic or prognostic biomarker in patients with CCA that underwent extended liver surgery.

Material and Methods: Osteopontin (SPP1) expression levels were analyzed in human and murine CCA tumor samples, using qPCR and IHC. Osteopontin serum concentrations were measured by ELISA in two cohorts consisting of 107 patients with cholangiocarcinoma undergoing tumor resection as well as 55 healthy controls. Results were correlated with clinical data.

Results: Osteopontin was significantly up-regulated in tumor tissue of patients with CCA and mice that underwent an experimental CCA model. Serum levels of osteopontin were elevated in patients with cholangiocarcinoma compared to healthy controls and patients with primary sclerosing cholangitis (PSC). Moreover, pre- and post-operative elevations of osteopontin showed a striking association with poor postoperative survival (Fig. 1).

Conclusions: Serum osteopontin levels represent a promising diagnostic and prognostic biomarker in patients with resectable CCA that might be helpful to guide preoperative treatment decisions and to identify patients that particularly benefit from extended liver

surgery.

Figure:

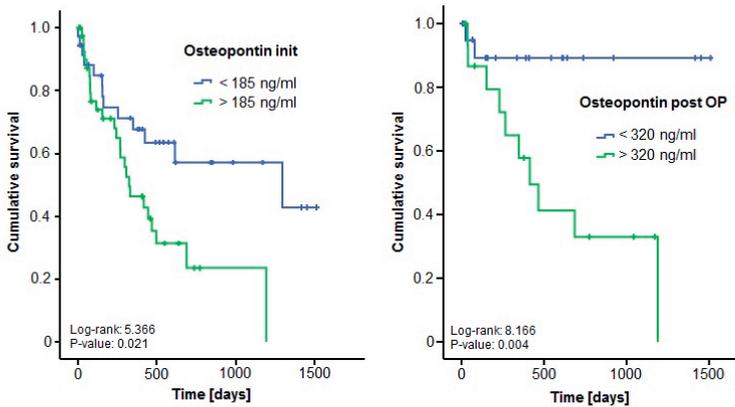


Fig. 1: Pre- and post-operative osteopontin serum concentrations predict patients' survival. Cox regression and Kaplan-Meier curve analysis, using an optimal cut-off value determined by Youden-index method, revealed a significantly impaired long term survival for CCA patients with pre- and post-operative serum osteopontin concentration of >185 ng/ml and >320 ng/ml, respectively.

Disclosure of Interest: None Declared

PRECLINICAL ANALYSIS OF SANGLIFEHRIN-BASED CYCLOPHILIN INHIBITORS SHOWING POTENTIAL FOR TREATMENT OF HEPATOCELLULAR CARCINOMA

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Introduction: It has long been known that cyclophilins are overexpressed in a number of cancers and that cyclophilins may be determinant for malignant transformation and metastasis. However, despite this prevalence of literature suggesting the relevance of cyclophilins in cancer, little evidence suggest that any of the many potent cyclophilin inhibitors are active against cancer in vivo.

Sanglifehrin A (SfA) and its natural congeners belong to a class of mixed non-ribosomal peptide/polyketide potent cyclophilin inhibitors and form a distinct chemical class from the more commonly studied ciclosporin-related compounds, such as Alisporivir and SCY-635.

Aims: The aim of this study was to investigate the antiproliferative effect of sanglifehrin-based cyclophilin inhibitors (Sf-cyp inhibitors) on cancer cell lines and their potential utility in the treatment of hepatocellular carcinoma (HCC).

Material and Methods: In vitro analysis of antiproliferative effects of Sf-cyp inhibitors and ciclosporin-based cyclophilin inhibitors, with a focus on cancer cell lines and non-malignant cells and comparative studies with standard of care drugs such as sorafenib.

Results: Sf-cyp inhibitors exhibited half-maximal growth inhibition of HCC cell lines in the nanomolar range in contrast to ciclosporin-based inhibitors which required micromolar concentrations to achieve similar effects. Inhibition of HCC growth was observed at the same concentrations as required for cyclophilin inhibition, measured as release of cyclophilin B (cypB) into the medium. In a panel of cancer-derived cell lines of different origin, HCC cell lines were very sensitive requiring nanomolar concentrations for growth

inhibition by the Sf-cyp inhibitors. Untransformed cell lines such as primary liver cells and fibroblasts were not affected. In comparison with sorafenib, the Sf-cyp inhibitors were more potent, requiring a 10-fold lower concentration to achieve half-maximal inhibition of growth.

Conclusions: Sf-cyp inhibitors may represent an intriguing addition to the options for treatment of HCC on the basis of drug-like properties, high liver exposure after oral administration and potent antiproliferative effects.

Disclosure of Interest: M. Tavecchio: Stockholder: Conflict with: NeuroVive Pharmaceutical AB, Employee: Conflict with: NeuroVive Pharmaceutical AB, A. Grönberg: Stockholder: Conflict with: NeuroVive Pharmaceutical AB, Employee: Conflict with: NeuroVive Pharmaceutical AB, E. Elmér: Stockholder: Conflict with: NeuroVive Pharmaceutical AB, Employee: Conflict with: NeuroVive Pharmaceutical AB, P. Gally: Consultant: Conflict with: NeuroVive Pharmaceutical AB, M. Gregory: Consultant: Conflict with: NeuroVive Pharmaceutical AB, Stockholder: Conflict with: NeuroVive Pharmaceutical AB, S. Moss: Consultant: Conflict with: NeuroVive Pharmaceutical AB, Stockholder: Conflict with: NeuroVive Pharmaceutical AB, M. Hansson: Stockholder: Conflict with: NeuroVive Pharmaceutical AB, Employee: Conflict with: NeuroVive Pharmaceutical AB.

CIRCULATING TUMOUR CELLS TO STRATIFY THERAPY FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA – A FOCUS ON DNA-PK

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Introduction: DNA-Protein Kinase (DNA-PK) promotes DNA damage repair & is both a candidate driver of hepatocarcinogenesis & mechanism of therapy resistance – its upregulation predicting a shorter time to radiological progression following arterial chemoembolization (TACE)[1]. Having developed a method enabling detection of circulating tumor cells (CTCs) in 65% of patients with HCC [2,3], showing associations with stage & prognosis [3], we have characterized DNA-PK expression in CTC.

Aims: To explore stratification biomarkers in CTC as an alternative to tissue biopsy.

Material and Methods: Blood samples (4ml) from 47 HCC patients underwent red cell lysis, CD45+ve white cell & platelet depletion. Samples were processed with the Imagemstream[®] MKII & images analysed using IDEAS[®] software. CTC detection was on the basis of size, DNA content and lack of CD45 expression [3]. CTC were further characterized with immunofluorescent antibodies – CK, DNA-PK, CD45 & DAPI. Clinical associations were explored.

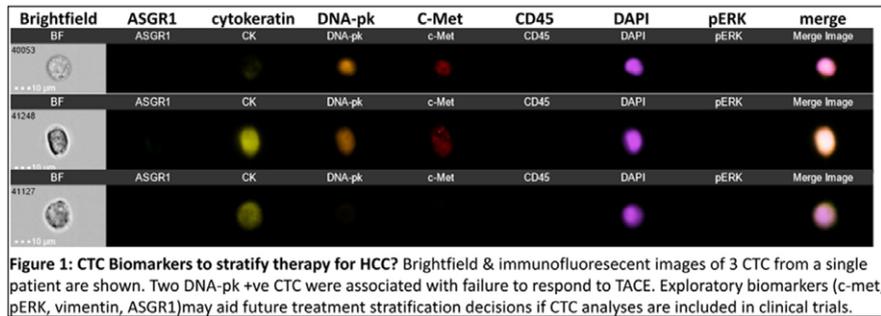
Results: CTC were detected in 32/47(68%) of patients. Response to treatment was documented in 23/24 (OLTx 1; resection 2; ablation 3; TACE 13; medical therapy 5), with time to radiological progression (TTP) documented in 34. As described previously, CTC >1/4ml (26/47) was associated with shorter TTP & survival. Neither presence nor number of CTC predicted response to treatment. In 15/47 (32%) patients, DNA-PK +ve CTC were detected. Although there were no significant differences in age, sex, underlying etiology, liver function, tumor stage or treatment, the presence of DNA-PK CTC was highly significantly associated with poor treatment response (Complete Response/Partial Response/Stable Disease/Progressive Disease: 0/5/0/5 vs 10/1/2/1 in absent group, $p < 0.001$, Chi-square; locoregional subgroup 0/5/0/2 vs 7/1/1/0; $p < 0.001$). Overall,

DNA-PK +ve CTC were associated with shorter TTP (median 7 months vs >30months, $p=0.012$). Survival studies are ongoing, but in those receiving locoregional therapy, 9 without DNA-PK CTC were alive, while 2/7 with DNA-PK CTC had died ($p=0.043$).

Conclusions: This pilot study suggests that DNA-PK +ve CTC predict a lack of response to locoregional therapy, shorter TTP & shorter survival. If validated, medical therapy or clinical trials – possibly combination studies with a DNA-PK inhibitor – should be considered for these patients, in preference to 1st line locoregional therapy (Figure 1).

1. Cornell et al. (2015) Clin Cancer Res
2. Dent et al (2016) In J Cancer
3. Ogle et al. (2016) J Hep

Figure:



ePOSTER ABSTRACTS

Disclosure of Interest: None Declared

INTEGRATED ANALYSIS OF EXOSOMAL MICRORNA, GENE AND PATHWAY REGULATORY NETWORKS IN FIBROSIS AND HEPATOCARCINOGENESIS

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Introduction: Exosomes are subcellular vesicles secreted from cell plasma membrane that have altered secretion and phenotype in cancer patients. Exosomes contain ribonucleic acids (RNA) including microRNAs (miRNA) that regulate gene expression. Hepatocellular carcinoma (HCC) is a hypervascular neoplasm with high levels of apoptosis and necrosis; to date there is a paucity of early diagnostic and prognostic biomarkers for HCC. We investigated the utility of circulating exosomes as plasma cancer biomarker in HCC.

Aims: An integrated analysis was performed to examine alterations in exosome secretion, dysregulation of their miRNA content and downstream pathways in HCC.

Material and Methods: Exosomes were isolated from human plasma using differential centrifugation and enumerated using NanoSight. Surface protein expression was characterized with flow cytometric analysis. Total RNA was extracted from patients with hepatitis without cirrhosis, chronic liver disease with cirrhosis, and HCC. miRNA expression was measured with the nCounter system (NanoString) and OpenArray real-time PCR platform. Differentially expressed miRNA were selected, and target genes and their signalling pathways were predicted using established bioinformatics algorithms.

Results: Plasma exosome concentration in HCC patients was significantly increased by 3.4 fold compared with normal controls ($p < 0.001$). Flow cytometry demonstrated a distinct subpopulation of HCC-related plasma exosomes in HCC. miRNA expression profiles were significantly different in exosomes of HCC patients compared with miRNA profile in cirrhosis and normal. Expression patterns for several miRNA including miR-320e, miR-146b, miR-376a, miR-192 and miR-118, were consistent across different technologies. Pathway analysis demonstrated that HCC exosomes, when compared to normal, contain differentially expressed miRNA targeting genes involved in the p53 ($p < 0.0001$) and PI3K/akt/mTOR ($p < 0.0001$) pathways. When comparing HCC with cirrhosis, significant



differential expression of miRNAs affecting genes involved in the dysregulation of AKT/JAK2/STAT3 ($p < 0.0001$) and Wnt/CTNNB1 ($p < 0.0001$) pathways was observed.

Conclusions: Exosome secretion is increased in patients with hepatocellular carcinoma and have a distinct phenotype on flow cytometry. Major carcinogenesis pathways are implicated in the differentially expressed miRNA gene signature of exosomes arising from HCC. These may have prognostic and therapeutic implications for genomics-guided management of HCC.

Disclosure of Interest: None Declared

LY3039478 A NOTCH GAMMA-SECRETASE INHIBITOR BLOCKS CHOLANGIOCARCINOMA GROWTH IN A PATIENT-DERIVED XENOGRIFT (PDX) MODEL

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Introduction: Recent studies have shown that the constitutive activation of Notch signaling is associated with the development of cholangiocarcinoma (CCA). Activation of the Notch receptor follows the proteolysis by the gamma-secretase enzyme that releases the active Notch intracellular domain (NICD) in the cytosol. NICD then translocated to the nucleus and modulates the expression of several target genes that drive carcinogenesis. LY3039478 is an inhibitor of the gamma-secretase complex that induces a reduction of the NICD downstream biological effects.

Aims: Our goal is to investigate the effectiveness of LY3039478 against CCA tumoral progression.

Material and Methods: HCCT, KMCHA-1, TFK-1, MZ-CHA1 and EGI-1 CCA cell lines were treated with LY3039478 for 24 and 48h at different concentrations. Notch signaling pathway protein expression was studied by Western Blot analysis and Immunohistochemistry. A patient derived xenograft (PDX) model was established and demonstrated to match the original tissue by immunophenotypical and gene expression analysis. Mice were treated with LY3039478 at 8mg/Kg by gavage daily.

Results: LY3039478 inhibits Notch signaling both in vitro and in vivo. In the CCA cell lines treated, low drug concentrations (10 μ M – 10 nM) decreased the levels of NICD expression. The immunostaining and microarray assay confirm the same protein expression and gene expression profiles in patient tissue and PDX tissue. Furthermore, in the PDX animals, LY3039478 significantly (p<0.005) reduces CCA tumoral growth compared to controls.



Conclusions: Here we report that inhibiting gamma-secretase activity results in a reduction of tumor progression, and that these preclinical experimental models can predict the clinical activity of LY3039478 in human CCA.

Disclosure of Interest: None Declared

IMPORTANCE OF GENETIC VARIABILITY OF HCV IN THE VIRAL HLA AG UNION AND ITS RELATIONSHIP WITH THE IMMUNE RESPONSE. RATIONAL BASES FOR OBTAINING A THERAPEUTIC VACCINE

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Introduction: Previous data from our research group show that patients with HCV genotype 1 expressing the DQB1 * 0301 allele have a combined response probability of 69%, while the remaining 31% do not respond to it, probably due to That the HCV immunodominant epitope (IE) against the DQB1 * 0301 allele is mutated, preventing its proper binding to the HLA molecule by inhibiting the CD4 + immune response.

Material and Methods: HCV EI (NS31253-1272) of 37 patients (21 with Sustained Virological Response, RVS, and 16 non-SVRs (6 relapsers, and 10 non-responders) were analyzed by pyrosequencing) determining the number of quasispecies / sample, number Mutations / quasispecies and the number of polymorphic sites.

In vitro cultures were also determined by flow cytometry if non-mutated EI (wild synthetic peptide; PS) is able to generate CD4 + proliferation in DQB1 * 0301 + patients, whereas a synthetic mutated peptide (PM) Is not able to generate such a response.

Results: In the pyrosequencing study, applying the quality controls, we found 34 different quasispecies. The number of quasi- variants (SVR: 0.48 ± 0.1 , non-SVR: 1.24 ± 0.3), mean number of quasi-species (SVR: 2.19 ± 0.2 , non-SVR: 4.75 ± 1.1 , $P > 0.05$), $P = 0.01$), and lower number of polymorphic sites (RVS: 1.43 ± 0.3 , non-RVS: 4.56 ± 1 , $P = 0.02$) than non-SVRs. In the study of the M1 positions most susceptible to mutation and their possible relation to the response, we observed three positions only mutated in patients with non-SVR, 5 (L / P) and 7 (L / P) and 15 (L / S) (Non-RVS = 4/16, RVS: 0/21, $p = 0.02$). In the in vitro study, we observed that in 4/7 patients (group 1) the CD4 + proliferation obtained with PS was higher than that obtained with the CN and with



the PM (PS: 2.74 ± 0.62 , CN: 0.92 ± 0.3 , MW: 1.15 ± 0.52 , $P = 0.039$). However, in the remaining 3/7 (group 2) we did not observe this pattern (PS: 4.37 ± 2.35 , CN: 3.55 ± 0.74 , PM: 4.06 ± 2.32 , $P = 0.7$). There are significant differences in the mean values between the CNs of both groups, so that group 2 presents a mean of CN higher than group 1 (3.55 ± 0.7 vs 0.92 ± 0.3 ; $P = 0.016$). This could explain that group 2 having such a high basal proliferation is not likely to increase CD4 + proliferation with peptide stimulation.

Conclusions: HLA-DQB1 * 0301 + patients showing a high genetic variability in HCI (NS31253-1272), have a lower rate of SVR due to a lower CD4 + proliferation caused by an incorrect viral HLA-Ag binding. Thus EI are potential candidates for the design of synthetic vaccines.

Disclosure of Interest: None Declared

DIFFERENTIAL EFFECT OF TRANSFORMING GROWTH FACTOR BETA FAMILY MEMBERS ON TUMOR INITIATING AND INVASIVE PROPERTIES IN PRIMARY LIVER CANCER

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Introduction: Transforming Growth Factor Beta (TGF-beta) is a major signaling pathway of the liver with pleiotropic effects on different processes and cell types. During cancer progression while TGF-beta signaling exerts tumor suppressor effects at pre-neoplastic and early tumor stages, cytostatic effects of TGF-beta are often lost in progressed stages due to (epi-) genetic disruption of several members of the signaling pathway. This progressed stage is characterized by activation of a "late TGF-beta signature" which promotes the phenotypic switch from tumor suppressor to promoter. Consequently, cancer cells display an epithelial-mesenchymal-transition (EMT) phenotype by acquiring invasive and prometastatic properties.

Material and Methods: Several established and newly generated primary hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) cell lines were exposed to TGF-beta1 and TGF-beta2 (1 ng/ml and 5 ng/ml) for 72 hr. Effect of TGF-beta on tumor-initiating potential was estimated by side population (SP) approach and sphere formation assays. Further, selected stemness markers were evaluated using flow cytometry. Invasive and migratory properties were assessed following the treatment and molecular changes were estimated by qRT-PCR.

Results: Treatment with TGF-beta1/-2 led to a significant reduction in colony and spheroid forming ability in all investigated cell lines. Consistent with the reduced in vitro tumorigenicity and spherogenicity, a drastic effect of TGF-beta on the putative tumor-initiating cell population was observed, reflected by the reduction in the frequency of the side population and down-regulation of stemness markers CD133 and epithelial cell



adhesion molecule (EpCAM). Interestingly, treatment with TGF-beta1 led to a significant increase in the expression of CD44 as well as activation of established EMT markers. Accordingly, a significant downregulation of E-Cadherin paralleled by upregulation in SNAIL transcription factor was observed. Consequently, enhanced migratory and invasive properties of HCC and iCCA were observed evidenced by increased wound healing and invasion.

Conclusions: In conclusion, we here confirm the cytostatic effect of TGF-beta1 and TGF-beta2 by reducing the frequency of stem-like cancer cells in both HCC and iCCA. Further, TGF-beta1 seems to be an important regulator of EMT as well as invasive properties in progressed primary liver cancers. These context-dependent dichotomic effects should be considered in TGF-beta based therapeutic approaches.

Disclosure of Interest: None Declared

UP-REGULATION OF c/EBP α BY SMALL ACTIVATING RNA SIGNIFICANTLY INCREASES POST PARTIAL HEPATECTOMY SURVIVAL IN DEN INDUCED CIRRHOTIC RATS

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Introduction: 80% of hepatocellular carcinoma patients are ineligible for liver resection as underlying cirrhosis renders insufficient future remnant liver volume. C/EBP α is a liver enriched transcription factor known to regulate the balance of cell proliferation and differentiation. We have previously demonstrated that up-regulation of C/EBP α in liver improves survival in chronic liver disease.

Aims: In this study we investigate in vivo the potential for C/EBP α up-regulation to improve post partial hepatectomy survival in cirrhotic rats.

Material and Methods: Cirrhosis was induced in Wistar rats by oral feeding of DEN for 9 weeks. At week 9 rats (n=10) were randomised and treated thrice per week i.v. with PBS, non-specific control siRNA or CEBPA saRNA. At week 10 animals underwent a 70% partial hepatectomy. In the neo-adjuvant study animals received treatment in week 9 only and were sacrificed at week 11. In the adjuvant study animals received treatment in both weeks 9 and 10 and were sacrificed at week 15.

Results: In the neo-adjuvant study animals treated with CEBPA saRNA had significantly higher week 11 survival (100%) vs non-specific RNA control (50%). At sacrifice on week 11 CEBPA saRNA treated animals had significantly higher liver regeneration rate than control, as well as significantly higher liver staining for proliferation markers BrdU, PCNA and Ki-67. In the adjuvant study CEBPA saRNA treated animals had significantly higher



week 15 survival (60%) vs non specific RNA control (10%). On sacrifice at week 15 CEBPA saRNA treated animals had significantly higher serum albumin and total serum bilirubin.

Conclusions: Up-regulation of CEBPA by small activating was demonstrated to increase liver regeneration in cirrhotic rats post partial hepatectomy which increased liver function as well as survival. The results suggest that up-regulation of C/EBPa may be promising adjuvant or neo-adjuvant therapeutic strategy for cirrhotic HCC patients undergoing or otherwise

Disclosure of Interest: None Declared

AKT INHIBITOR ARQ 092 AND SORAFENIB ADDITIVELY INHIBIT PROGRESSION OF HEPATOCELLULAR CARCINOMA AND IMPROVE IMMUNE SYSTEM IN CIRRHOTIC RAT MODEL

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Introduction: Longer exposure to classical treatment of advanced hepatocellular carcinoma (HCC), sorafenib, often over-activates AKT pathway, leading to HCC resistance. Moreover, AKT pathway itself is activated in almost half of HCC cases.

Aims: We investigated the efficacy of combination of sorafenib with allosteric Akt inhibitor ARQ 092 in a diethylnitrosamine (DEN)-induced cirrhotic rat model with HCC.

Material and Methods: 28 rats were DEN-injured during 14 weeks to obtain cirrhosis with fully developed HCC, then randomized into 4 groups: control, sorafenib, ARQ 092 or combination of ARQ 092+sorafenib; (n=7/group) and treated for 6 weeks. Tumor progression was followed by MRI every 3 weeks. Pathological analysis and immunohistochemistry were blindly analysed. Flow cytometry analyses, RT-PCR, and western-blot were performed.

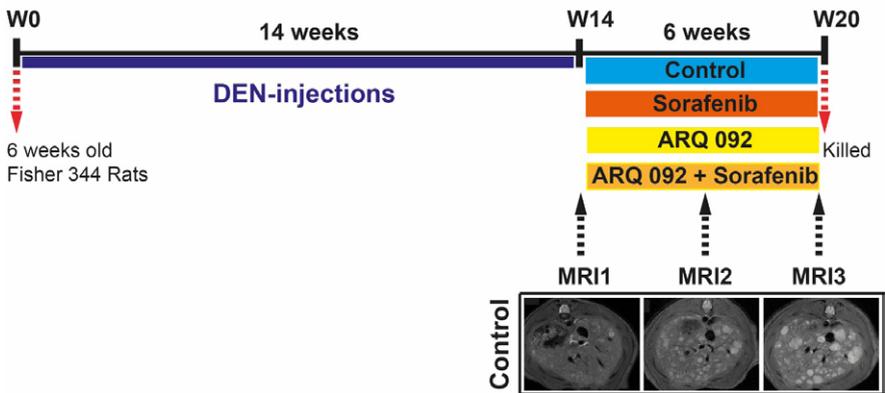
Results: Tumor progression was significantly reduced by combination treatment (53 %) compared to the control (158 %; p<0.0001) sorafenib (106 %; p=0.006) or ARQ 092 group (105 %; p=0.010). Mean number of tumors was lower in combination group (n=21.2) when compared to the control (n=100.4; p<0.0001) or sorafenib group (n=69.2; p=0.002). Similarly, tumor mean size was significantly reduced in combination group (3.1 mm) compared to the control group (9.9 mm; p<0.0001), sorafenib group (6.4 mm; p=0.019) or ARQ 092 group (6.3 mm; p=0.031). Tumor decrease was associated with a significant reduction in tumor cell proliferation and an increased apoptosis. CD34

staining showed reduced angiogenesis in combination group compared to the control ($p < 0.0001$) or sorafenib group ($p < 0.0001$) with significantly decreased HIF expression in tumor tissues. The results from Sirius red staining showed a decrease in fibrosis of animals treated with ARQ 092 alone ($p = 0.0004$) or with combination of ARQ 092 and sorafenib ($p = 0.0001$), accompanied with strong downregulation of TGF β , Collagen1 and ACTA1 expression levels. Granulocyte/T-cells ratio in blood was decreased in all treated groups compared to the control group and accumulation of neutrophils in liver tissue was significantly reduced. Western blot analysis of liver tissues showed a significant reduction of phosphorylation of AKT and its downstream signalling actors mTOR and S6K1 in both ARQ 092 and combination groups.

Conclusions: Combination of ARQ 092 and sorafenib exerted additive effect in controlling tumor progression and improved immune response in blood and liver. Our results confirm the importance of targeting AKT in HCC.

Figure:

Treatment Protocol



Disclosure of Interest: Z. Macek Jilkova: : None Declared, A. Zeybek Kuyucu: : None Declared, K. Kurma: : None Declared, S. T. Ahmad Pour: : None Declared, G. Roth: : None Declared, G. Abbadessa: Employee: Conflict with: ArQule Inc, Y. Yu: Employee: Conflict with: ArQule Inc, V. Leroy: : None Declared, P. Marche: : None Declared, T. Decaens: : None Declared

EFFECT OF RECK GENE POLYMORPHISMS ON HEPATOCELLULAR CARCINOMA SUSCEPTIBILITY AND PROGRESSION IN EGYPTIAN PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide. In Egypt, HCC was reported to account for about 4.7% of chronic liver disease (CLD) patients. The reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) gene is a transformation suppressor gene against activated ras oncogenes. RECK gene may play a role in carcinogenesis and metastasis.

Aims: To analyze the association between RECK gene single nucleotide polymorphisms (SNPs) and hepatocellular carcinoma susceptibility and progression among the Egyptian patients.

Material and Methods: RECK gene rs16932912 SNP and rs11788747 SNP were estimated using real-time PCR technique in 100 adult Egyptian patients with HCC (50 patients have tumor size > 4 cm and 50patients with tumor size ≤ 4 cm and 200 healthy control subjects

Results: Rs16932912 polymorphism on HCC:

There was significant decrease in the frequency of the homozygous GG genotype of rs16932912 polymorphism in studied HCC cases ≤ 4cm as compared to that of control group. There was non-significant difference in the frequency of the homozygous GG genotype, homozygous mutant AA genotype, heterozygous mutant AG genotype and the risk value of the (AG+AA) genotype in studied HCC cases with tumor size > 4 cm as compared to that of control group.

Rs11788747polymorphism on HCC:

There was non-significant difference in the frequency of the heterozygous mutant AG genotype, homozygous AA genotype, homozygous mutant GG genotype and the risk value of (AG+AA) genotype for patients with HCC tumor size size > 4 cm and tumor size ≤ 4 cm as compared to that of control group.



Conclusions: RECK gene may play a role in HCC carcinogenesis and metastasis. More studies are needed to investigate the different RECK gene polymorphisms and their biological function in HCC Egyptian patients.

Disclosure of Interest: None Declared

THROMBIN GENERATION TEST AND RISK OF PORTAL VEIN THROMBOSIS IN PATIENTS WITH LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA.

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Introduction: Studies that explore the pro-thrombotic state associated with neoplastic disease and its correlation with the risk of developing portal vein thrombosis (PVT) in patients with hepatocellular carcinoma (HCC) are lacking.

Aims: The aim of the present study was to evaluate the pro-thrombotic role of HCC in cirrhotic patients as well as to correlate coagulation profile of these patients with PVT incidence.

Material and Methods: Cirrhotic patients with and without HCC were prospectively enrolled in the study. All patients underwent platelet count, determination of pro and anticoagulant factors, thrombination test (TG) [with and without thrombomodulin (TM)]. During follow-up, PVT onset in both patients with and without HCC was recorded.

Results: 76 cirrhotic patients, 41 with HCC and 35 without HCC, were enrolled. Forty-eight healthy volunteers were included as the control group. Volume of active HCC was $>5 \text{ cm}^3$ in 22 patients. Levels of pro and anticoagulation factors were similar between patients with and without HCC, but fibrinogen was increased in HCC patients with active volume $>5 \text{ cm}^3$ HCC compared to those with $<5 \text{ cm}^3$ HCC bulk ($350 \pm 124 \text{ mg/dL}$ vs $237 \pm 100 \text{ mg/dL}$) and to cirrhotics without HCC ($261 \pm 126 \text{ mg/dL}$) ($p=0,006$). Platelet count was significantly increased in HCC patients compared to non-HCC patients. Endogenous thrombin potential (ETP) and lag time of TG were higher ($p<0.001$) and lower ($p<0.005$) in HCC patients in comparison to patients without HCC, respectively. Patients with HCC $>5 \text{ cm}^3$ showed a significant increase of ETP when compared to HCC $<5 \text{ cm}^3$ ($p<0.01$). Correlation between ETP and fibrinogen plasmatic level was found in HCC ($r=0.730$,

p=0,001). One-year-incidence of PVT was 24% (10/41) and 11% (4/35) in HCC and non-HCC patients, respectively (p=0,04). In the HCC group, 5/12 PVT occurred in patients in Child Class A. ETP ratio in HCC patients was associated with PVT risk at multivariate analysis (p<0.001).

Conclusions: Cirrhotic patients with HCC demonstrate a pro-thrombotic hemostatic imbalance resulting in an increased risk of PVT development. Thrombin-generation test seems to be a sensitive method to identify hypercoagulability, which would otherwise be undetected by routine laboratory testing. Further investigations are needed to determine whether patients with HCC should receive prophylactic anticoagulation for PVT prevention.

Disclosure of Interest: None Declared

WHOLE-EXOME SEQUENCING IN BRAZILIAN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Genetic alterations in hepatocarcinogenesis are important events in the development and progression of hepatocellular carcinoma (HCC). Emerging technologies to perform genomic analyses have been important tools to improve tumor characterization.

Aims: The aim of this study was to evaluate the whole-exome sequencing in subjects with chronic hepatitis C and hepatocellular carcinoma.

Material and Methods: We evaluated the whole-exome sequencing in six patients with hepatocellular carcinoma (HCC) and cirrhosis due to chronic hepatitis C (CHC), and in two subjects with CHC, but without liver cancer (one with mild fibrosis and other with cirrhosis). The exome capture was performed using the Nextera Exome Rapid Capture kit (Illumina Inc., San Diego, CA, USA). Then, the captured DNA was sequenced on Illumina Genome Analyzer IIx (GAIIx), based on the Solexa or SBS technology (Sequencing-by-Synthesis) using the TruSeq SBS kit v5 (Illumina Inc., San Diego, CA, USA), configured to 2x75bp paired-end. The reads were analyzed for quality, and those with phred-score higher than 30 were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (BWA, version 0.7.12). The variants were called with the Genome Analysis Toolkit (GATK, version 3.5) and annotated with Spneff (version 4.2).

Results: The whole-exome sequencing of all samples generated 135,699 variants (one variant for each 22,388 bases). We found 15,449 somatic mutations, of which 6,806 were in the 3'untranslated region (UTR); 2,929 were missense mutations; 2,803 silent mutations; and 1,128 were in the 5'UTR. The most mutated genes were MUC4 (n=76); ZNF717 (n=65); HLA-DRB1 (n=38); and PDE4DIP (n=36). When evaluating the HCC samples, the most mutated genes were RSPH3 (n=3; one missense mutation and 2 silent); and NOTCH4 (n=3; one missense mutation and 2 silent). The variants MORN1 (intron), DUSP28 (5'UTR) and TP63 (3'UTR) were observed only in HCC patients.



Conclusions: These are the preliminary results of a pilot study evolving whole-exome sequencing in Brazilian HCC patients. At this point, we could identify some genes of interest in this group of subjects, but more studies are needed to confirm these findings.

Disclosure of Interest: None Declared

POTENTIAL DIAGNOSTIC AND PROGNOSTIC VALUE OF LYMPHOCYTIC MITOCHONDRIAL DNA DELETION IN RELATION TO FOLIC ACID STATUS IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) is one of the most leading causes of death worldwide.

Aims: studying mtDNA deletion as diagnostic and prognostic molecular marker in relation to serum folic acid level in Egyptian patients with HCV related HCC.

Material and Methods: The prospective case control study was conducted on ninety adult patients; 50 patients with HCC, 20 with liver cirrhosis (LC) and 20 with chronic hepatitis C (CHC), in addition to 10 healthy subjects. Serum folic acid was measured using ELISA and lymphocytic mtDNA deletions was measured using real-time PCR. HCC patients were followed up over a period of one year dating from initial presentation. The diagnostic accuracy of mtDNA deletions frequency was evaluated using receiver-operating characteristic (ROC) curve analysis. Correlations between different variables were calculated using Spearman's Correlation Coefficient. Survival analysis was analyzed with the Kaplan-Meier method.

Results: There was a significant elevation of mtDNA deletions and a significant decrease in serum folic acid in HCC group compared to other groups (P: <0.01& P< 0.05 respectively).

Lymphocytic mtDNA deletions had a sensitivity of 82%, specificity of 60% at cut off (Δ Ct) 2.65 with AUC 0.818 and 95% CI; (0.72-0.9) for HCC diagnosis.

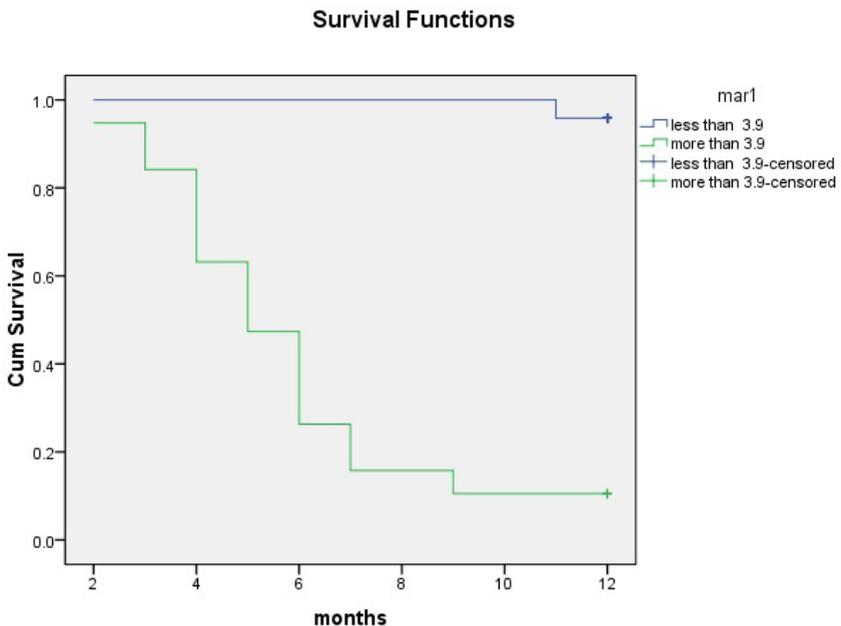
Regarding the clinicopathological features of HCC, we found that mtDNA deletions frequency significantly correlated with HCC size ($r= 0.9, P <0.01$) but none significantly with the number of HCC nodules ($r=0.0240, P:0.8$) and serum AFP level ($r=0.16, P:0.26$). Serum folate level negatively correlated with HCC size, foci number, serum AFP

and lymphocytic mtDNA deletions; however, this correlation did not reach statistical significance.

Also, the median survival time for HCC patients with high mtDNA deletions ($\Delta Ct \geq 3.9$) was significantly shorter (5.7 ± 0.6 months) than those patients with low mtDNA deletions frequency (11.9 ± 0.04 months) (fig.).

Conclusions: This is the first study to our knowledge that explored mtDNA deletions and folate status in Egyptian patients with HCV related HCC and is the first to evaluate mtDNA deletions as a diagnostic marker for HCC at a cutoff value of 2.65 (ΔCt) with a sensitivity of 82% and a specificity of 60%. Our findings implied a causal relationship between folate deficiency and mtDNA deletions frequency among Egyptian patients with HCC. Moreover, mtDNA deletions correlated with the clinic-pathological features and poor survival in HCC patients.

Figure:



Disclosure of Interest: None Declared

HETEROLOGOUS IMMUNE VACCINATION INDUCES SPECIFIC THERAPEUTIC CD8 T-CELL IMMUNE RESPONSES AGAINST TUMOR-ASSOCIATED ANTIGEN ALPHA-FETOPROTEIN EXPRESSED IN HEPATOCELLULAR CARCINOMA

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Introduction: CD8 T cells are a major component of the adaptive immune system and responsible for the recognition and elimination of malignant cells by major histocompatibility complex class I (MHC I)-restricted cytotoxicity. Immunotherapies are capable of inducing potent immune responses against tumour-associated antigens (TAA). The TAA alpha-fetoprotein (AFP) is highly upregulated in hepatocellular carcinoma (HCC) and serves as a diagnostic marker and as a potential target for immunotherapies.

Aims: The aim of this project is the establishment of a therapeutic AFP-specific heterologous immune therapeutic vaccination protocol targeting HCC.

Material and Methods: An orthotopic HCC mouse model was established in vivo using the 'Sleeping Beauty' transposon system. Hydrodynamic injection was performed to transfect murine hepatocytes with plasmids containing oncogenic NRas G12V linked to murine AFP (mAFP) in combination with myristoylated Akt1 and short hairpin against p53 (shRp53). High-affinity binding mAFP epitopes were optimized by EpitOptimizer to further improve binding affinity to MHC I molecules. A heterologous vaccination protocol consisting of primary dendritic cell immunization followed by a boost with soluble heteroclitic mAFP peptide, Poly I:C and an agonistic CD40 antibody will be performed in tumour-bearing mice.



Resected tumours from MHC haplotype HLA-A*02:01 patients will be collected and mass spectrometry as well as proteomics analysis performed to analyze MHC-bound peptides to assess the entirety of expressed tumour proteins, respectively. Potential neoantigens will be validated by whole exome sequencing. Additionally, HCC cells will be isolated from tumours and established in culture; the HCC cells will undergo the aforementioned methods and verify preceding results.

Results: Flow cytometric data demonstrated a massive expansion of specific CD8 T cell immune responses against mAFP. Immunization with the optimized peptide resulted in a frequency of up to 30% mAFP-specific CD8 T cells of total CD8 T cells compared to <1% after immunization with the wildtype peptide. T cells were detected by intracellular cytokine staining and flow cytometry.

Conclusions: The TAA mAFP is a promising target to establish effective immunotherapeutic treatments. In contrast to conventional vaccination approaches, the combination of primary dendritic cell immunization with subsequent injection of agonistic, co-stimulatory antibodies is able to massively expand tumour-specific CD8 T cells, capable of targeting AFP-expressing HCC.

Disclosure of Interest: None Declared

CASE-CONTROL STUDY NESTED IN A PROSPECTIVE COHORT OF MICROBIOME FOUND IN CIRRHOTIC PATIENTS WITH AND WITHOUT HEPATOCELLULAR CARCINOMA.

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Introduction: Changes in microbiome have been described in patients with cirrhosis. Although in murine models, a pro-oncogenic role of intestinal microbiome has been observed, no specific microbiome profile in patients with hepatocellular carcinoma (HCC) has been reported to date.

Aims: We aimed to compare microbiome found in cirrhotic patients with or without HCC.

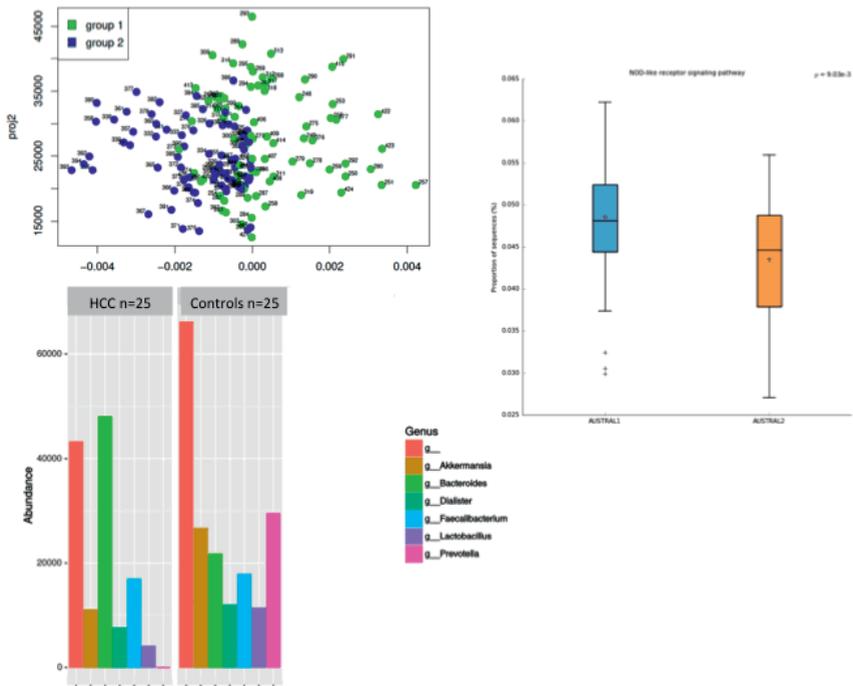
Material and Methods: From child Pugh A/B cirrhotic patients who were prospectively followed up, patients with HCC (cases) were matched with controls in a 1:1 ratio according to age, gender, aetiology and severity of portal hypertension. Computed Tomography or Magnetic Resonance Imaging discarded HCC in all controls. Exclusion criteria: immunosuppression, active alcoholism, prior or concomitant use of pre/probiotics, other active neoplasm, current antibiotic treatment, diarrhoea, any malabsorption disorder or inflammatory bowel disease. A sample of faecal stool was collected noninvasively at any time of the day and store in -70°. Each sample was aliquoted for final processing and DNA extraction using QIAmp DNA Stool Mini Kit. Sequencing of the V3-V4 region of the 16S rRNA gene was performed on the Illumina MiSeq Platform. Bioinformatics analysis of the data was done using a custom QIIME pipeline (<http://qiime.org/>). Microbiome assessment was performed blinded from any clinical data.

Results: From 407 cirrhotic patients, 25/25 cases and well-matched controls were included. Baseline characteristic were age 64 ± 8 years, 88% males, body mass index (BMI) 28 ± 4 kg/m², hepatitis C virus 26%, Child Pugh A/B 74% and 26%, respectively. Barcelona Clinic Liver Cancer stages in HCC patients were 0 (n=2), A (n=12), B (n=5)

and C (n=6). Non-significant differences were observed between cases and controls. A significant different microbiome was observed in the ratio bacteroides/prevotella. Patients with HCC had lower quantities of prevotella sp and a higher proportion of bacteroides species when compared to controls.

Conclusions: We found a different pattern of microbiome in patients with HCC when compared to patients without liver cancer. This pattern has been influencing the inflammatory milieu in HCC, since it is associated with increased activation of NOD-like receptor signalling pathways.

Figure:



Disclosure of Interest: F. Piñero: Grant: Conflict with: National Institute of Cancer. “Asistencia financiera a proyectos de investigación en cáncer de origen nacional III”- INC- Dr M Silva, M. Vazquez : None Declared, P. Baré: : None Declared, M. Sciarra: : None Declared, M. Mendizabal: : None Declared, C. Rohr: : None Declared, C. Alonso: : None Declared, F. Fay: : None Declared, M. Silva: Grant: Conflict with: National Institute of Cancer. “Asistencia financiera a proyectos de investigación en cáncer de origen nacional III”- INC- Dr M Silva

EpCAM-POSITIVE CIRCULATING TUMOR CELLS AS LIQUID BIOMARKER FOR EARLY MICROMETASTASES AND HCC RECURRENCE RISK

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Introduction: Without liver transplantation, early HCC (BCLC stage A) has a limited prognosis due to recurrence rates of up to 70% after curative resection or ablation. Recurrence within two years is believed to be caused by intrahepatic micrometastases untraceable by current imaging techniques. Recently, we have demonstrated that the presence of EpCAM-positive circulating tumor cells (CTC) is associated with systemic disease and inferior overall survival (Schulze et al., Int J Cancer 2013).

Aims: Hence, the aim of this study was to investigate CTC detection as liquid biopsy to identify patients with high HCC recurrence risk.

Material and Methods: 67 patients undergoing HCC resection between 2011 and 2015 were prospectively enrolled. 24 hours prior to surgery, blood specimens were obtained, and processed with the CellSearch™ system, detecting and enumerating EpCAM-positive/keratin-positive CTC. Ten patients with incomplete data regarding HCC recurrence, secondary liver transplantation, or perioperative death were excluded. Primary endpoint was recurrence free survival (RFS). Tumor grading, tumor size, angioinvasion, and resection margins were also assessed as predictors for RFS.

Results: 13 women and 44 men (63.6±11.1 years) were enrolled. Baseline characteristics were equally distributed between patients with and without CTC. CTC positive patients had a significantly higher recurrence risk with a hazard ratio (HR) of 2.3 compared to CTC negative patients (p=0.027). Furthermore, RFS for CTC positive patients was significantly shorter with a median of 5.0±1.5 months compared to 12.0±2.5 months in CTC negative patients (p=0.039). As expected, incomplete resection (R1) was identified as an additional parameter associated with shorter RFS (HR=2.7, p=0.035), but the

predictive power of CTC status was independent of R1. Microscopic vascular invasion (V1) was equally distributed between patients with and without CTC (4/9 vs. 17/47, $p=0.639$), and showed no correlation with RFS (HR=0.8, $p=0.634$).

Conclusions: Bloodstream detection of CTC prior to surgery discloses an elevated HCC recurrence risk, and a shorter RFS after curative resection, independent of vascular invasion (V1) or resection margins (R1). Thus, CTC could serve as biomarker for systemic disease, and to identify patients urgently needing adjuvant systemic therapy. To our knowledge, this is the first study demonstrating a clinical impact of CTC detection as liquid biopsy in Western patients with early HCC.

Disclosure of Interest: None Declared

ASS1 IMMUNOHISTOCHEMISTRY IDENTIFIES UNCLASSIFIED HEPATOCELLULAR ADENOMA. EXPERIENCE OF A SINGLE FRENCH LIVER CENTER

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Introduction: In our center all hepatocellular adenoma (HCA) are classified routinely by immunohistochemistry. Unclassified HCA (UHCA) are defined by default (HCA markers negative).

Aims: To test UHCA with ASS1 antibodies (a protein belonging to the Arginine metabolic pathway), a marker identified by proteomic analysis in UHCA and to correlate with clinicopathological data.

Material and Methods: From a total of 218 resected cases (189F/29M) there were 70 H-HCA, 69 IHCA, 22 b-HCA [15 ex3], 32 b-IHCA [19 ex3], 15 UHCA and 10 not classifiable (massive hemorrhage/necrosis in 8 cases, waiting identification in 2 cases). ASS1 IHC was performed in all UHCA, 3 HCA of each other subtype and 3 focal nodular hyperplasia (FNH).

Results: All 15 UHCA were women, mean age 40 (range 27-48); all on oral contraceptives, mean of 22 years (range 11-30) in 10/15 cases. BMI was raised in 11 cases, mean 30 (range 19.7- 45.7). Mode of discovery was death by hemorrhagic rupture of the liver, severe hemorrhage (intra-tumoral, intrahepatic, or peritoneal), pain, and chance in 1, 5, 6, and 3 cases respectively. The number of nodules was 1, 2, or ≥ 5 in 9, 4 and 2 cases respectively. Associated diseases were diabetes type 2, arterial hypertension in 4 and 3 cases (one of renal origin) respectively. Non tumoral liver (NT) was steatotic in 10 cases: $\geq 60\%$, 30-60%, 10-30% in 6, 2 and 2 cases respectively. Areas of hemorrhage, small or



large, recent or old, macroscopically visible were present in 13 cases, only microscopic in another one, absent in 1 case. In 13 cases, the tumors (T) had the same aspect: non encapsulated, well differentiated proliferation, composed of clear often hypereosinophilic packed hepatocytes, well vascularized by numerous arteries and veins, without noticeable inflammation, ductular reaction, or steatosis. In 2 cases there were criteria of malignant transformation: one classified as borderline HCA and another one with several HCC foci. ASS1 was overexpressed in T compared to NT. In T, staining was diffusely or heterogeneously distributed with a various intensity, whereas in NT, ASS1 was expressed only in periportal and septal zones. In all other HCA subtypes and FNH, ASS1 expression was downregulated (from absent to small patchy areas) compared to NT.

Conclusions: ASS1 immunostaining allows the classification of UHCA previously defined by default (7 % of HCA), an HCA subgroup observed in women and with a high risk of hemorrhage. ASS1 staining needs to be evaluated on liver biopsy to test its relevance for patient management.

Disclosure of Interest: None Declared

PERIPHERAL T CELL SUBPOPULATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: RELATION TO ABLATION THERAPY

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Introduction: Locoregional therapy has become increasingly important for patients with HCC because of advances in techniques, survival benefit, and a favorable safety profile. Ablative techniques share, irrespective of their mechanism to induce cell death, the ability to stimulate immunological responses. These responses are validated through the measurement of peripheral immune cells in the systemic circulation.

Aims: To investigate changes in the peripheral immune cells presented in CD4, CD8 and CD4/Cd8 ratio after HCC ablation by different procedures and the relation between these changes and ablation result.

Material and Methods: This study investigated 73 HCC patients who were admitted to Tropical Medicine Department at Mansoura University Hospital, Egypt. The patients were stratified into three groups according to ablative technique used. RFA was performed for 24 cases, MWA for 24 and TACE for 25 cases. All patients underwent full history taking, clinical examination, full basic investigations, triphasic abdominal computerized tomography before and 4 weeks after the treatment and lymphocyte subset assay by flow cytometry 1 day before, and 4 weeks after the treatment. Then each group subdivided into successful and unsuccessful subgroup according to the result of ablation by CT.

Results: After treatment, CD4+ cells and CD4/CD8 ratio remarkably increased ($P < 0.001$), and the CD8+ cells significantly decreased ($P < 0.002$) with concomitant increase in the CD4+/CD8+ ratio ($P < 0.001$) in the RFA group; CD4+ cells markedly increased after treatment ($P < 0.001$), with increase in CD4/CD8 ratio ($P < 0.007$) but there were no significant differences in CD8+ cells in the MWA group; the CD4+ cells and CD4/CD8 ratio dramatically decreased after treatment ($P < 0.001$), and the CD8+ cells increased significantly ($P < 0.001$) in the TACE group. After division of each group to successful

and unsuccessful subgroups, the changes in CD4, CD8, and CD4/CD8 ratio remained comparable to that occurred in the groups.

Conclusions: Various ablation procedures of HCC are associated with significant changes in peripheral T cell subpopulation. These changes mostly were due to the ablation of tumor cells but these changes cannot predict the success of ablation or recurrence of previously ablated one.

Disclosure of Interest: None Declared

IMPACT OF NATURAL KILLER CELLS RECEPTORS GENE HAPLOTYPES ON THE DEVELOPMENT OF HEPATOCARCINOMA IN CIRRHOTIC PATIENTS

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Introduction: Impaired natural killer (NK) cells function and distribution have been observed in patients with hepatocarcinoma(HCC). Killer immunoglobulin-like receptors(KIRs) are key regulators of NK-mediated immune responses and their expression, which is genetically determined, is highly heterogeneous and regulated by different haplotypes

Aims: In this study we aimed to analyse the genetic pattern of KIRs and their human leukocyte antigen(HLA) ligands in cirrhotic patients with and without HCC in order to identify a potential correlation between the expression of inhibitory/activating KIRs and tumour presence.

Material and Methods: Cirrhotic patients with and without HCC were included. The immunogenetic characteristics of the patients were compared to those of healthy individuals extracted from the Sardinian bone marrow donor registry. High resolution (4 digits) typing of HLA A, B, C and 14 KIRs gene loci was performed in both patients and controls. Subjects were divided into 2 groups according to homozygosity for KIR haplotype A (AA), heterozygosity or homozygosity for KIR haplotype B (Bx). They were also stratified according to the numbers of activating/inhibitory KIRs, the type of KIRs related HLA-ligands and the combinations with their receptors.

Results: 113 patients were included: 77(68%) had HCC. HCV infection was the primary cause of liver disease (77%). Compared to controls, cirrhotic patients showed higher

frequency of HLA-C*05 allele (27% vs 17.5%, $p=0.001$), while HLA-A*02 allele was more common among HCC patients compared to non-HCC (30% vs 18%; $p=0.05$). No significant difference was observed in the frequency of activating/inhibitory KIR genes and KIR aplotypes between patients and controls. Conversely, non-HCC patients showed a higher frequency of the inhibitory KIR gene 3DL1 compared to HCC patients (100% vs 87%, $p=0.03$). The frequency of KIR2DS4, the only activating KIR gene of aploptype A, was comparable between HCC and non-HCC group. However, homozygosis for the deletion variant of KIR2DS4 was significantly more common in HCC group (17% vs 3% $p=0.03$), indicating that a higher proportion of HCC patients with KIRs haplotype A did not express any activating KIR genes compared to only 1 non-HCC patient.

Conclusions: Loss of activating KIR2DS4 is more frequently observed among HCC patients, suggesting a decreased cytotoxic function of NK cells and therefore a negative impact on immunosurveillance and tumour control.

Disclosure of Interest: None Declared

DISCOVERY TO FIRST-IN-MAN STUDIES OF A MULTI-PEPTIDE-BASED HEPATOCELLULAR CARCINOMA VACCINE ADJUVANTED WITH CV8102 (RNADJUVANT – HEPAVAC

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Introduction: Hepatocellular (HCC)/normal adjacent tissue matched samples have been collected for HLA immunopeptidome analysis. 17 HCC samples from HLA-A*02+ patients and 15 samples from HLA-A*24+ patients have been analysed by mass spectrometry (LC-MS/MS). RNA-expression profiles have been established for 12 HCC samples. HLA-presentation/expression of peptides on primary HCC samples (as well as mRNA expression) were compared to normal tissue samples from relevant organs (including heart, brain, lung, kidney, liver, nerve, skin etc.) present in the Immatics' database.

Material and Methods: A total of 16 peptides have been selected and confirmed for immunogenicity for the HepaVac vaccine and are currently synthesized according to GMP standard. Of these, 7 are restricted to HLA-A*02; 5 to HLA-A*24 and 4 to HLA class II. Formulation development studies have been undertaken leading to a suitable and stable pharmaceutical form. An analytical method was developed which allows the characterization of each individual peptide within the HepaVac vaccine (IMA970A).

Results: A single-arm, first-in-man trial entitled HepaVac-101 is designed to investigate in patients with very early, early and intermediate stage of HCC the off-the-shelf multi-peptide-based HCC vaccine (IMA970) plus the CV8102 adjuvant (RNAdjuvant®) following a single pre-vaccination infusion of low-dose cyclophosphamide acting as an immunomodulator. The study drugs are applied without concomitant anti-tumor therapy with the intention to reduce risk of tumor recurrence/progression in patients who have received all indicated standard treatments. The primary endpoints are safety, tolerability, and immunogenicity. Secondary/exploratory endpoints are additional immunological parameters in blood (e.g. regulatory T-cells, myeloid-derived suppressor cells, impact of the standard therapy on the natural immune response), infiltrating T-lymphocytes in tumor tissue, biomarkers in blood and tissue, disease-free survival/progression-free survival and overall survival. Once safety of this vaccination approach has been determined in the first 10-20 patients the addition of a checkpoint inhibitor will be considered. Suitable patients enrolled in Tuebingen are invited to participate in a trial extension investigating an actively personalized vaccine (APVAC) plus CV8102.

Conclusions: The HepaVac project started in September 2013 and is supported by the European Commission's 7th Framework Program under the Grant Agreement Nr. 602893 (www.hepavac.eu).

Disclosure of Interest: None Declared

OSTEOPONTIN PROMOTOR GENE POLYMORPHISM AT LOCUS (-443C/T) AND DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC HEPATITIS C PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, particularly in Egypt, where hepatitis C virus (HCV) is highly prevalent. Serum alpha-fetoprotein (AFP) is the most widely used tumor marker for detection and monitoring of HCC but with low sensitivity. The identification of alternative serum markers for HCC is needed, Osteopontin (OPN), an integrin-binding glycopospho-protein, that has been proved to be over-expressed and associated with tumor invasion, progression and metastasis in various cancers, including HCC. Single nucleotide polymorphisms (SNPs) at the promoter region of OPN, regulating its expression, might be a novel prognostic marker for HCC.

Aims: to study serum Osteopontin level, and Osteopontin gene promoter (- 443C/T) single nucleotide polymorphism in cirrhotic HCV patients with and without HCC.

Material and Methods: This study was conducted on seventy patients classified into four groups: Group I consisted of twenty patients having HCC without metastasis. Group II included ten metastatic HCC patients, Group III contained twenty patients with HCV related liver cirrhosis and lastly Group IV, twenty healthy subjects as a control. Serum Osteopontin was measured by ELISA, Osteopontin gene promoter (-443C/T) SNP was detected by allelic discrimination using fluorogenic 5' nuclease assay.

Results: Serum Osteopontin was significantly higher in HCC group than liver cirrhosis patients. It was significantly higher in metastatic HCC group in comparison to cirrhotic and HCC groups, significant positive correlation was found between serum OPN and tumor size, and BCLC score. Presence of T allele was found to be associated with 2.5 fold risk of developing HCC and 9 fold risk of developing metastasis, however C allele was found to be protective against developing HCC and metastasis. Patients who carried TT



genotype tended to have higher mean serum Osteopontin level compared to those with CC and CT genotype and the difference was statistically significant. ($p < 0.001$) Diagnosis of HCC among patients with HCV related cirrhosis could be suggested when serum OPN is assessed at a cutoff value of > 25 ng/ml, on the other hand, metastasis is diagnosed in HCC patients when OPN is assessed at cut off value > 106.5 ng/ml.

Conclusions: Serum Osteopontin and Osteopontin promotor gene polymorphism at locus -443 are promising novel diagnostic and follow up tools of HCC in cirrhotic HCV patients.

Disclosure of Interest: None Declared

LIVER TRANSPLANTATION IN THE HEPATOCELLULAR CARCINOMA (HCC) SETTING: A SINGLE-CENTER EXPERIENCE FROM BRAZIL.

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Introduction: Hepatocellular carcinoma (HCC) is a major complication in cirrhotic patients. Liver transplantation has been considered an effective treatment for HCC, particularly in those within Milan criteria, with an overall survival after liver transplant about 70% in 5 years.

Aims: We present the experience of liver transplantation in HCC patients at a single Center from the Southeast of Brazil.

Material and Methods: From May 2001 until May 2016, 357 patients were submitted to deceased donor liver transplantation at Medical School of Ribeirao Preto-University of Sao Paulo, Brazil. Among them, 105 subjects (29.4%) had HCC.

Results: The mean age of HCC patients was 56.2 years, and 85.7% were male. Concerning the underlying etiology of liver disease, 56.2% of HCC patients had chronic hepatitis C, followed by 20% with alcoholic liver disease. The majority of the patients were Child-Turcotte-Pugh A (56%). Dynamic image (MRI or CT scan), with radiological features of typical HCC, was the main diagnostic tool (87.6%), followed by biopsy (7.6%), and incidental finding (4.8%). Single nodule was present in 77.1% of the patients. All subjects underwent liver transplant within Milan criteria. However, HCC downstaging was performed in 12.4% of the patients. Treatment modalities utilized for tumor control until liver transplant were: chemoembolization (63.8%), percutaneous ethanol injection (12.5%), radiofrequency ablation (7.5%), and combined treatment (16.2%). Drop out due to HCC progression whilst waiting for liver transplantation occurred in 9.5% (10/105) of the patients. Among them, two had been submitted to HCC downstaging before liver transplant indication. In the explanted liver, vascular invasion was found in 10.5%, HCC



out of Milan criteria in 6.7%, and poorly differentiated tumor in 2.9%. HCC recurrence was diagnosed in 5.7% of the subjects. Overall survival after one year of liver transplant was about 74.5%.

Conclusions: These are the initial results in deceased donor liver transplantation in HCC patients at a university hospital from the Southeast of Brazil.

Disclosure of Interest: None Declared

ASSESSMENT OF THE DIFFERENCE IN LIVER STEATOSIS, MEASURED BY CONTROLLED ATTENUATION PARAMETER, BETWEEN PATIENTS WITH HCV-RELATED ADVANCED HEPATIC FIBROSIS VERSUS HCV-RELATED HEPATOCELLULAR CARCINOMA

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Introduction: Steatosis is a well-documented feature of hepatitis C virus (HCV) infection, but its stability and evolution over time have not been well characterized. There is an association between steatosis decrease and progression to cirrhosis. However, the association between steatosis and advanced fibrosis versus development of hepatocellular carcinoma (HCC) has not been evaluated. The Controlled Attenuation Parameter (CAP) was evaluated as an immediate and efficient process to detect and quantify hepatic steatosis with good sensitivity, specificity, and accuracy.

Aims: To assess the difference in liver steatosis, measured by CAP, between patients with HCV-related advanced hepatic fibrosis versus HCV-related HCC.

Material and Methods: This cross-sectional study included 133 patients with HCC, attending the multidisciplinary HCC clinic, Kasr Al-Aini hospital, Cairo University and 66 patients with chronic hepatitis C (CHC) who are naïve to treatment between October 2015 and June 2016. Clinical, laboratory characteristics were recorded. Liver stiffness and CAP were obtained by using the FibroScan®502, touch (Echosens, Paris, France). The device estimates liver stiffness in kilopascal (kPa) and liver steatosis in decibel per meter (dB/m). The operator used ultrasonography to locate a liver portion away from HCC and large vascular structures.

Results: The included HCC and CHC patients had advanced fibrosis ($\geq F3$). The mean CAP value was significantly lower in HCC group 209.5 \pm 57.1 dB/m vs CHC; 259.9 \pm 54.9

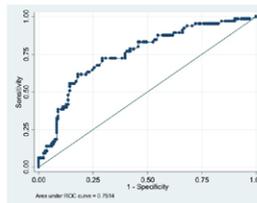
dB/m. ROC curve revealed an AUC of 0.75 for the differentiation between 2 groups. At a cutoff value of 237 dB/m, sensitivity 72.3%, specificity 70.7%, positive likelihood ratio 2.5, and negative likelihood ratio 0.4 in the differentiation between HCV-related advanced liver diseases versus HCC. Logistic regression analysis revealed an odds ratio of 6.4 for the diagnosis of HCC associated with CAP value <237. Multivariate analysis was done, controlling for age, gender, BMI, blood triglycerides and cholesterol levels, and revealed a significantly increased odds for the diagnosis of HCC (OR of 4.3, p=0.006) with CAP<237 dB/m.

Conclusions: The progression of HCV-related chronic liver disease is associated with a decrease in steatosis score, particularly towards advanced fibrosis and HCC. Reduction of steatosis below 237 dB/m is more likely to be associated with HCC

Figure:

Baseline characteristics of the studied groups

	CHC group (n=66)	HCC group (n=133)	P value
Age			
Median (IQR)	50 (10)	62 (9)	<0.001
Gender			
Male/Female	23/43	105/28	<0.001
BMI			
Median (IQR)	28 (4.1)	26.4 (4.2)	0.01
DM (Yes/No)	16/50	2/116	<0.001
Platelets	143 (107)	119.5 (63)	0.005
Bilirubin			
Median (IQR)	0.7 (0.5)	1.2 (0.9)	<0.001
INR			
Median (IQR)	1.1(0.2)	1.22 (0.2)	<0.001
AFP			
Median (IQR)	7.3 (8.4)	69.74 (262.7)	<0.001
Total Cholesterol			
Mean (SD)	149 (33.25)	107.64 (36.68)	<0.001
Triglycerides			
Median (IQR)	97 (55)	74 (43)	<0.001
Liver stiffness			
Median (IQR)	18 (10.5)	27.7 (21.4)	<0.001
CAP			
Mean (SD)	259.96 (54.9)	209.57 (57.1)	<0.001
Steatosis score			
S0	19	92	<0.001
S1	10	22	
S2	20	8	
S3	16	11	



ROC curve for the discriminatory power of CAP in the differentiation of HCV-related Liver disease from HCC

Disclosure of Interest: None Declared

COMPARATIVE STUDY BETWEEN RADIOFREQUENCY ABLATION ALONE AND IF COMBINED WITH PERCUTANEOUS ACETIC ACID INJECTION IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and a major cause of mortality. Radiofrequency ablation (RFA) and percutaneous acetic acid injection (PAI) are commonly used methods for treatment of HCC. Hepatitis C is a major health problem in Egypt leading to progression from chronic active hepatitis to HCC. It is estimated that the problem of HCC will increase until it reaches its peak in the year 2018.

Aims: The aim of this study was to compare the efficacy and safety of combined RFA and PAI injection versus RFA alone for ablation of HCC lesions less than 5 cm in diameter.

Material and Methods: Our study was conducted on 60 patients having single lesion of HCC \leq 5 cm in diameter. Patients were randomized into 3 groups (20 patients each); RFA group: Patients treated with RFA alone. PAI group: Patients treated with PAI alone. RFA+PAI group: Patients treated with combined RFA & PAI. After a written consent, all patients were clinically, laboratory and radiologically evaluated. Follow up of the patients of the three groups was done for about 6 months with special emphasis on recurrence of HCC, any remote complication related to the procedure, development of liver decompensation (ascites, jaundice, encephalopathy, bleeding tendency), hematemesis, or death.

Results: Regarding primary success In our study, the total success rate was (85%) in the three groups. Success rate in RFA group was 80%. Success rate PAI group was 85%. Success rate RFA+PAI group was 90%. CT findings after 6 months: 47 patients showed maintained ablation while 3 patients showed re-enhancement (local recurrence). Complications of the procedures: abdominal pain, fever, hematemesis and pleural effusion

were the most common early complications encountered in our study. While ascites and portal vein thrombosis were the most common late complications.

Conclusions: US guided RFA and PAI give good results and cure with minimal side effects in management of HCC. Acetic acid enhanced RFA is a very effective method of ablation in small and medium sized HCCs. Combined techniques give the best results for management of HCCs in comparison to each individual technique.

Figure:

Table: Success rate of the three procedures after 1 month.

Results		RFA group (n = 20)	PAI group (n = 20)	RFA + PAI group (n = 20)	P value
		No (%)	No (%)	No (%)	
According to spiral CT & biopsy	<i>Complete ablation</i>	16 (80%)	17 (85%)	18 (90%)	$P1=0.376$ $P2=0.633$
	Partial ablation	4 (20%)	3 (15%)	2 (10%)	
Partial ablation	<i>Failure with re-ablation</i>	2 (10%)	0 (0%)	1 (5%)	$P1=1.0$ $P2=0.171$
	Failure with no further treatment	2 (10%)	3 (15%)	1 (5%)	

Disclosure of Interest: None Declared

EFFECTIVENESS OF HEPATITIS B VACCINE WITH VARIOUS DOSES AND TYPES UNDER RAPID VACCINATION SCHEDULE AMONG ADULTS

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Introduction: Hepatitis B Virus (HBV) infection is a very important public health issue. The prevalence of HBV among adults is much higher than children in China. Vaccination under the regular schedule with 0-1-6 months, however, did not attain the highly adherence among adults. It is essential to figure out the effectiveness of rapid vaccine schedule.

Aims: To explore the effectiveness of four types of Hepatitis B vaccines, including '10µg HepB-SCY', '20µg HepB-SCY', '20µg HepB-CHO' and '10µg HepB-HPY', under rapid vaccination schedule with 0-1-2 months among adults.

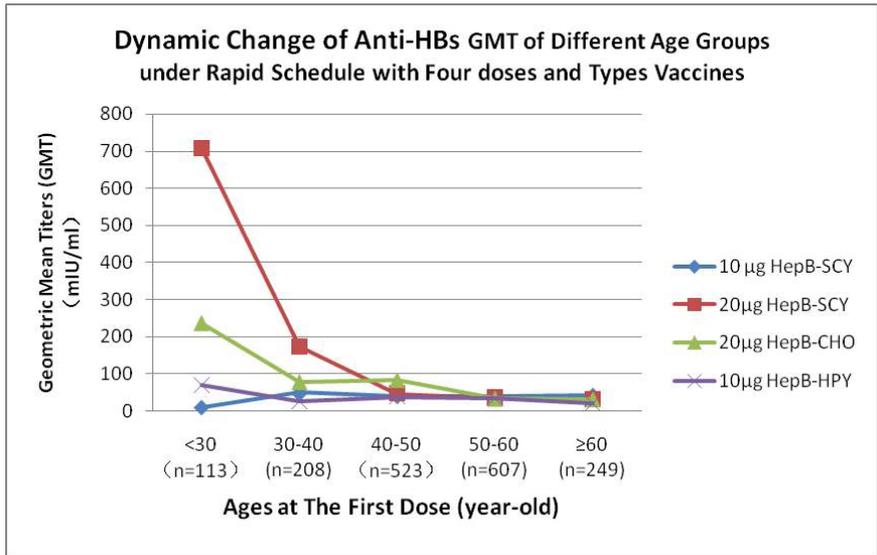
Material and Methods: The adults who were not younger than 20 years old, with HBV related five indicators negative or isolated anti-HBc positive were selected in Chaoyang District, Beijing City. They were allocated to 4 groups by communities and given three doses of vaccine (10µg HepB-SCY, 20 µg HepB-SCY, 20 µg HepB-CHO, 10µg HepB-HPY) at month 0, 1, and 2. Blood samples were collected when finishing the third dose vaccinated later 1-2 months, to test anti-HBs levels by Chemiluminescent Microparticle Immunoassay. Questionnaires were conducted by face to face. Chi-square test, Mantel-Haensel Chi-square test, Kruskal-Wallis rank test and multiple logistic regression were used in the statistical analysis.

Results: 1772 participants finished vaccination and observation. Their average age was 48.5 years-old, and 62.75% of them were female. The anti-HBs positive rates in the group of 10µg HepB-SCY, 20µg HepB-SCY, 20µg HepB-CHO and 10µg HepB-HPY were 79.49%, 84.34%, 82.50% and 74.15% respectively (P=0.005). Their corresponding geometric mean titers (GMT) were 39.53 mUI/ml, 62.37 mUI/ml, 48.18 mUI/ml, 33.64 mUI/ml respectively (P=0.025). The total anti-HBs positive rate and GMT were 79.01% and 41.18 mUI/ml. The 4 group levels of Anti-HBs GMT were descending with age.

The Anti-HBs GMT differences among groups were reducing with age. As a result of Logistic modeling, ‘vaccine type and dose’, age and smoke were associated with Anti –HBs statistically after controlling the ‘whether isolated anti-HBc positive or not’.

Conclusions: The schedule of 0-1-2 month with 20µg dose could achieved the anti-HBs positive rates with 80% or up. Adults should be vaccinated with 20µg HepB-SCY or HepB-CHO before 30 years old. The rapid vaccination schedule of 0-1-2 month is a supplement of routine.

Figure:



Disclosure of Interest: None Declared

TRANSARTERIAL CHEMOEMBOLIZATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND PORTAL VEIN THROMBOSIS

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Introduction: Treatment of HCC with portal vein thrombosis (PVT) remains challenging. Surgical resection has a poor prognosis. Sorafenib is recommended according to the guidelines but the mean survival rate is 10.7 months.

Aims: To detect the survival rate in patients with HCC and portal vein thrombosis treated with TACE and compares it with the survival rate of Sorafenib in the literature.

Material and Methods: During 24 months, 100 consecutive patients with advanced HCC and portal vein thrombosis were treated with TACE. The etiology in all patients was Hepatitis C virus. All the patients were compensated. Mean age was 61.5 years, 63 (63%) were males.

Results: Overall survival in patients with HCC and PVTT treated with TACE was 9.9 months. No significant difference was detected between our results and Sorafenib results in the literature.

Conclusions: TACE is a safe procedure in selected patients with HCC and PVTT, no significant difference in the overall survival between TACE and Sorafenib, However Sorafenib is much expensive with more systemic side effects.

Disclosure of Interest: None Declared

THE DIAGNOSTIC AND PROGNOSTIC VALUES OF SERUM PIVKA-II IN THAI PATIENTS WITH HEPATITIS B-RELATED HEPATOCELLULAR CARCINOMA

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Introduction: Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) is a promising serum marker of hepatocellular carcinoma (HCC). Despite its potential diagnostic value, most studies of PIVKA-II has been mainly performed in countries while hepatitis C virus infection is common.

Aims: The aims of this study were to evaluate the diagnostic and prognostic roles of serum PIVKA-II in Thai patients with hepatitis B-related HCC.

Material and Methods: Four groups were studied, which included 251 patients with HCC, 47 patients with liver cirrhosis (LC), 104 patients with chronic hepatitis (CH) and 50 healthy subjects. Serum PIVKA-II and alpha-fetoprotein (AFP) levels were measured by automated methods.

Results: Serum PIVKA-II levels were significantly higher in patients with HCC than in the other groups. Among patients with HCC, there was a weak correlation between PIVKA-II and AFP values ($r^2=0.315$; $P<0.001$). Area under receiver operating characteristics (ROC) curves in differentiating HCC from non-HCC were 0.933 (95% CI; 0.908-0.958) for PIVKA-II, 0.915 (95% CI; 0.888-0.941) for AFP, and 0.971 (95% CI; 0.955-0.986) for the combined tests. At the optimal cut-off value (60 mAU/mL), PIVKA-II had sensitivity and specificity of 98% and 85%, respectively. In patients with early HCC, elevated PIVKA-II level (≥ 60 mAU/mL) was found in 36.5% of cases with high AFP (≥ 20 ng/mL) and 63.5% of those with low AFP levels (<20 ng/mL). By multivariate analysis, PIVKA-II level was significantly correlated with large tumor sizes and advancing BCLC stage. The overall survival of patients with low PIVKA-II levels before undergoing TACE was better than that of patients with high PIVKA-II levels (45 months and 12 months, respectively, $P=0.002$ by the log-rank test).

Conclusions: Serum PIVKA-II was a useful diagnostic and prognostic marker for HBV-related HCC. The combined use of serum PIVKA-II and AFP could improve the diagnosis of early HCC.

Disclosure of Interest: None Declared

EFFECTIVENESS OF PERCUTANEOUS ETHANOL INJECTION IN RELATION TO HEPATOCELLULAR CARCINOMA SIZE: A SINGLE CENTRE EXPERIENCE

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Introduction: Percutaneous ethanol injection (PEI) was the first percutaneous treatment approved for hepatocellular carcinoma (HCC), but it has been progressively replaced by thermal ablation due to its predictable ablation volume and better efficacy in nodules >20mm. In field-practice, PEI remains still used in selected patients with very small or high-risk located nodules, and data on its efficacy in relation to nodule volume are scanty.

Aims: Aim of this study was to evaluate PEI response rate in nodules with different size.

Material and Methods: Clinical records of 291 naïve HCC patients treated with PEI between 1991 and 2010 at our Unit were retrospectively analysed. Tumor response and recurrence were evaluated at CT or MRI after four weeks, and then every six months from the procedure according to mRECIST (modified Response Evaluation Criteria in Solid Tumors) criteria. Main outcome was complete tumor-response (CTR), secondary outcomes were HCC recurrence and time to progression (TTP).

Results: Median follow-up was 20 months (range: 2-189). All patients had cirrhosis; 172/291 (59.1%) were Child A; 88/291 (30.2%) Child B and 31/291 (10.6%) Child C. The overall rate of CTR was 58.7% (171/291). It was 81.3% (61/75) in patients with lesions sized 10-20mm (Group 1); 59% (52/88) in patients with lesions of 21-30mm (Group 2); 60% (36/60) for lesions 31-40mm (Group 3), and 29.5% (20/68) for lesions >40mm (Group 4). Among patients with CTR, 42 patients had more than one lesions: 11 patients in Group 1, 18 in Group 2; 8 in Group 3 and 5 in Group 4. In patients who did not achieved CTR 59/120 had more than one lesion. The overall and local recurrence rate was 46% (28/61) and 36% for Group1, 52% (27/52) and 15% for Group 2, 50% (18/36) and 28% for Group3, and 60% (12/20) and 30% for group 4, respectively. Median TTP was 21 months in Group 1; 11 months in Group 2, 12 months for Group 3 and 9 months for Group 4. Median overall survival was 40 months (range: 2-189) in Group 1,

28 months (range: 2-130) in Group 2, 28 months (range: 2-183) in Group 3, 23 months (range: 2-82) in Group 4.

Conclusions: PEI represents a curative treatment for hepatocellular carcinoma but its efficacy is mainly influenced by the size of HCC nodule. Although the introduction of thermal ablative treatments, in selected cases PEI may be still employed even in nodules >20mm.

Disclosure of Interest: None Declared

CLINICAL PROFILE OF HEPATOCELLULAR CARCINOMA IN INDIAN PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and is an important cause of morbidity and mortality in patients of liver cirrhosis. HCC is associated with various infectious (chronic hepatitis B and C) and non infectious (alcohol, nonalcoholic steatohepatitis) risk factors.

Aims: This study was planned to evaluate the clinical presentation, etiology, biochemical parameters and tumor characteristics in HCC patients.

Material and Methods: Patients diagnosed with HCC as per European Association for the study of the Liver (EASL) criteria were prospectively enrolled. This included dynamic contrast enhanced CT/MRI as well as fine needle aspiration cytology where the radiology was inconclusive or tumor was small. Various parameters including clinical presentation, etiology and tumor characteristics (among others) were recorded.

Results: A total of 98 patients diagnosed with HCC were enrolled. Most of the patients were males (73.5%) with a mean (\pm SD) age of 46.8 (\pm 12.2) years. The most common etiology of HCC was hepatitis B alone (31.6%) or with associated alcoholic liver disease (10.2%), followed by alcoholic liver disease (27.6%), hepatitis C (16%) and cryptogenic cirrhosis (14.3%). Of the 98 patients, 77 patients had cirrhosis (78.6%) of which 64 patients (65.3%) had decompensated cirrhosis. Of the 77 patients, 16.9%, 46.8% and 36.4% patients were in CTP stage A, B and C respectively. The serum alphafetoprotein (AFP) levels were normal in 15.3% patients. The AFP levels were >200 ng/ml in 53.1% patients and they were >400 ng/ml in 37.8% patients. When subclassified according to BCLC stage, 6.1%, 30.6%, 38.8% and 25.5% patients were in BCLC stage A, B, C and D respectively. Most of the patients had a solitary tumor (60.2%). Rest of the patients had 2 (17.3%), 3 (9.2%) and >3 (13.3%) tumors.

Conclusions: HCC was most common in males in the fifth decade. Hepatitis B infection was the most common cause of HCC followed by alcoholic liver disease. Most of the patients presented in advanced stage of cirrhosis. Serum AFP levels were elevated in a majority of patients. Most patients had a solitary tumor at presentation.

Figure:

Profile of HCC patients

Symptoms	Number	Percentage
Abdominal pain	40	40.8
Altered sensorium	32	32.7
Upper gastrointestinal bleed	12	12.2
Signs		
Icterus	52	53.1
Pedal edema	68	69.3
Ascites	62	63.2
Hepatomegaly	42	42.8
Splenomegaly	36	36.7
Biochemical parameters		
Bilirubin, mg/dl (Mean ± SD)	5.8 ± 1.2	
AST, IU/L (Mean ± SD)	92 ± 33	
ALT, IU/L (Mean ± SD)	49 ± 12	
Albumin g/dl (Mean ± SD)	2.9 ± 0.6	
ALP, IU/L (Mean ± SD)	221 ± 56	
INR (Mean ± SD)	1.78 ± 0.6	
AFP		
<10 ng/ml	15	15.3
10 - 200 ng/ml	31	31.6
200 - 400 ng/ml	15	15.3
>400 ng/ml	37	37.8
CTP class		
A	13	16.9
B	36	46.8
C	28	36.4

Disclosure of Interest: None Declared

TRANSARTERIAL CHEMOEMBOLIZATION COMPLICATIONS AND ITS MOST COMMON CAUSES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Aims: To identify the most common complications of TACE in the treatment of HCC and detect the most common causes of such complications

Material and Methods: During 12 months, 200 consecutive patients with advanced HCC were treated with conventional TACE (chemotherapeutic agent mixed with lipiodol), the etiology in all patients was Hepatitis C virus. Complications in the following 1.5 months after the procedure were detected. Mean age was 59 years, 125 (62.5%) were males.

Results: After 1.5 months, 101 (50.5%) patients were clinically free with no complications related to the procedure. Eighty (40%) patients showed post-TACE syndrome, 72 of them showed no additional complications, 4 showed renal dysfunction and 4 presented with pneumonia. Decompensation of cirrhosis developed in 19 patients (9.5%), 7 of them died. Post-TACE syndrome was more in patients with HCC larger than 5 cm and in patients who received high dose of lipiodol. Decompensation of cirrhosis was more in patients with Child-Pugh class B or C

Conclusions: TACE is a safe procedure however it is associated with some complications, the most common one is post-TACE syndrome. Tumor size larger than 5 cm and lipiodol dose are the most common factors increasing the incidence of the post-TACE syndrome

Disclosure of Interest: None Declared

HEPATOCELLULAR CARCINOMA IN CENTRAL SLOVAKIA: COHORT FROM TERTIARY REFERRAL CENTRE

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Introduction: Hepatocellular carcinoma (HCC) from various geographical regions differs significantly in epidemiologic, demographic and clinical characteristics.

Aims: To analyze and to describe the cohort of patients (pts) with HCC from Liver Unit in Slovakia.

Material and Methods: Retrospective analysis of consecutive pts seen in Liver Unit of regional university hospital (catchment area with 662 121 inhabitants). Inclusion criterion: Diagnosis (Dg) of HCC according to EASL guidelines 2001, 2005 and EASL-EORTC guidelines 2012 as recorded in electronical database Care Center of Roosevelt hospital. Exclusion criterion: Impossibility to retrieve sufficient data for final analysis. Study interval: July 2007 – Nov 2016.

Results: Cohort consisted of 207 pts, 95% with liver cirrhosis, 76% men. Median age was 61,73 years (21-86). Etiology of underlying liver disease: ALD-106 pts (48%); HCV-39 pts (17%); HBV-28 pts (13%); NASH-22 pts (10%); cryptogenic-15 pts (7%); pts without Ci-10(4%); others (PBC, MW, HH)-3(1%). Forty nine cases (24%) were diagnosed by surveillance, other 68% presented as non – surveillance, 8 % of pts were unknown. The average of HCC lesions in pts performed by surveillance was 5,5cm and performed by non-surveillance was 8.6cm.

BCLC classes **a) whole cohort:** A-30pts(15%); B-61(29%); C-74(36%); D-42(20%); **b) according to Dg-modality** (Dg. by surveillance vs. non-surveillance): A-15/49(31%) vs. 12/140(9%); B-21/49(43%) vs. 38/140(27%); C-8/49(16%) vs. 55/140(39%); D-5/49(10%) vs. 35/140(25%). Treatment: Surgical resection-17pts (7%); liver transplant (LTx)-14(6%); RFA-20(8%); DEB-TACE-60(24%); sorafenib-88(35%); best of supportive care- 46(19%), 3 pts are waiting for LTx. Data for survival analysis were available for every 207 pts. Median survival in whole cohort was 17,34 months(m)

(0,06-111,6); survival in BCLC classes: A- 37,25m (2,2-111,6); B-21,25m (0,56-85,6); C-14,2m (0,06-91,9); D-2,95m (0,06-23,8).

Conclusions: 1) Demographics in this cohort resemble those of HCC in western world, except from absence of gender age difference. 2) Alcoholic liver disease was the commonest etiology of underlying liver disease. 3) Its stage was cirrhosis in 95% of cases. 4) The most important finding was that only 24% of HCC cases were detected via surveillance program. 5) There was marked right-sided shift in BCLC distribution with ensuing treatment allocation and survival. 5) One possible explanation of rather good survival in BCLC-C could be the availability of sorafenib.

Disclosure of Interest: None Declared

ULTRASOUND-GUIDED PERCUTANEOUS IRREVERSIBLE ELECTROPORATION (IRE) OF HEPATOCELLULAR CARCINOMA (HCC) NOT SUITABLE FOR SURGERY OR THERMAL ABLATION: INITIAL REPORT ON SAFETY AND EFFICACY FROM A WESTERN CENTER

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Introduction: IRE is a new non-thermal ablation technique for ablation of liver tumors that uses electrical pulses inducing necrosis of tumoral cells without damage of vascular or biliary structures.

Aims: We report our western experience on the first seven patients treated with IRE.

Material and Methods: Seven patients (5 males; age range 49-67 years, mean 56y) with HCC not suitable for surgery or thermal ablation consecutively seen in our Institution were included in the study. Diagnosis of HCC was based on hystological diagnosis in all patients. Only one patient had liver cirrhosis. HCC diameter ranged from 2 to 6 cm (mean 2.6cm). All nodules were located at liver hylum and in all cases dilatation of biliary tree was present. Only one patient had a non-metallical biliary stent. The only controindication for IRE was the presence of a cardiac disease. The follow-up ranged from 6 to 24 months (mean 13 months). IRE was performed percutaneously under ultrasound guidance using Nanoknife ® system and insertion of 2 needles (19 G) at a distance of 2 mm. Efficacy of procedure was evaluated with CEUS and enhanced CT one month after IRE.

Results: On imaging, complete necrosis was achieved in all patients. Only in one patient 2 sessions of IRE were needed to obtain complete necrosis. Six patients are still alive, while one patient died 6 months after IRE for stroke. No deaths occurred after procedure. Only one patient presented with a small, symptomless hematoma found on US seven days after IRE.

No other complications (either major or minor) occurred: in particular no injury to biliary tree was observed.



Conclusions: IRE of HCC not suitable for resection or ablation seems safe and effective in treatment of HCC closed to vascular and/or biliary structures. A larger number of cases will confirm such promising tool.

Disclosure of Interest: None Declared

HAND-FOOT-SKIN REACTION OF GRADE TWO OR HIGHER WITHIN SIXTY DAYS AS THE BEST RESPONSE CRITERION FOR SURVIVAL PREDICTION IN HEPATOCELLULAR CARCINOMA TREATED BY SORAFENIB

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Introduction: Sorafenib-related adverse events have been reported as surrogates of treatment response for hepatocellular carcinoma (HCC); however, there remains no agreement on the definition of responders.

Aims: We aim to evaluate the predictive abilities of different criteria for sorafenib response based on adverse events and to identify the most discriminatory one as a surrogate marker.

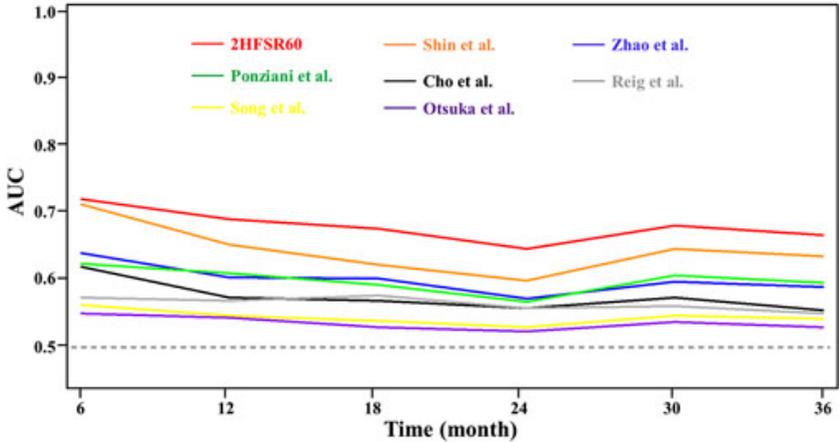
Material and Methods: From January 2010 to December 2014, a total of 320 consecutive HCC patients treated with sorafenib for more than eight weeks at our center were recruited. Considering the severity, type and timing of adverse events, twelve different categories of sorafenib response were defined. By comparing the discriminatory abilities of these categories for overall survival (OS), an indicative criterion was defined, and its predictive value was adjusted by multivariate Cox regression models and validated in various study population subsets.

Results: Using concordance (C) index analyses and time-dependent receiver operating characteristic (ROC) curves, the development of a grade ≥ 2 hand-foot-skin reaction within 60 days of sorafenib initiation (2HFSR60) was the most discriminating responder criterion. Based on that defined criterion, 166 (51.9%) sorafenib responders achieved significantly decreased risks of death (by 58%; adjusted hazard ratio [HR] 0.42) and progression (by 44%; adjusted HR 0.56) compared to those of non-responders (both

p<0.001). Notably, this criterion consistently showed effective discrimination among most subgroups and superior predictive ability compared to previous definitions.

Conclusions: Compared with other criteria to define sorafenib response based on adverse events, 2HFSR60 has the optimal discriminating ability for survival benefit in HCC treated by sorafenib.

Figure:



Disclosure of Interest: None Declared

METRONOMIC CAPECITABINE VERSUS BEST SUPPORTIVE CARE AS SECOND-LINE TREATMENT IN HEPATOCELLULAR CARCINOMA: A RETROSPECTIVE STUDY

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Introduction: No current proven second-line therapy is available for patients with hepatocellular carcinoma (HCC). Preliminary studies suggest that capecitabine may be safe and effective in HCC patients.

Aims: The aim of this study was to retrospectively evaluate the safety and efficacy of metronomic capecitabine (MC) as second-line treatment in patients who had progressed or were intolerant to first-line sorafenib (S).

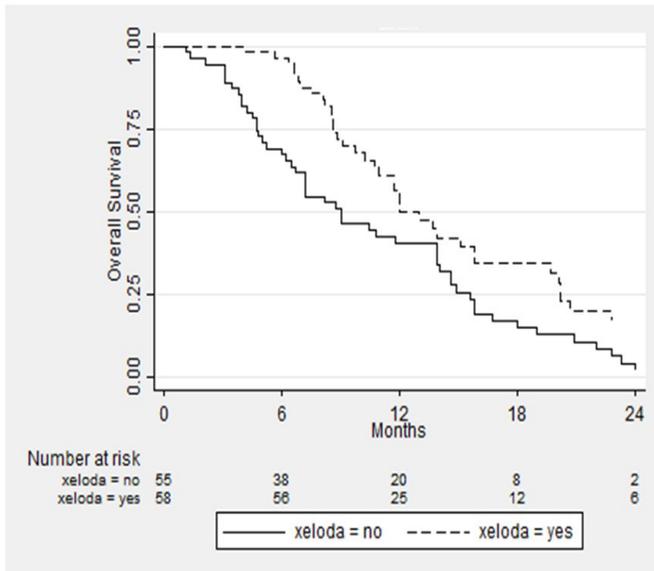
Material and Methods: In this multicentric study we retrospectively analysed data of HCC patients unresponsive or intolerant to S. Patients with advanced- or intermediate-stage HCC refractory to S, were eligible for our analysis. Patients treated with CM received the therapy at the metronomic dosage of 500 mg every 12 h. The centers treated the patients with MC whenever they were ineligible for protocol enrolment or the center had no second-line clinical trials ongoing. Patients treated with BSC alone included patients eligible for second-line treatment (either MC or clinical trial) but not complying with it.

Results: One hundred and thirteen consecutive patients with HCC were available for the analysis. Fifty-eight patients were treated with CM from May 2011 to November 2015, and 55 patients were treated with BSC alone from December 2007 to September 2015. Median follow-up was 9 months (range 1-36 months). In patients treated with CM median PFS was 3.1 months (95% CI: 2.7-3.5). Median OS was 12.0 (95% CI: 10.7-15.8) for patients receiving CM, and 9.0 (95% CI: 6.5-13.9) for patients treated with BSC (fig 1). The result from univariate unweighted Cox regression model showed 46% reduction

of death risk for patients on capecitabine(95%CI:0.357-0.829;p=0.005),compared with patients on BSC alone.After weighting for potential confounders, death risk remained essentially unaltered(45%;95%CI: 0.354-0.883;p=0.013).The best tumour response in patients treated with CM was partial response in 3 patients(5.4%),stable disease in 21 patients(37.5%)and progression disease in 32 patients(57.1%),according to mRECIST criteria.No complete response was observed.Twenty-three(39.7%)patients had at least one AE. The most frequent drug-related AEs were dermatologic toxicity(20.7%)and thrombocytopenia(6.9%).Patients treated with CM reported a significant association ($p = 0.011$) between the presence of HFS and disease control rate.

Conclusions: CM seems a safe second-line treatment for HCC patients in terms of management of adverse events,showing a potential anti-tumour activity which needs further evaluation in phase III studies.

Figure:



Disclosure of Interest: None Declared

EVALUATION OF LIVER STIFFNESS AS A PREDICTOR OF HEPATOCELLULAR CARCINOMA ABLATION OUTCOME AFTER PERCUTANEOUS MICROWAVE ABLATION OR TRANSARTERIAL CHEMOEMBOLIZATION: A COHORT STUDY

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Introduction: Liver stiffness increases after the development of Hepatocellular carcinoma (HCC) while HCC interventional maneuvers cause further elevations in liver stiffness. Transient elastography for Liver stiffness measurement (LSM) using Fibroscan is a simple noninvasive method of proven efficacy.

Aims: This study aims to assess the changes in LSM following microwave ablation (MWA) or trans-arterial chemoembolization (TACE) and the relation of these changes to HCC outcome

Material and Methods: This study included 113 patients with HCV-related HCC attending the multidisciplinary HCC clinic, Kasr Al-Aini hospital, Cairo university between March 2014 and October 2015 who underwent either MWA or TACE. Baseline fibro scan was performed then 3 and 6 months post-intervention. Tumor response was rated using the modified Response Evaluation Criteria in Solid Tumors (RECIST) guideline, overall survival analysis, and LSM changes were compared between both procedures.

Results: The median (IQR) value of HCC size was 3.6 (2.8) cm for TACE group and 3 (2) cm for MWA group. MWA showed higher rates of complete ablation (77.4%) than TACE (31.7%) (P-value=0.004). none of our patients showed progressive disease in follow up. Regarding baseline LSM, 4 (3.5%) patients had F2 liver fibrosis, 10 (8.8%) patients had F3, 4 (3.5%) patients had F3-F4 and the rest of patients had F4. Baseline LSM was higher in TACE group but without statistical significance. fourteen patients died and 20 patients missed their 6 months fibroscan follow up, thus fibroscan was performed

for the remaining 78 patients that confirmed the same results of LSM after 3 months. the increase in LSM 3 and 6 months post-intervention was statistically significant in TACE group (p-value<0.001) but not in MWA group (p-value=0.4). Patients showed HCC complete ablation had statistically significant lower baseline LMS than those with incomplete ablation (partial response and stable disease) and their 6 months increase in LSM was also significantly lower. Logistic regression revealed that with each unit increase in baseline stiffness, 3% reduction in the odds of complete ablation is expected and this didn't change after controlling for the type of treatment. Child-Pugh class, number, and size of HCCs were our independent prognostic factors by cox proportional analysis.

Conclusions: The increase in LSM is significant after TACE than MWA. Lower pre-ablation LSM is a predictor of complete ablation.

Figure:

Change in liver stiffness at 3 and 6 months after treatment*

	Baseline liver stiffness	Liver stiffness at 3- months	P value
The whole group (no=113)	28 (15)	30.2 (18.6)	<0.001
TACE (no=82)	29 (14.8)	33 (15.5)	<0.001
Microwave (no= 31)	24.8 (15)	27.1 (16.7)	0.4

	Baseline liver stiffness	Liver stiffness at 6- months	P value
The whole group (no=78)	28 (14.9)	31.3 (17.7)	<0.001
TACE (no=57)	28.4 (14.9)	33.4 (13.8)	<0.001
Microwave (no= 21)	25.1 (16.1)	26 (20.6)	0.2
Complete ablation (n= 38)	24.8 (19.1)	28.1(14.9)	0.001
Incomplete ablation (40)	30.8 (15.3)	33.9 (16.5)	0.0003

*Data are presented as median and IQR

Disclosure of Interest: None Declared

PORTAL VEIN INFILTRATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: THE IMPACT OF CORRECT CLASSIFICATION

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Introduction: Portal vein invasion (PVI) is known to have a significant impact on the prognosis of patients with hepatocellular carcinoma (HCC). Patients with PVI are classified as stage C in the BCLC score and systemic therapy is recommended. Nevertheless, patients with minor PVI are frequently misclassified in clinical practice due to radiological challenges in determining malignant PVI or non-adherence to clinical guidelines. The concept of resection or TACE in limited PVI is sometimes followed with the assumption of a negligible influence on survival.

Aims: Aim of this study is the reevaluation of portal vein infiltration and the analysis of the impact a possible misclassification.

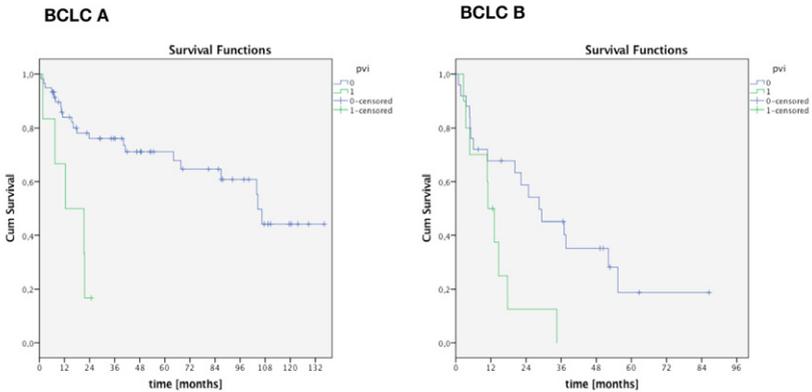
Material and Methods: 395 patients with HCC of a total of 1413 were extracted from the clinical registry of our tertiary referral center as an ongoing effort to reevaluate the extent of PVI in all patients treated between January 2000 and December 2015. PVI was diagnosed retrospectively by re-evaluating all available contrast enhanced CT or MRI by an experienced radiologist focused on liver imaging. The extent of PVI was documented using the classification suggested by the Liver Cancer Study Group of Japan ranging from Vp0-Vp4: Vp0=no PVI; Vp1=segmental; Vp2=right anterior or posterior PV; Vp3= right or left PV; Vp4=main trunk. The influence on survival was calculated for each BCLC stage.

Results: 181/395 patients were classified with PVI. Median age at diagnosis was 65.3 years, 148 patients (81.8%) were male. Etiology of liver disease was alcohol (46.4%), viral hepatitis (28.7%), NASH (5.5%), and others (9.5%). No liver disease was present

in 18 patients (9.9%). No liver cirrhosis (LCI) was present in 22 patients (12.2%). LCI was classified as Child Pugh stage A/B/C in 43 (23.8%)/73 (40.3%) and 43 (23.8%) of patients. BCLC classification prior to PVI reevaluation in patients with PVI was A/B/C/D in 6/10/109/56 of cases. Comparing the overall survival (OS) of patients initially classified as BCLC A with or without PVI was 12.5 months vs. 104.5 months ($p=0.001$). In patients initially classified as BCLC B the OS was 11.0 months vs. 28.5 months ($p=0.015$) in BCLC B.

Conclusions: Even minor PVI leads to a dismal prognosis. Meticulous evaluation of cross sectional imaging is crucial for the clinical management of patients with HCC. Once PVI has been diagnosed, such patients have to be classified as advanced stage. The guidelines should be followed closely, irrespective of the extent of PVI.

Figure:



Disclosure of Interest: None Declared

PATHOLOGICAL AND RADIOLOGICAL FINDINGS IN EARLY STAGE HEPATOCELLULAR CARCINOMA: A CORRELATIVE STUDY

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Aims: To compare gross pathological and radiological findings in early stage hepatocellular carcinoma (HCC).

Material and Methods: Thirty patients with hepatitis C virus-related cirrhosis and single, treatment-naïve HCC ≤ 5.0 cm in diameter, underwent surgical resection. Macroscopic features of each tumor, including the presence of capsule/s, types of margins and cut surface of nodule/s (homogeneous or non-homogeneous), were compared with ultrasonography (US), contrast-enhanced (CE) US (CEUS), and CE computed tomography (CT) findings. These latter were analyzed by expert readers.

Results: Gross pathology identified 30 HCC nodules: 23 encapsulated with an expanding growth (Type 1) and seven non-encapsulated with an infiltrative growth (Type 2). Type 1 HCC included three subtypes: 1A (no. = 3) consisting in a soft-tissue sharply-defined encapsulated nodule; 1B (no. = 18) consisting in a sharply-defined encapsulated nodule containing some smaller nodules each of them with capsule, and 1C (no. = 2) consisting in a cluster of nodules each of them with capsule. US and CT showed a 100% sensitivity, specificity and diagnostic accuracy in assigning each HCC to the two main gross pathological types. US sensitivity for the assignment of subtypes ranged from 50.0% to 100.0%, its specificity from 88.5% to 100% and its diagnostic accuracy from 86.2% to 100.0%. The intra-observer agreement for subtype attribution by US ranged from 0.72 to 0.94 (Cohen's K), whereas the inter-observer agreement was 0.8 (Fleiss's K). CT sensitivity for the assignment of subtypes ranged from 50.0% to 100.0%, its specificity from 83.3% to 100% and its diagnostic accuracy from 82.8% to 100.0%. The intra-observer agreement for subtype attribution by CT ranged from 0.71 to 0.83 (Cohen's K), whereas the inter-observer agreement was 0.77 (Fleiss's K). During a mean follow-up of 40 months (SD: 7 months), 12/30 (40%) patients died for disease progression. Estimated 3- and 5-year disease-free survival rate were 55% and 33% in patients with subtype 1A; 24% and 17%

in those with subtype 1B and 0.0% in those with subtype 1C and type 2 HCC. The 3- and 5-years first recurrence rate was 72% and 83% for patients with type 1 HCC vs 100% for those with type 2 (HR: 3.33, 95% CI, 1.13-9.75, P-value = 0.028).

Conclusions: Early stage HCCs show distinctive gross pathologic patterns which can be accurately identified by means of standard imaging techniques. These patterns correlate with different clinical behaviours.

Disclosure of Interest: None Declared

CONE BEAM COMPUTED TOMOGRAPHY TACE IS MORE EFFECTIVE THAN TRADITIONAL TECHNIQUE IN BCLC A HCC PATIENTS INELIGIBLE TO SURGERY

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Introduction: HCC mortality is still high despite the improvement in cancer diagnostic and therapeutic tools in the last years. The decision-making process in HCC treatment is mainly based on the Barcelona Clinic Liver Cancer (BCLC) staging system that considers both clinical and tumor characteristics. BCLC-A patients should undergo surgical ablation or hyperthermic treatment but they are often not eligible due to comorbidities or tumor position. Trans-arterial-chemoembolization (TACE) in these cases is performed either with traditional radiologic procedures or with Cone Beam Computed Tomography (CBCT) that allows a better 3D reconstruction of the HCC nodule and its vascularization.

Aims: Our study aims to evaluate the efficacy of TACE performed with CBCT or with traditional techniques in the subpopulation of patient in BCLC-A ineligible to surgery or hyperthermia, and BCLC-B.

Material and Methods: Between January 2012 and June 2016 56 patients were included in the study and 109 procedures were performed. BCLC scores at the time of treatment are A1-A3 in 32 treatments (29%), A4 in 29 treatments (27%) and B in 48 treatments (44%). Diagnosis of HCC is done considering EASL criteria and the radiologic response was evaluated at one month after treatment with the mRECIST score.

Results: The two groups were homogenous with no statistical differences in their characteristics. CBCT proved to be more effective than traditional Therapy in BCLC-A patients (79% vs. 26%, $p < 0.001$). Patients in BCLC B, instead, have similar response regardless of the treatment received (31% vs 6%, CBCT and traditional group respectively, NA).



Conclusions: In BCLC A patients TACE performed with CBCT is significantly more effective than the conventional procedure. This is probably due to a more precise identification of the small nodule(s) and blood supply. When the lesion is larger (group B) the advantage of CBCT disappears.

Disclosure of Interest: None Declared

DETERMINANTS OF SURVIVAL AND TREATMENT OUTCOME IN HEPATOCELLULAR CARCINOMA: A SINGLE CENTER EXPERIENCE

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Introduction: Strongly related to prognosis and guiding treatment selection, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used staging system for hepatocellular carcinoma (HCC). However, in daily clinical practice there is significant heterogeneity in patient characteristics and outcome.

Aims: To assess whether outcomes of treatment specific landmark studies can be reproduced in daily clinical practice and explore determinants associated with poor survival.

Material and Methods: All consecutive patients with HCC diagnosed between January 2008 and December 2013 in a single tertiary center were retrospectively evaluated by assessing medical records. Overall survival (OS) was analysed using the Kaplan-Meier method and compared to treatment specific landmark studies. Additionally, patients treated with Radiofrequent Ablation (RFA), Transarterial Chemoembolization (TACE) or sorafenib were categorized in subgroups based on meeting or not meeting the eligibility criteria each landmark study. Analysis of subgroups and prognostic determinants was done using the log-rank test and Cox-regression analysis.

Results: In total 239 patients were identified. Median OS after liver transplantation (n=14), resection (n=48), RFA (n=57), TACE (n=109) and sorafenib (n=77), was 69, 78, 78, 20 and 10 months. Median OS in patients with BCLC stage 0/A was 65 months, compared to 20, 11 and 2 months in BCLC stage B, C and D. Adherence to a surveillance program, lower BCLC stage and alfa-fetoprotein ≤ 100 were significantly associated with a better survival ($P < 0.001$), whereas underlying liver cirrhosis was not ($p = 0.474$).

In patients treated with RFA or sorafenib, there was no difference between patients meeting or not meeting the landmark eligibility criteria ($p = 0.125$ and $p = 0.704$). Interestingly,



patients treated with TACE who did not meet the inclusion criteria, had a significantly better survival (median OS 39 vs 18 months, $p<0.001$). These patients were younger (62 vs. 69 years; $p<0.001$), had a smaller size of the largest tumor (46 vs 62 mm, $p=0.009$), and more often 1 lesion (50 vs. 22.6%, $p=0.003$) compared to patients that did meet the inclusion criteria.

Conclusions: Survival outcomes in daily clinical practice were comparable to treatment specific landmark studies. Surveillance, AFP and BCLC stage were identified as determinants of survival. Better survival was observed for patients treated with TACE who did not meet the landmark eligibility criteria due to younger age and smaller tumor burden.

Disclosure of Interest: None Declared

OBSTRUCTIVE JAUNDICE FROM HEPATOCELLULAR CARCINOMA IS ASSOCIATED WITH POORER OUTCOMES OVERALL DESPITE SUCCESSFUL BILIARY DRAINAGE

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Introduction: Obstructive Jaundice caused by Hepatocellular carcinoma (HCC) is uncommon, estimated between 0.5-13% of cases with HCC. In our centre, we felt these patients had a worse outcome than HCCs without biliary obstruction (BO). Published outcomes to date are limited to Eastern populations and show a good response to stenting but a relatively poor outcome overall. There is no Western study looking at this cohort of patients, particularly their outcomes.

Aims: Our aim was to determine the outcome of patients with HCC developing or presenting with BO in a UK population.

Material and Methods: Records of all patients with HCC from Liverpool region, UK; referred to the regional liver centre at Aintree University Hospital were analysed. Demographics, evidence of cirrhosis, Child Pugh Status, type and level of BO, bilirubin at the time of Endoscopic Retrograde cholangiography (ERCP) and survival post procedure were recorded. Analysis was performed comparing the demographics and outcomes of those with BO to those patients with HCC without BO.

Results: 8 patients identified over 6 years (2009-2014) out of a total 629 with HCC (1.3%). Median age 72.5 in the BO group vs. 69 ($p=0.506$); no difference in gender. There were fewer cirrhotic patients with BO compared to those without BO, 25% vs. 86.5% ($p<0.001$). 87.5% of patients had proximal biliary obstruction compared to 12.5% with distal BO ($p=0.833$). All patients with BO had an ERCP performed. Median survival in those with BO from HCC was shorter: 111 days vs. 320 ($p=0.001$). In the BO group, there was no difference in survival if patients were stented with metal stents vs. plastic stents

($p=0.177$) or depending on whether obstruction was due to external compression from tumour rather than intrabiliary, infiltrative HCC ($p=0.782$).

Conclusions: Patients with BO caused by HCC have a poorer outcome than other patients with HCC. This persists despite successful stenting and resolution of jaundice and appears similar in our UK population to those published in Eastern populations. Stenting to palliate jaundice is still felt appropriate given the median survival of 111 days.

Disclosure of Interest: None Declared

TRANSARTERIAL CHEMOEMBOLIZATION SHOWS NO SUPERIORITY THAN BLAND EMBOLIZATION AS THE ADJUVANT THERAPY AFTER CURATIVE HEPATECTOMY FOR HEPATOCELLULAR CARCINOMA: A RETROSPECTIVE COHORT STUDY

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Introduction: Hepatocellular carcinoma (HCC) is prevalent globally and its outcome is very dismal. Hepatectomy is still the mainstay of HCC treatment. Effective adjuvant therapies after resection are lack and become the top unmet need in HCC research. All three randomized controlled trials (RCTs) showed that adjuvant transarterial chemoembolization (TACE) improves the prognosis. On the other hand, no matter as the bridge treatment before liver transplantation or the first-line treatment of unresectable HCC, TACE failed to prove its superiority to bland transarterial embolization (TAE).

Aims: To compare the prognostic significance of adjuvant TACE versus TAE after curative HCC resection in a single-center, non-randomized, retrospective cohort study.

Material and Methods: 136 HCC patients who received curative liver resection in Shandong Cancer Hospital were enrolled in the study. 36 patients received only liver resection and defined as Hx group. 70 patients received adjuvant TACE after the liver resection and defined as HxTACE group. 30 patients received adjuvant TAE and defined as HxTAE group. For adjuvant TAE, 5 to 10 ml lipiodol was injected into proper and left/right hepatic artery according to the primary location of the resected tumor. For adjuvant TACE, selected chemotherapeutic reagents were injected prior to lipiodol. The Kaplan-Meier method was used to compare survival between the groups.

Results: The three groups showed no significant difference in age, gender, pre-operative liver function laboratory tests, postoperative complications, tumor size, etc. Compared with the Hx group, the HxTACE and the HxTAE groups showed significant more

advanced tumor stage (BCLC [Barcelona-Clinic Liver Cancer] staging; Hx vs. HxTACE, $P=0.0013$; Hx vs. HxTAE, $P=0.0281$). Despite this, compared with the Hx group, the HxTAE group showed significantly improved 1-year OS ($P=0.0439$), and the 2-year OS improvement was of the borderline significance ($P=0.0998$) (Fig 1). The HxTACE group also showed similar trends as HxTAE group (Fig 2). Both HxTAE and HxTACE groups showed improved DFS without statistic significance. When compared the HxTAE with the HxTACE groups, no significance in either PFS or OS of any endpoints was found (Fig 3).

Conclusions: Our data indicate there are no significant differences in both PFS and OS between patients undergoing TAE or TACE as the adjuvant therapy. In this issue, additional transarterial chemotherapy shows no significant superiority over bland embolization.

Figure:

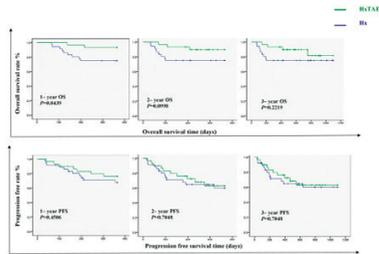


Figure 1 Kaplan-Meier survival analysis, Hx vs. HxTAE

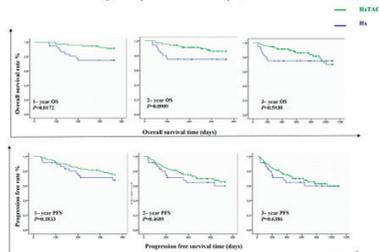


Figure 2 Kaplan-Meier survival analysis, Hx vs. HxTACE

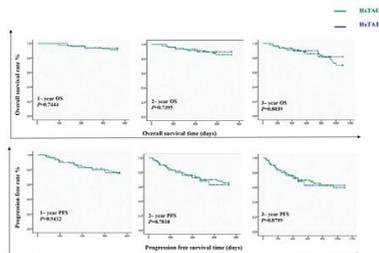


Figure 3 Kaplan-Meier survival analysis, HxTAE vs. HxTACE

Disclosure of Interest: None Declared

COULD BLOOD INDICES PREDICT THE EARLY RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER TRANS-ARTERIAL CHEMOEMBOLIZATION ?

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Introduction: The pathogenesis of HCC is based on inflammation. Host inflammatory response plays an important role in carcinogenesis and disease progression. Systemic inflammatory response has been revealed to have prognostic significance in a variety of cancers. Neutrophil to lymphocyte ratio (NLR) has been proposed to predict prognosis of hepatocellular carcinoma. Also Red blood cell distribution width (RDW) has been reported as an inflammatory biomarker.

Aims: to investigate the association of different blood indices including Neutrophil to lymphocyte ratio (NLR), Red blood cell distribution width (RDW), Monocyte Granulocyte to lymphocyte ratio (MGLR) and Platelets lymphocyte ratio (PLR) and early recurrence of HCC after conventional TACE.

Material and Methods: This study includes 147 patients out of 250 patients diagnosed to have HCC. All the patients belong to BCLC A or B class with single lesion either Child – Pugh class A or B liver function and mean size was (4.5×4.1 cm). Neutrophil lymphocyte ratio (NLR), Red blood cell distribution width (RDW), Monocyte granulocyte lymphocyte ratio (MGLR) and Platelets lymphocyte ratio (PLR) were measured before TACE. All patients underwent conventional TACE by injecting a mixture of lipiodol and doxorubicin powder (according to body surface area) and follow up Triphasic CT was done after one month with evidence of complete response with good lipiodol uptake of the tumors. Follow up of the patients was done every 6 months over 36 months.

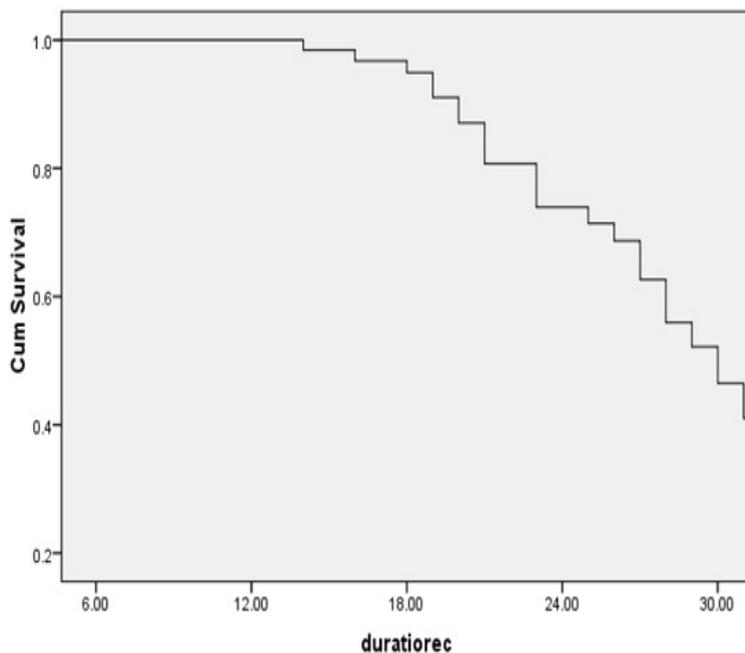
Results: Tumor size (P value=.033), AFP level(P value =.001), Child-Pugh score (P value =.001) and Monocyte granulocyte lymphocyte ratio (MGLR) (P value.001) were significantly associated with early tumor recurrence. In the logistic regression analysis the

Monocyte granulocyte lymphocyte ratio (MGLR) was significantly associated with early HCC recurrence after TACE (OR 1.157)(95% CI 1.015-1.318).

Conclusions: Monocyte granulocyte lymphocyte ratio (MGLR) could predict early recurrence of HCC after conventional TACE.

Figure:

Survival Function at mean of covariates



Disclosure of Interest: None Declared

PERCUTANEOUS ABLATION OF ADVANCED HCC AFTER DOWSTAGING WITH SORAFENIB

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Introduction: Sorafenib therapy in advanced stage Hepatocellular carcinoma (HCC) achieve a RECIST response in a small rate of patients ranging 2-10%.

Aims: We report our experience in a series of patients with advanced HCC who underwent ablation after successful downstaging with sorafenib.

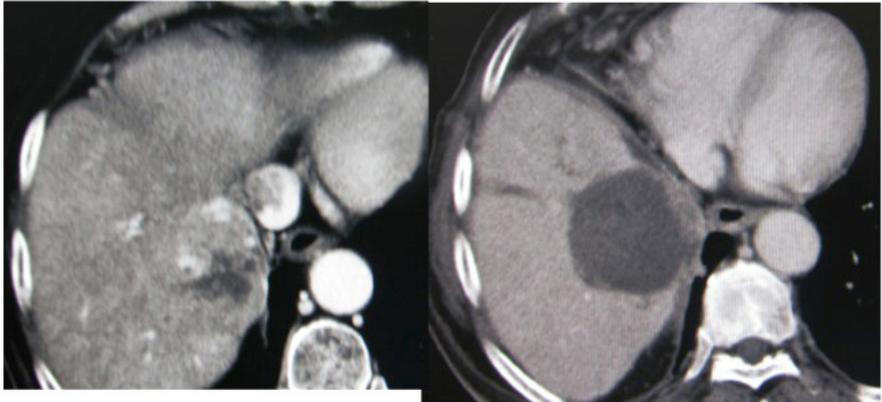
Material and Methods: 125 consecutive Child-Pugh A class cirrhotics (87 males, age 48–86, mean: 68 years) with BCLC/C-stage-HCC, not eligible for locoregional therapies, where treated with Sorafenib (Nexavar, Bayer HealthCare). Thrombosis of main or segmental branches of portal vein was present in 33/125 (26%). Follow-up entailed 3 phase CT every 3 months in the first year and every 6 months thereafter. Responder to Sorafenib at imaging follow-up were reconsidered for locoregional therapies.

Results: 23/125 (18.4%) were forced to early withdrawal of Sorafenib because of severe side effects. 58/125 (46.4%) showed an evident progression of HCC at US and CT controls and therefore stopped Sorafenib (non responder). 44/125 (35.2%) were considered responder to Sorafenib. Among these 44 patients, 33/125 patients (26.4%) showed a reliable stabilization of HCC burden at follow-up CT and 11/125 patients (8.8%) showed evident downsizing of the tumor according RECIST criteria. 6 out these 11 patients were considered eligible for locoregional treatment at the 6 month follow-up in 4 cases and at the 9 months follow-up CT control in 2 cases, respectively. Basal imaging (before Sorafenib treatment) in these 6 patients showed: Multiple large (>4cm) HCC nodules in all cases; Right portal vein thrombosis in 1 case; Segmental portal vein thrombosis in 1 case; Inferior vena cava partial thrombosis in 1 case. Residual HCC nodules and portal or caval tumor thombus after Sorafenib treatment in these patients were treated with one or multiple (up to 3) sessions of Radiofrequency (4 cases) and/or Microwawe (3 cases) and/or ethanol injection (1 case) and/or Electrochemotherapy (1 case). Post ablation CT showed complete necrosis of the treated HCC nodules in 4 patients and partial response in 2 cases. During follow-up 4/6 patients died at 15,18,20 and 24 months after treatment. 2 patients are still alive at 24 and 36 months follow-up. New nodules at follow-up CT

have been detected in 5/6 patients. A single patient, still alive, is disease free at 36 months follow-up.

Conclusions: In a small rate of patients with advanced HCC, Sorafenib can achieve an effective downstaging (8.8% in our series) and can also allow a curative ablation treatment.

Figure:



Disclosure of Interest: None Declared

METFORMIN EFFECTS ON CLINICAL OUTCOME IN ADVANCED HCC PATIENTS RECEIVING SORAFENIB: VALIDATION STUDY

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Introduction: Data from several retrospective studies and meta-analysis have demonstrated a risk reduction of about 50% of developing HCC in cirrhotic patients treated with metformin for DM2. In 2005 we published a paper where we have assessed the outcome of patient with HCC treated with metformin and sorafenib. The data show that the concomitant use of sorafenib and metformin was associated with a median PFS of 2.6 months compared to 5.0 months for patients receiving sorafenib alone ($p = 0.029$). The median OS of patients treated with the combination was 10.4 months compared to 15.1 months for those who were not given metformin ($p = 0.014$).

Aims: The aim of this study was to validate the prognostic significance of metformin in patients with HCC treated with sorafenib.

Material and Methods: 280 patients with HCC consecutively treated with sorafenib twice daily between March 2008 and August 2016 were included in the study. Patients who had been taking insulin for at least 5 years at the time of the HCC diagnosis were considered patients with diabetes treated with insulin, whereas those who had been on metformin at for at least 5 years when HCC was diagnosed were considered patients with diabetes treated with metformin."

Results: The concomitant use of S and M was associated with a median PFS of 1.9 months (95% CI 1.7-2.5) compared to 4.4 months (95% CI 2.5-8.2) for patients who have not received M ($p=0.002$) and compared to 6.3 months (95% CI 3.2-10.1) for patients who have received insulin ($p<0.00001$). The concomitant use of S and M was associated with a median OS of 6.6 months (95% CI 3.9-8.4) compared to 10.8 months

(95% CI 9.7-14.8) for patients who have not received (p=0.001) and compared to 14.4 months (95 CI 10.2-18.3) for patients who have received insulin p=0,0001).

Conclusions: These findings could be explained by an increased tumor aggressiveness and resistance to Sorafenib in patients treated with Metformin. Metformin usually enhanced the activity of Sorafenib, but probably molecular alterations in transporter genes or transcription factors involved in Metformin molecular action and pharmacokinetics could contribute to a different response to these drugs combination. Further studies are needed to identify possible mechanisms of resistance that may occur during treatment with Sorafenib.

Disclosure of Interest: None Declared

LASER ABLATION IS SUPERIOR TO TACE IN LARGE SIZE HEPATOCELLULAR CARCINOMA: A CASE-CONTROL STUDY

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Introduction: Currently, the standard treatment with transarterial chemoembolisation (TACE) for patients showing solitary large (≥ 40 mm) hepatocellular carcinoma (HCC) is unsatisfactory with occurrence of serious side effects. Data from literature suggest the alternative use of thermal ablation.

Aims: AIM: to evaluate the efficacy and safety of Laser Ablation (LA) in comparison to TACE in patients with HCC and large tumor size.

Material and Methods: Between January 2009 and December 2012, 82 cirrhotic patients (58/24 Male/Female; median age age 72; Child-Pugh A/B: 71/11) with a single nodule of HCC ≥ 40 mm were enrolled in this case-control study. Forty-one patients (29/12 Male/Female; mean age 72, range 54-88 yrs; Child-Pugh A/B: 37/4; median size of the nodule 46 mm, range 40-75) were treated with LA at the Liver Unit of the "Cardarelli" Hospital (Naples-Italy). The control group consisting of 41 patients (29/12 Male/Female; mean age 72, range 49-86 yrs; Child-Pugh A/B: 34/7; median size of the nodule 50 mm, range 40-80) treated with TACE, was obtained from the ITA.LI.CA. database.

The diagnosis of HCC was done according to the international guidelines and patients were staged according to BCLC Staging System (BCLC stage A/B: 27/14 and 18/23, for LA and TACE, respectively). Response to therapy was evaluated according to the mRECIST criteria. Survival was calculated from the time of cancer diagnosis to death with values censored at the date of the last follow-up.

Results: Twenty-six (63.4%) and 8 (19.5%) patients documented a complete response after LA and TACE, respectively ($p < 0.001$). The rate of complete response in relation to nodule size (40-50 mm vs > 50 mm) is shown in figure 1.

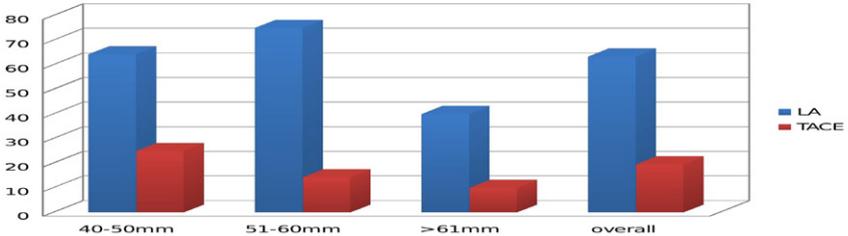
Logistic binary regression analysis showed that LA (OR 7.23; 95%CI: 2.57-20.32) and CHILD class A (OR: 8.92; 95% CI: 0.98-80.91) were the only independent predictors of complete response.

The cumulative survival rates at 12 and 36 months were 90.2% and 55.4 % in patients treated with LA and 85.4% and 48.8% in patients treated with TACE. The disease recurrence was observed in 13 LA-treated patients (24%) and in 24 TACE-treated patients (58.5%).

Conclusions: LA is a more efficacious therapeutic option than TACE in patients with large HCC, independently of the nodule size.

Figure:

Figure 1. Efficacy of Laser Ablation and TACE in relation to nodule size.



Disclosure of Interest: None Declared

THE SURVIVAL BENEFIT OF LAPAROSCOPIC ABLATION OVER TRANS-ARTERIAL CHEMOEMBOLIZATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA INELIGIBLE FOR LIVER RESECTION OR PERCUTANEOUS ABLATION

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Introduction: Different options are available for hepatocellular carcinoma (HCC) treatment according to tumor characteristics and patients liver function. Trans-arterial-chemioembolisation (TACE) is the first-line treatment for patients ineligible for liver resection or percutaneous ablation.

Aims: Aim of our study was to compare outcome of patients with HCC treated with laparoscopic ablation versus patients treated with TACE.

Material and Methods: Two HCC patients populations were used for the analysis: 485 patients treated with laparoscopic ablation (LA) as first therapy in the period 2004-2015 and 410 patients that received TACE as first treatment in the period 2008-2015. After propensity score analysis we obtained two comparable groups (n=175 for each) to evaluate the overall survival. A simulation analysis was also used to define survival benefit between the groups in different BCLC stages.

Results: Laparoscopic ablation showed a significantly superior long-term survival compared with TACE in unmatched patients (median survival 47 vs 30 months, $p < 0.05$) but after sample size reduction due to propensity score analysis (175 vs. 175 patients) the difference between groups became not significant (median survival 46 vs. 32 months, $p=0.117$). With the application of the median survival simulation (995 patients undergoing LA vs. 995 undergoing TACE) we showed a significant survival benefit of LA over TACE



in each BCLC stage (48 months in stage 0, 17 in stage A, 7 in stage B). The variables that most influenced the survival benefit were MELD score and patient age.

Conclusions: In HCC patients ineligible for percutaneous ablation or liver resection, LA should be evaluated as potential therapeutic strategy before considering TACE, whenever BCLC stage.

Disclosure of Interest: None Declared

PROSPECTIVE VALIDATION OF A SCORE TO PREDICT HEPATOCELLULAR CARCINOMA (HCC) IN PATIENTS WITH HCV CIRRHOSIS THAT TAKES INTO ACCOUNT SUSTAINED VIROLOGICAL RESPONSE (SVR). INFLUENCE OF DIRECT-ACTING ANTIVIRALS (DAAs)

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Introduction: A score to predict HCC in patients with HCV compensated cirrhosis has been recently developed using 5 variables: age/platelets/GGT/Alcohol/SVR (ANRS/CO12/CirVir. Hepatology 2016). Training and validation sets included mainly patients with SVR obtained with IFN.

Aims: To analyze the predictive value of the score in a series of patients with HCV cirrhosis in which most SVR were obtained with DAAs.

Material and Methods: Between Oct/92 and Mar/16, 385 patients with HCV cirrhosis, Child A/B, were consecutively included in a HCC surveillance program (96 excluded by prior decompensation). Of the 289 analyzed, 71% were males, 94% Child A and 65% infected by GT-1. At inclusion, 16 patients had SVR (12-IFN /4-DAAs) and 112 achieved it during follow-up (23-IFN/89-DAAs). As in the original study, patients with SVR during follow-up were considered before and after SVR for the corresponding time. Finally, the score was analyzed in 401 patients: 4% age > 50 years (2 pts), 22% excessive alcohol consumption (1 pts), 40% platelet count 100-150x10³/mm³ (2 pts), 30% platelet count <100x10³/mm³ (3 pts), 61% GGT>UNL (2 pts) and 68% absence of SVR (3 pts).

Results: During a mean follow-up of 46±54 months, HCC was diagnosed in 46 patients, with a cumulative probability at 1, 5 and 10 yrs. of 1.7%, 11.4% and 27.2% respectively, and an annual incidence of 2.9%. According to the score, 14% were in the low risk group (≤3 pts), 48% in the intermediate risk group (4-7 pts) and 38% in the high-risk group (≥8 pts). The probability of developing HCC at 1, 5 and 10 yrs. were 0% in the low risk group, 3%, 6.6% and 15.3% in the intermediate risk group and 2.2%, 18.8% and 43.4%

in the high risk group ($p=0.001$). These figures were virtually identical to those obtained in the original study. The AUC of the score in predicting the risk of CHC was 0.69(0.62-0.76). Among the 126 patients with SVR, 41% were in the low-risk group, 59% in the intermediate risk group and 1% in the high-risk group. During a mean follow-up of 21 ± 35 months, 4 patients (3%), all in the intermediate risk group, developed HCC (3-DAA and 1-IFN).

Conclusions: These results validate in an external cohort the usefulness of the ANRS/CO12/Cirvir score in predicting the risk of developing HCC in patients with HCV liver cirrhosis without prior decompensation. In addition, they demonstrate its usefulness in the era of DAAs based treatments. SVR obtained with DAAs does not seem to modify the risk of developing HCC compared to that observed after IFN therapy, at least in the short term.

Disclosure of Interest: A. Castaño: : None Declared, C. Alvarez-Navascues: Consultant: Conflict with: Bayer, Abbvie, Sponsored Lectures (National or International): Conflict with: Abbvie, Gilead, C. Rodriguez-Escaja: : None Declared, M. A. de Jorge: : None Declared, L. Gonzalez-Dieguez: Sponsored Lectures (National or International): Conflict with: Gilead, Abbvie, E. Rubio: : None Declared, V. Cadahia: : None Declared, M. Varela: Consultant: Conflict with: Bayer, Sponsored Lectures (National or International): Conflict with: Bayer, Abbvie, Gilead, M. Rodriguez: Consultant: Conflict with: Bayer, Gilead, Sponsored Lectures (National or International): Conflict with: Gilead, Abbvie.

COMPARISON BETWEEN DE-NOVO OCCURRENCE AND RECURRENCE OF HEPATOCELLULAR CARCINOMA (HCC) AFTER DIRECT-ACTING ANTIVIRALS (DAAs) IN CIRRHOTIC PATIENTS WITH HEPATITIS C: A REAL-LIFE COHORT STUDY

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Introduction: The clinical outcome of cases treated with the DAAs are still controversial, particularly regarding the development of HCC. Some reports could confirm the inability of DAAs to prevent cancer in some patients at risk.

Aims: We prospectively analyzed cases with cirrhosis and chronic hepatitis C after DAAs in a real-life setting to describe the development of HCC and the differences between forms with de novo occurrence or recurrence of tumor.

Material and Methods: One hundred and 87 out-patients (59+11yrs;101 experienced) treated with DAAs (90% SOF-based) were assessed for SVR12. Stage of liver disease was F4 in 160 cases (108/52 CP-A/B), among them 12 patients with a previous treatment for HCC(free-time from HCC before DAAs 25±17mos); F3 in 23 and F1-F2 in 4 cases. HCC-development was confirm by MRI with hepatospecific contrast and/or by liver biopsy. All cases were tested for alfa-fetoprotein (AFP), SCCA-IgM (Xeptagen, Italy) and HCV-RNA levels in serum (PCR).

Results: SVR12 was achieved in 170 cases (91%)(15 relapsed, 2 do). Twenty cases (11%) developed HCC: 14 de novo and 6 with recurrence. The main features of the two groups are shown in the table:

HCC development type:	Occurrence	Recurrence	p-level
Cases with HCC/Treated (%)	14/175(8)	6/12(50)	<0.001
Age (yrs;mean±SD)	59±11	67±11	
Gender, n. M/F (%M)	9/5(64)	2/4(33)	
Genotype, n. with HCV-1/2/3/4 (%HCV-1)	9/1/3/1(64)	3/1/2/0(50)	
Child-Pugh, n. class A/B (%CP-B)	9/5(36)	0/6(100)	0.03
Esophageal varices, n. cases (%)	5(36)	3(50)	
Therapy duration (wks)	21±5	22±14	
Therapy response, n. relapsers/SVR12 (%relapse)	8/6(57)	0/6(0)	0.04
HCC-development from DAAs-initiation (mos)	7,3±4,7	7,2±4,4	
AFP levels at diagnosis (ug/L)	33,6±86,5	136,2±263,1	
SCCA-IgM at diagnosis (AU/mL)	353±343	440±296	
BCLC stage, at diagnosis, n. class 0/A/B/C/D	5/2/7/0/0	3/2/1/0/0	
BCLC stage at last follow-up, n. class 0/A/B/C/D	3/*3/5/2/0	*2/0/1/1/1	
HCC-treatments (none, TACE, MW, Resection, OLTx)^	1/5/6/2/0	3/2/0/0/1	
Mortality/OLTx or listed for OLTx	*1 dead/3 listed	*1 OLTx	
Time of follow-up (mos)	8,2±4,2	7,2±4,4	

Conclusions: The use of DAAs showed a poor prevention of HCC in cases with advanced cirrhosis (CP-B) and previous history of HCC, since 50% of these patients experienced a recurrence of liver cancer, despite the rate of SVR12 obtained in 100% of cases. All cases with tumor showed an aggressive clinical outcome, with resistance to conventional treatments and rapid progression of HCC. Only the liver transplant at the initial stage of tumor seems to ensure a life expectancy.

Disclosure of Interest: None Declared

CLINICAL OUTCOMES OF PATIENTS WITH RECURRED HEPATOCELLULAR CARCINOMA AFTER CURATIVE SURGICAL RESECTION: IN RELATION TO RECURRENCE TIME

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Introduction: The clinical outcome of hepatocellular carcinoma (HCC) patients with postoperative recurrence varies in relation to the time of recurrence.

Aims: In the present study, we analyzed the relationship between the recurrence time and clinical outcome of HCC patients with recurrence after curative surgical resection.

Material and Methods: A total of 112 consecutive patients with recurred HCC after curative surgical resection were subjected. They were regularly followed for a median 57 months (range: 6 – 196) with serum AFP concentration and imaging studies, such as dynamic CT or MRI, at 3-6 months interval after surgery. During the follow up period, 42 cases (38%) recurred within 12 months (early recurrence) and the other 70 (62%) after 12 months following surgical resection (late recurrence). The mean size of recurred HCC was 1.7cm. The recurred HCCs were mostly SN type (70%); 29% multi-nodular (MN) and 1% infiltrative type. Microvascular invasion (MVI) was noted in 26 cases (23%). Extrahepatic metastasis was associated in 13 cases. The patients were treated with TACE (94%), RFA (13%), sorafenib therapy (10%), radiotherapy (6%) or surgical resection (4%).

Results: During the follow-up period, 10 patients were died. The 1, 3, 5-year post-recurrence survival rates were 96%, 92% and 86%, respectively. Interestingly, the patients with early recurrence had significantly shorter post-recurrence survival periods compared with those with late recurrence. [1, 3, 5-year post-recurrence survival rates (%): 89, 79 and 72 vs. 100, 100 and 95, respectively; P<0.001] Compared with patients with late



recurrence, patients with early recurrence were associated more frequently with MN or infiltrative type of HCC ($P<0.01$), MVI ($P<0.001$) and poor differentiation of resected HCC ($P<0.001$). Multivariate analysis revealed that the presence of MVI and poor differentiation of resected HCC were independent predisposing factors of early recurrence. Besides, Patients with early recurrence responded poorly to the treatments. ($P<0.001$)

Conclusions: Our data indicate that early postoperative recurrence results in poor clinical outcomes in HCC patients treated with curative surgical resection, and that MVI and poor differentiation of HCC are the independent predisposing factor of early recurrence in these patients. Thus, especially in HCC patients with MVI or poor differentiation of tumor, it may be necessary to combine adjuvant anticancer therapy even after curative surgical resection.

Disclosure of Interest: None Declared

FACTORS ASSOCIATED WITH TUMOR RECURRENCE AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: PROSPECTIVE COHORT ON 371 PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is now the leading etiology for liver transplantation (LT). Patient's selection criteria are based on retrospective studies and are based on factors associated with HCC recurrence risk.

Aims: The aim of this study was to assess tumor recurrence risk factors at 2 years after LT for HCC in a prospective cohort of patient listed for LT for HCC in France.

Material and Methods: 15 LT centers have actively participated to this study (NCT01198704). Overall survival analysis was done with Kaplan Meier method and survival free with Fine and Grey method (competitive risk) with death considered as a competitive event.

Results: Between April 2009 and December 2012, 371 patients were listed for LT for HCC in one of the 15 participating centers. 17 patients were secondarily excluded, 354 patients were followed. At listing: mean age was 57.8 (53-63), 89.8% were male, diabetes was diagnosed in 33.2% of the cases, liver cirrhosis was due to alcohol in 68.5%, HCV in 30.6, NASH in 14.4%, HBV in 10.2% and others in 6.5% of the cases. Median AFP level was 7 ng/mL (4-21.2), and median MELD score was 11.94 (8-14). On imaging, the mean diameter of the largest tumor was 23.87 mm (16-29) 48.4% of patients have solitary tumor; tumor portal thrombosis was suspected in 2.7%. Finally, Milan criteria

were fulfilled in 78.3%, « Up to seven » in 94% and AFP score in 93.9% of the cases. During the waiting time: median waiting time on list was 7.6 months [IQR: 3,8-12,1] for transplanted patients. At LT: 279 patients were transplanted. On the explant analysis, median number of HCC was 2 (1-4), no tumor was found in 3.4% of the cases (n=7). Non tumor liver was normal (F0) in 2.6%, F4 in 96.7%, F3 in 2.6% and F1 in 0.7% of the cases. Post-LT follow-up: with 24 months of follow-up, cumulative incidence of tumor recurrence was 11.56% (IC95% [8.03-15.79]) and overall survival was 86.87% (IC95% [82.18-90.39]). Uni-variate and multivariate analysis of factors associated with 2 years tumor recurrence risk will be presented. Cumulative incidence for tumor recurrence at 2 years for patients within AFP criteria at listing was 9.78% (IC95% [5.94-14.75]) compared to 15.38% (IC95% [24.76-38.78]) for patients beyond AFP criteria.

Conclusions: This prospective study based on 371 patients listed for LT for HCC independently confirmed the AFP score for patient's selection.

Disclosure of Interest: None Declared

EFFECTIVENESS OF DRUG-ELUTING BEAD-TRANSARTERIAL CHEMO-EMBOLIZATION IN INTERMEDIATE STAGE OF HEPATOCELLULAR CARCINOMA

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Introduction: According to the Barcelona Clinic Liver Cancer (BCLC) staging system, intermediate stage contains very heterogeneous hepatocellular carcinoma (HCC) patients. Recently, subclassification of intermediate stage on the basis of Milano criteria and up to 7 criteria is proposed.

Aims: In this study, the effectiveness of drug-eluting bead-transarterial chemo-embolization (DEB-TACE) in intermediate stage was investigated.

Material and Methods: 120 patients (M: F=90:30; median age=76; Child A: B: C=72:44:4; BCLC stage A: B: C: D=6:85:23:6) with unresectable HCC who received DEBTACE in our hospital were studied. The objective radiological response was classified according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) v.1.1 by using dynamic CT at one or two months after therapy. Adverse events were evaluated using NCI CTCAE v. 4.03. According to Bolondi's subclassification, the patients of BCLC B stage were divided into four groups (B1: 24, B2: 31, B3: 19, B4: 10). The response rate and tumor factor associated response in these patients group were examined.

Results: The overall response rate and disease control rate in intermediate stage were 36% and 89%, respectively. Considering the subclassification, the response rate in B1 group (61%) was significantly higher than that of B2+B3 group (29%). Although B2+B3 group was constituted by the patients who did not satisfy the up to 7 criteria, only in the patients with less than 7 tumors, the response rate (60%) was similar to that of B1 group. Tumor factors associated response and found to be significant on univariate analysis were simple gross classification (simple nodular type) and number of tumor. Tumor diameter was not associated with the response.



Conclusions: For the treatment of intermediate stage of HCC, although DEB-TACE is considered to be most effective in B1 group, it is suggested that DEB-TACE is also effective in the patients with less than 7 tumors in B2+B3 group.

Disclosure of Interest: None Declared

FALSE-NEGATIVE LIVER ULTRASOUND LIMITS BENEFITS OF HCC SURVEILLANCE

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Introduction: The aim of liver ultrasound (US) surveillance in cirrhosis is to detect hepatocellular carcinoma (HCC) at a stage amenable to curative therapy. However, the effectiveness of HCC surveillance is influenced by both timing and the sensitivity of ultrasound.

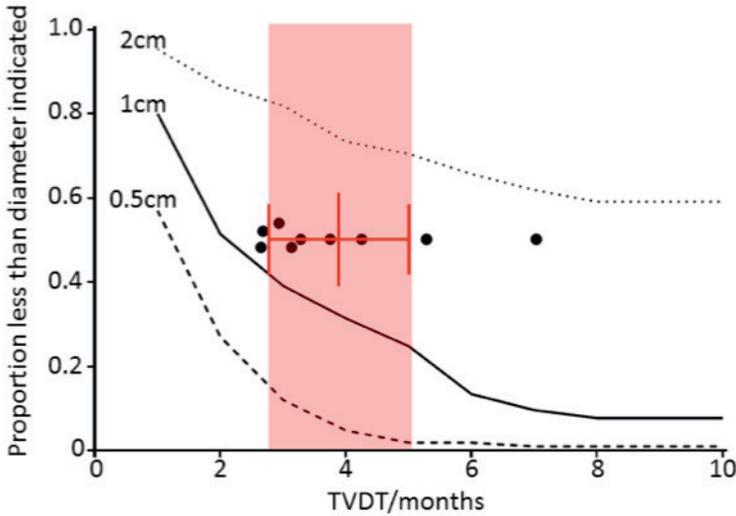
Material and Methods: We conducted a retrospective study of new diagnoses of HCC (n= 481) made at a UK tertiary liver transplant centre(The Royal Free Hospital) between April 2012 and March 2015. Of 481 patients diagnosed with HCC in this period, 108 had previous imaging surveillance for HCC. 97 were identified with no previous surveillance. We assessed the impact of surveillance on tumour diameter at diagnosis, rates of potentially curative intervention and survival. To estimate rates of false-negative US, we retro-extrapolated tumour diameter from diagnosis to the last "normal" surveillance ultrasound using a range of tumour volume doubling times (TVDT).

Results: In the surveillance group the mean interval time between imaging was 210 ± 24 days ($\pm 95\%$ CI) (target 182 days). Mean tumour size was 2.901 ± 0.33 and 7.922 ± 1.12 cm in the surveillance and non-surveillance group respectively ($p < 0.0001$). 51% of patients under surveillance received potentially curative treatment (radiofrequency ablation, resection or transplant), compared with 21% of patients presenting for the first time (Fisher's exact test, $p < 0.0001$). Only 15% of patients of the surveillance cohort received a liver transplant (vs 1% in the non-surveillance group). Subjects diagnosed under surveillance had significantly higher cumulative survival from diagnosis (hazard ratio 0.4480, 95% CI 0.3021 to 0.6640, $p = 0.0002$). Taking upper and lower 95% CI of mean TVDT values from nine studies of primary untreated HCC, the false-negative rate of USS in the presence of lesions > 1 cm is between 56-79% (Figure 1).

Conclusions: Ultrasound surveillance for HCC increases the chance of curative treatment and survival, although the benefit is modest and prolonged survival may be in part

attributable to lead-time bias. Despite surveillance intervals close to the recommended target of 6 months in our cohort, we have identified very high rates of false-negative US which delay diagnosis substantially. This finding is at odds with published estimates of US sensitivity for HCC detection (60% in a recent meta-analysis) but akin to estimates when explant histology is the reference standard (34% versus 70% for MRI). MRI surveillance may improve rates of HCC detection at a curable stage and therefore long-term survival.

Figure:



Disclosure of Interest: S. Demma: : None Declared, P. O'Donoghue: : None Declared, J. O'Beirne: : None Declared, A. Marshall: : None Declared, T. Meyer: : None Declared, W. Rosenberg: Grant: Conflict with: Siemens Healthcare Diagnostics, Consultant: Conflict with: Siemens Healthcare Diagnostics, Janssen, Merck, Gilead, GSK, Sponsored Lectures (National or International): Conflict with: Siemens Healthcare Diagnostics, Roche, Other: Conflict with: iQur Limited, D. Macdonald: : None Declared

VALIDATION OF A SIMPLE SCORING SYSTEM TO PREDICT SORAFENIB EFFECTIVENESS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Sorafenib is the recommended treatment in patients with advanced stage hepatocellular carcinoma (HCC). Nonetheless, it is expensive and effective in nearly 7% of patients. Furthermore, sorafenib may cause adverse effects, deteriorating quality of life. Therefore, an accurate selection of patients is needed. In a previous study we constructed a simple scoring system based on the occurrence of main sorafenib off-target effects (OTE). This score was able to predict patient's outcomes after four weeks of therapy.

Aims: The aim of the present study is to validate this score in an independent, real-life cohort of HCC patients treated with sorafenib.

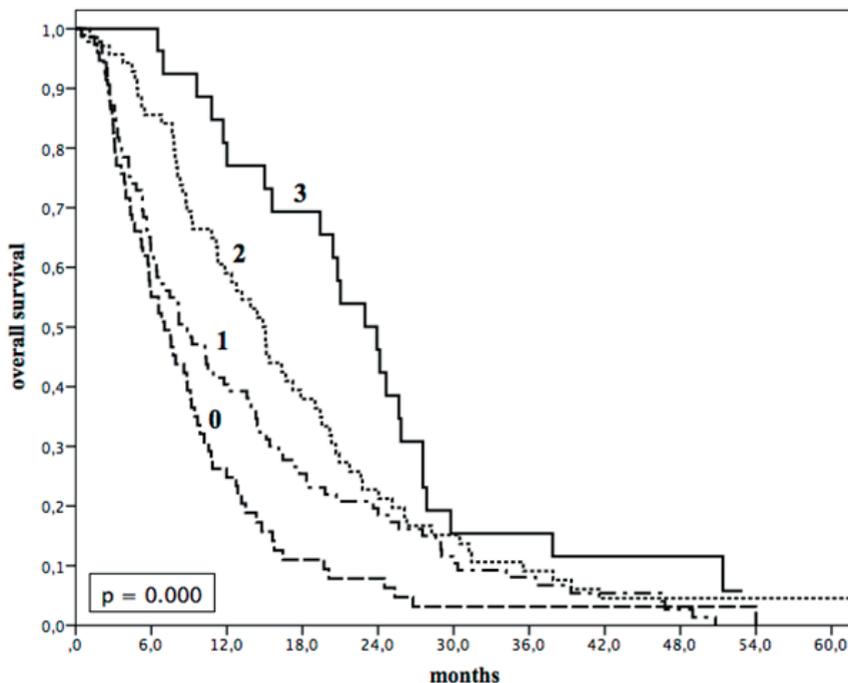
Material and Methods: Clinical records of 275 outpatients treated with sorafenib in 8 Italian centers from September 2008 to September 2015 were retrospectively analysed. Skin toxicity, diarrhoea and arterial hypertension, occurring within the first month of therapy, were the OTEs considered to calculate the score. At each OTE was assigned 1 point if present; otherwise 0 point. Therefore the score ranged between 0 and 3.

Results: Median overall survival(OS) was 10.8 months (95% CI, 9.0-12.6); median time-to-progression(TTP) was 5.1 months (95% CI, 4.4-5.7). A progressive increase in median OS and TTP was observed from patients with score 0 to patients with score 3 ($p = 0.000$). The survival probability at 6, 12, and 24 months was 55.1%, 24.5%, and 7.9% in patients

with score 0; 62.8%, 40.4%, and 19.6% in patients with score 1; 85.6%, 59.0%, and 22.8% in patients with score 2; 100%, 80.9%, and 46.2% in patients with score 3, respectively (figure). At radiological evaluation, complete response was observed in 1 patient (0.4%), partial response in 41 (15.2%) patients, stable disease in 117 (43.5%) patients, with an overall disease control rate of 59.1%. The disease control rate in patients with score 0, 1, 2, 3 was 34.3%, 51.6%, 80.9%, and 96.3%, respectively ($p = 0.000$). Complete or partial response was not observed in patients with score 0, but it occurred in 12.1%, 23.5% and 44.4% of patients with score 1, 2 and 3 respectively ($p = 0.000$). Multivariate analysis showed that only performance status and the simple score were independently associated with OS.

Conclusions: We validated a scoring system useful to predict outcomes in sorafenib treated patients with HCC. This score is simple to calculate and for its characteristics is an ideal tool to be implemented in daily clinical practice.

Figure:



Disclosure of Interest: None Declared

EXTERNAL VALIDATION OF THE ITA.LI.CA PROGNOSTIC SYSTEM FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA: A MULTICENTER COHORT STUDY

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Introduction: Several staging systems for HCC patients have been developed. BCLC classification is still considered the best in predicting HCC patients' survival, but few prognostic limitations have emerged. Recently the Italian Liver Cancer (ITA.LI.CA) new prognostic score, showing strong ability to predict individual survival was proposed.

Aims: Aim of our study is to provide an external validation of the ITA.LI.CA system in an independent and large Western cohort.

Material and Methods: From September 2008 to April 2016, 1508 cirrhotic patients with incident HCC were consecutively enrolled in 27 Italian institutions (EpaHCC cohort). Clinical, tumor and treatment-related variables were collected, patients stratified according to BCLC, ITA.LI.CA staging and prognostic score, Hong Kong Liver Cancer (HKLC), Cancer Liver Italian Program (CLIP), Japanese Integrated System (JIS), and MESIAH. Harrel's C index, the Akaike Information Criterion (AIC) and likelihood ratio test were used to compare predictive ability of different systems. A subgroup analysis for treatment category (curative vs palliative) was performed.

Results: Median follow up was 44 months (IQ 23-63) and median overall survival was 34 (IQ 13-82). Patients enrolled had a median age of 71 years, were mainly males and hepatitis C carriers. According to ITA.LI.CA tumor stage 246 patients were in stage 0, 472 in stage A; 657 in the stages B1-3; 133 in stage C. The ITA.LI.CA prognostic system showed the best discriminatory ability (C-index = 0.77) and monotonicity of gradients, compared to the different HCC prognostic systems. The superiority of the score was also confirmed after stratification of the population for treatment strategy (curative vs. palliative).

Conclusions: This is the first study that externally validated the ITA.LI.CA prognostic system for HCC in a large cohort of Western patients with incident HCCs. ITA.LI.CA score system performed better than other available systems, including BCLC, even after stratification by curative or palliative treatment. This new system including both a tumor staging and an integrated prognostic score appears to be particularly useful in clinical practice to predict individual HCC prognosis.

Disclosure of Interest: None Declared

PRELIMINARY DATA ON LEVEL OF CA 19-9 AND ITS PROGNOSTIC VALUE IN HCC PATIENTS TREATED BY CONVENTIONAL TACE REGARDING HCC RECURRENCE

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Introduction: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. CA19-9 is a glycoprotein that predicts poor prognosis in pancreatic and biliary malignancies. HCC is associated with increased level of CA19-9 in a portion of patients although its clinical and pathological significance is still unknown.

Aims: this study evaluated CA19-9 as a prognostic marker in HCC patients treated by conventional Trans-Arterial Chemoembolization (TACE) regarding HCC recurrence.

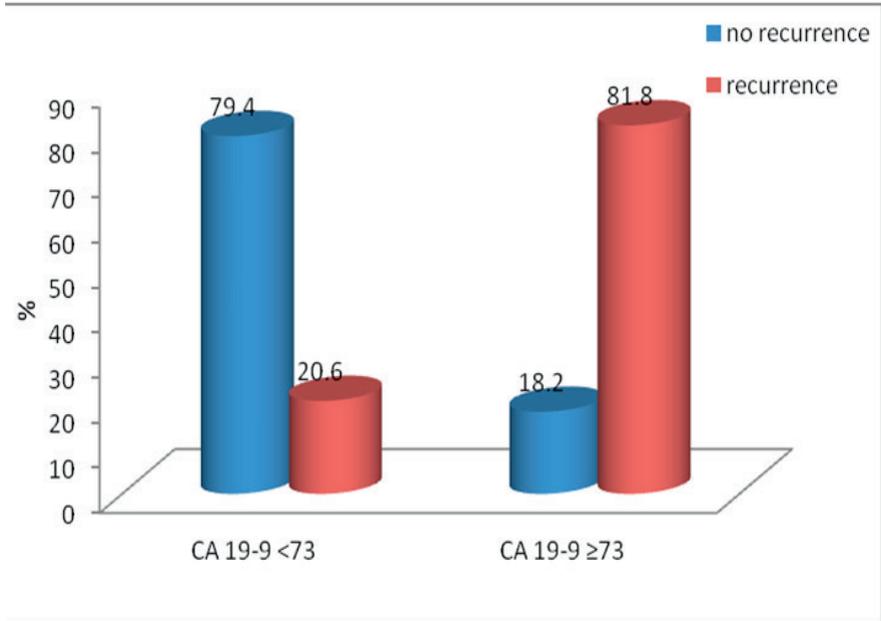
Material and Methods: This study includes 108 patients with elevated serum CA 19-9 above normal limit (37U/ml) out of 427 patients diagnosed to have HCC at Mansoura University Hospitals – tropical medicine department. Criteria of patients selection was according to child score A-B7 through (s.Bilirubin <1.5, INR <1.1, s.Albumin 2.9 to 3.2, no ascites to easily controlled ascites with diuretics, and no hepatic encephalopathy). All studied patients belong to BCLC-B class with single lesion and size range (4.5cm to 5.5cm); all underwent conventional TACE by injecting a mixture of lipidol and doxorubicin (according to body surface area x 50mg doxorubicin powder). Serum level of CA 19-9 were measured before conventional Trans arterial Chemoembolization (TACE) and were correlated with clinical and radiological findings. Follow up were performed every 3 months to determine patient's recurrence for 12 months.

Results: Out of 108 patients with HCC 43 cases had pre TACE serum CA 19-9 >73 u/ml and 65 cases had serum CA 19-9 <73u/ml. High serum CA 19-9 didn't correlate with Patient's age, sex, AFP, viral status and tumor size. only 56 patients had complete response of HCC after conventional TACE out of these 56 patients 22 patients with CA 19-9 > 73 u/ml and 34 patients with CA 19-9 <73 u/ml with close follow up every 3 months for 12

months. Then we observed the following; from the 22 patients with CA 19-9 > 73 u/ml 18 patients experienced recurrence before 12 months with a percentage of 81.8% but from the 34 patients with CA 19-9 <73 u/ml only 7 patients experienced recurrence before 12 months with percentage of 20.5%.

Conclusions: Pre TACE serum CA 19-9 > 73u/ml is associated with high recurrence rate of HCC before 12 months after conventional TACE.

Figure:



Disclosure of Interest: T. beshar: : None Declared, M. hassany: : None Declared, H. elalfy: Consultant: Conflict with: mansoura university hospital, A. Elmokadem: : None Declared, A. Elmorsy : : None Declared, M. Elshennawy: : None Declared, A. elnakib: : None Declared, M. elbandary: : None Declared

AGGRESSIVE BEHAVIOR OF HCV-RELATED HEPATOCELLULAR CARCINOMA: COMPARATIVE ANALYSIS BETWEEN PATIENTS TREATED OR NOT FOR HCV USING DIRECT ACTING ANTIVIRALS

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Introduction: With recent advances in hepatitis C virus (HCV) management for cirrhotic patients using direct acting antivirals (DAA), conflicting reports appeared as regards impact of using DAA on incidence of hepatocellular carcinoma (HCC) development. However, scarce reports commented on the aggressive behavior of HCC in such patients.

Aims: We aimed to analyze differences in tumor behavior between patients who presented with HCV-induced HCC and who were either treated or not for HCV using DAA.

Material and Methods: We did a comparative analysis between all HCV-related HCC patients who presented to our multidisciplinary HCC clinic, Kasr Al-aini hospital, Cairo University during the period between October 2014 till October 2016 and they were HCV managed using sofosbuvir based therapies (Group I). Another matching group (for age, gender and Child Pugh status) for patients who presented to the clinic during the same period is added (Group II) and did not receive DAA. Comparative analysis between both groups as regards the tumor characteristics as well as the response to treatment was performed.

Results: Both groups were age, gender, Child score and performance status matched. Group I included 89 patients while group II included 207 patients. No significant difference was detected between both groups as regards the number of lesions (P=0.3), their site (P=0.2) and their size (P=0.5). However, group I showed a more infiltrative pattern of their lesions while group II had more circumscribed and better delineated lesions. Moreover, incidence of portal vein thrombosis and significant abdominal lymphadenopathy were significantly higher in group I than group II (P=0.03 and 0.03

respectively). Serum levels of alpha fetoprotein were similarly significantly higher in first group (P=0.02). These factors significantly impacted the response to HCC management (P=0.03). Incidence of complete responses to ablations were 47.2% and 49.8% for group I and II respectively while incomplete responses were 12.4% and 25.1% respectively. Supportive treatment without ablation showed higher incidences in group I (40.4%) than group II (25.1%).

Conclusions: Tumor behavior in HCC patients who were managed for HCV using DAA was more aggressive than patients not treated for HCV. This was more evident as regards portal vein thrombosis, abdominal lymphadenopathy as well as the imaging morphology of the lesions. These factors significantly impacted the chance to HCC ablation and the rates of response to treatment.

Figure:

		HCC with DAA (group I) N=89	HCC without DAA (group II) N=207	P value
Age, years		57.9 ± 6.6	58.5 ± 7.2	0.4
Male gender, n* (%)		71 (79.8%)	151 (73.3%)	0.2
Child score, n (%)	A	71 (79.8%)	148 (71.5%)	0.1
	B	18 (20.2%)	59 (28.5%)	
AFP, ng/ml, median (range)		40 (1.9-60500)	19.6 (6-928)	0.02
Number of lesions, n (%)	Single	60 (67.4%)	123 (59.4%)	0.3
	Two	9 (10.1%)	31 (15%)	
	Multiple	20 (22.5%)	53 (25.6%)	
Site of lesions, n (%)	Right lobe	62 (69.7%)	145 (70%)	0.2
	Left lobe	17 (19.1%)	26 (12.6%)	
	Both lobes	10 (11.2%)	3.6 (17.4%)	
Size of lesions, cm, mean ±SD		4.2 ± 2.5	4.4 ±2.3	0.5
Portal vein thrombosis, n (%)		9 (10.1%)	8 (3.9%)	0.03
Significant Lymphadenopathy, n (%)		9 (10.1%)	8 (3.9%)	0.03
Response to ablation	Complete ablation	42 (47.2%)	103 (49.8%)	0.008
	Incomplete ablation	11 (12.4%)	52 (25.1%)	
	Supportive treatment	36 (40.4%)	52 (25.1%)	

*Number

Disclosure of Interest: None Declared

NATURAL HISTORY OF HYPOVASCULAR HEPATOBILIARY PHASE HYPINTENSE NODULES ON GADOXETIC ACID-ENHANCED MR IMAGING IN CIRRHOTIC PATIENTS DURING SURVEILLANCE PROGRAM

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Introduction: The introduction of hepatobiliary contrast agents such as gadoxetic acid in magnetic resonance (MR), has led to the identification of non-hypervascular liver nodules that show only hypointensity in the hepatobiliary phase (HB). Risk of HCC transformation of these nodules has never been assessed prospectively in surveilled cirrhotic patients.

Aims: We prospectively assessed the natural history of these hypovascular nodules.

Material and Methods: Between 2009 and 2016, non-hypervascular HB hypointense nodules detected in cirrhotic patients who underwent MR to integrate ultrasound surveillance, and not technically eligible for biopsy, were prospectively followed-up by MR. Only patients without previous HCC diagnosis or with prior HCC underwent curative treatment but free from recurrence for at least 2 years, were included. Baseline clinical and MR features, and nodule growth rate, were analysed to assess the risk of HCC transformation.

Results: Fifty-eight consecutive hypovascular HB hypointense nodules in 31 cirrhotic patients were prospectively enrolled and followed-up. Of these 58, 38 (65%) were detected at the time of enrollment, 20 (35%) appeared during the follow-up MR imaging. At the end of the study, 28 (48%) nodules acquired the typical HCC vascular pattern, 30 (52%) had no MR feature modification. Overall, 3 different evolutionary MR patterns were observed: 30 (52%) nodules remained unchanged (Pattern A) after a median follow-up of 28 months (range 18-84); 24 (41%) developed arterial hypervascularization and washout (Pattern B) after a median follow-up of 16 months (range 6-39); 4 (7%) after a median follow-up of 36 months (range 24-65) presented washout in the portal/venous phase and subsequently

developed arterial hypervascularization (Pattern C). At multivariate analysis T1 in- and out-phase hyperintensity ($p=0.01$), nodule growth during the follow-up ($p<0.0001$) and history of HCC ($p=0.01$) were significantly related to HCC evolution. When at least one of these parameters was present, sensitivity and specificity for HCC evolution were 92.3% and 76.7%, respectively; the presence of all three parameters had specificity and positive predictive value of 100% and a likelihood ratio for positive test of $+\infty$.

Conclusions: Nearly half of hypovascular HB hypointense nodules detected during surveillance evolve into overt HCC. Presence of T1 in- and out-phase hyperintensity and history of HCC at baseline, as well as nodule growth during the follow-up, are significantly related to HCC evolution.

Disclosure of Interest: L. Ielasi : None Declared, A. Granito : None Declared, M. Renzulli : None Declared, M. Galassi : None Declared, E. Guidetti : None Declared, F. Piscaglia: Sponsored Lectures (National or International): Conflict with: BAYER, BRACCO, EISAI, ESAOTE, R. Golfieri : None Declared, L. Bolondi: Sponsored Lectures (National or International): Conflict with: BRACCO, BAYER

PREVIOUS AND RESOLVED HBV INFECTION IS NOT A RISK FACTOR FOR THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA (HCC) IN PATIENTS WITH LIVER CIRRHOSIS DUE TO HCV OR ALCOHOL

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Introduction: Several studies, mainly in patients with HCV-related cirrhosis, have shown an increase in HCC development among those with previous HBV infection.

Aims: To know the influence of past HBV infection on the risk of HCC development in a cohort of patients with liver cirrhosis due to HCV or alcohol.

Material and Methods: 956 patients with Child A/B cirrhosis due to HCV (n=340) or alcohol (n=616) included in a HCC screening program were analyzed. Most were male (79%), mean age 54.6±8.5 yrs. AntiHBc and antiHBs were determined in all cases. HBsAg-positive patients were excluded. The association of antiHBc positivity and HCC development was analyzed by Kaplan-Meier and adjusted for other classic HCC risk factors (age, sex, tobacco, platelet count, esophageal varices, AFP, previous cirrhosis decompensation) by Cox regression.

Results: AntiHBc was positive in 210 patients (22%), in 138 of them (65.7%) with antiHBs. AntiHBc prevalence did not change along the study. AntiHBc presence was more frequent among patients with HCV (39.1%vs12.6%; p<0.001) or HIV infection (75 vs19%; p<0.001). Age was similar between antiHBc positive and negative patients (53.7±8.4 vs.54.8±8.6 years; p=0.09) and the prevalence was similar in males (22.1%) and females (21.3%) (p=0.79). During a meanfollow-up of 65.8±58.8 months, 161 patients (16.9%) developed HCC. There were no significant differences in the cumulative probability of developing HCC at 15 years between antiHBc positive and negative in the global series (44.6%vs.33.3%; p=0.58), in alcoholic cirrhosis (29.4%vs.29.4%; p=0.44) or in HCV cirrhosis (52.8vs 38.2%; p=0.32). After adjusting with other variables potentially related to HCC development, antiHBc was not a risk factor in the global series (p=0.81),

in alcoholic cirrhosis ($p=0.57$) neither in HCV cirrhosis ($p=0.63$). HCC incidence was significantly higher in antiHBc negative patients ($n=746$) than in those with isolated antiHBc ($n=72$) (33.3%vs.9.4%; $p=0.015$), but the difference disappeared after adjusting for other variables. HCC development was independently associated with older age, male sex and lesser platelet count and prothrombin activity and with HCV infection.

Conclusions: Previous and resolved HBV infection is not a risk factor for the development of HCC in patients with alcoholic or HCV-related cirrhosis. Variables independently associated with HCV development in this cohort were age, male sex, platelet count, prothrombin activity and HCV infection.

Disclosure of Interest: M. A. de Jorge: : None Declared, L. Gonzalez-Diequez: Sponsored Lectures (National or International): Conflict with: Gilead, Abbvie, C. Rodriguez-Escaja: : None Declared, C. Alvarez-Navascues: Consultant: Conflict with: Bayer, Abbvie, Sponsored Lectures (National or International): Conflict with: Gilead, Abbvie, A. Castaño: : None Declared, V. Cadahia: : None Declared, E. Rubio: : None Declared, M. Varela: Consultant: Conflict with: Bayer, Sponsored Lectures (National or International): Conflict with: Bayer, Abbvie, Gilead, M. Rodriguez: Consultant: Conflict with: Bayer, Gilead, Sponsored Lectures (National or International): Conflict with: Abbvie, Gilead

UTILITY OF SCCA-IgM LEVELS IN THE PREDICTION OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS

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Introduction: Early detection of hepatocellular carcinoma (HCC) still is difficult due to the lack of adequate biomarkers that show high sensitivity and specificity. Currently, AFP is the most used biomarker but the real impact is controversial.

Aims: To evaluate the potential role of SCCA-IgM as a biomarker in the prediction of long- term HCC in patients with cirrhosis.

Material and Methods: Retrospective study including 215 cirrhotic patients (Child A 73%, B 22%, C 5%) followed-up prospectively every six months to screen HCC by ultrasound according to EASL guidelines. The overall cohort was obtained from Spain (71.1% 155/215) and Italy (28.9% (62/215). Patients underwent to evaluate SCCA-IgM by ELISA (Hepa-IC, Xeptagen, Venice, Italy). Patients were followed-up during 48 months, being censored at time of the appearance of HCC.

Results: There were 20.9% (33/215) of HCC (an annual incidence of 5.2%). Patients with HCC showed higher levels of SCCA-IgM than those without it (349+547 vs. 245+281 AU/mL; p=0.097). Besides, other variables like age and Child-Pugh B/C were also significantly associated. In multivariate analysis, age (OR, 1.07; 95% IC, 1.03-1.12; p=0.001), Child-Pugh B/C (OR, 2.19; 95% IC, 1.02-4.69; p=0.04) and levels of SCCA-IgM (OR, 1.001; 95% IC, 1.000-1.002; p=0.010) and AFP (OR, 1.02; 95% IC, 1.01-1.03; p=0.0001) were independently associated with HCC (Fig. 1a). Patients with SCCA-IgM >180 AU/mL (cut-off obtained by ROC analysis) showed 21.9% (23/106) of HCC vs. 11.8% (13/109) in those with SCCA-IgM <180 AU/mL (p=0.047). AFP and SCCA-

IgM combination allow to identify a group with low risk of developing HCC (NPV 95%) (Fig. 1b-1c).

Conclusions: SCCA-IgM, in combination with AFP, could represent a new biomarker for the identification of very low risk of long-term HCC (NPV 95%). This approach could make reconsidering the consume of resources in the screening of HCC.

Figure:

Variable	HCC (N=36)	HCC Free (n=179)	Univariate	Multivariate
Sex (Men)	80.6% (29/36)	75.2% (131/179)	P=0.423	
Age ± SD (years)	62 ± 8	57 ± 10	P=0.002	OR 1.07 [95%CI 1.03-1.12]; p=0.001
Child-Pugh (B/C vs. A)	37.1% (13/35)	21.3% (38/179)	P=0.050	OR 2.19 [95%CI 1.02-4.69]; p=0.044
Cirrhosis Etiology			P=0.077	
Alcohol	50% (18/36)	55.9% (100/179)		
VHC	44.4% (16/36)	22.3% (40/179)		
VHB	2.8% (1/36)	12.3% (22/179)		
Other	2.8% (1/36)	9.5% (17/179)		
Albumin ± SD (mg/dL)	3.7 ± 0.7	3.9 ± 0.6	P=0.189	
Bilirubin ± SD (mg/dL)	1.60 ± 1.02	1.58 ± 1.02	P=0.832	
Creatinin ± SD (mg/dL)	1.09 ± 1.34	0.82 ± 0.23	P=0.314	
Platelets ± SD (x 10 ⁹ /L)	103 ± 41	118 ± 60	P=0.151	OR 0.99 [95%CI 0.98-1.00]; p=0.092
AST ± SD (IU/mL)	66 ± 54	49 ± 35	P=0.089	
ALT ± SD (IU/mL)	48 ± 40	40 ± 37	P=0.253	
AFP ± SD (IU/mL)	17.2 ± 34.5	5.9 ± 10.4	P=0.067	OR 1.02 [95%CI 1.03]; p=0.0001
Prothrombin ± SD (%)	71 ± 19	73 ± 18	P=0.635	
SCCA-IgM ± SD	349 ± 547	245 ± 281	P=0.087	OR 1.01 [95%CI 1.000-1.002]; p=0.010

Figure 1a.- Basal characteristics of patients developing HCC vs. non-HCC within 4-years follow-up.

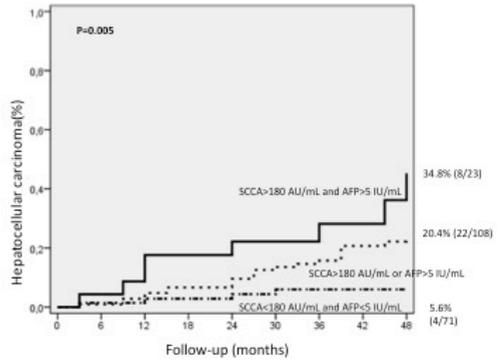


Figure 1b. Cumulative proportion of HCC over time based on the combination of two predefined cut-off for SCCA-IgM and AFP.

Variable	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
SCCA-IgM >180 AU/mL	21.9%	88.2%	55%	64%
AFP > 5 IU/mL	28.6%	87.8%	48.8%	78.1%
SCCA-IgM >180 AU/mL or AFP > 5 IU/mL	22.9%	94.4%	86.4%	39.4%
SCCA-IgM >180 AU/mL and AFP > 5 IU/mL	34.8%	87%	24.4%	92.4%

Figure 1c.- Sensibility, specificity and predictive values of AFP and SCCA-IgM in the prediction of long-term HCC.

Disclosure of Interest: None Declared

PREDICTION AND PREVENTION OF LIVER FAILURE AFTER EXTENSIVE LIVER RESECTIONS FOR LIVER CANCER: THE ROLE OF FUNCTIONAL TESTS

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Introduction: Hepatic resection is the therapy of choice for malignant and symptomatic benign hepatobiliary tumors. Whereas imaging studies allow volumetric assessment of the liver segments, only indirect information is provided concerning the quality of the liver parenchyma and its actual functional capacity.

Aims: This study deals with the preoperative hepatobiliary scintigraphy (HBS) and ¹³C-methacetin breath test for the measurement of liver function with the ultimate goal to design a method to identify patients at risk of liver failure following liver resection.

Material and Methods: The study includes two group of high-risk patients: main (n=53) and control arm (n=35). The patients of both groups have passed standard clinical and laboratory tests, the values of total bilirubin, albumin and prothrombin time showed no decrease in liver function. CT volumetry and ^{99m}Tc-technophyt HBS with ¹³C-methacetin breath test were performed in all test group patients. Patients with low FLR or/and compromised liver function were underwent staged liver resections or anatomical segmental resections. Liver function determined with HBS was compared with methacetin breath test by unified scale.

The hepatic failure were observed by ISGLS criteria on postop day 5.

Results: A strong positive association (r 0.71) was found between preoperative liver function reserve(LFR) determined with HBS and ¹³C-methacetin breath test results in patients with primary and metastatic liver tumors. Receiver operating characteristic (ROC) curve analysis demonstrated high and good quality ¹³C-methacetin breath test and HBS for liver function reserve in predicting postoperative liver failure (AUC = 0,85 and 0,7 respectively). FRL function, measured by a combination of ¹³C-methacetin breath test and dynamic HBS (SE \geq 100%), SP \geq 67%, -VP \geq 100%), was able to accurately

predict actual postoperative remnant liver function. Postoperative liver failure occurred in eight patients of test group (15,1%), decreased in a half ($p<0,001$) compared with control group (26%).

Conclusions: As the regenerative capacity of the liver is related to the quality of liver parenchyma, the success of resection largely depends on parameters of liver function. Preoperative ^{99m}Tc -technephyt hepatobiliary scintigraphy and ^{13}C -methacetin breath test are a valuable techniques to estimate the risk of postoperative liver failure for patients with primary tumors as well as for patients with metastatic liver disease..

Disclosure of Interest: None Declared

EXTENT OF PORTAL INVASION IN PATIENTS WITH HCC: THE MORE, THE WORSE?

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Introduction: Portal vein invasion (PVI) is known to have a significant impact on the prognosis of patients with hepatocellular carcinoma (HCC). Nevertheless, the degree of invasion can vary from sub-/segmental invasion to complete occlusion of the main trunk of the portal vein (PV).

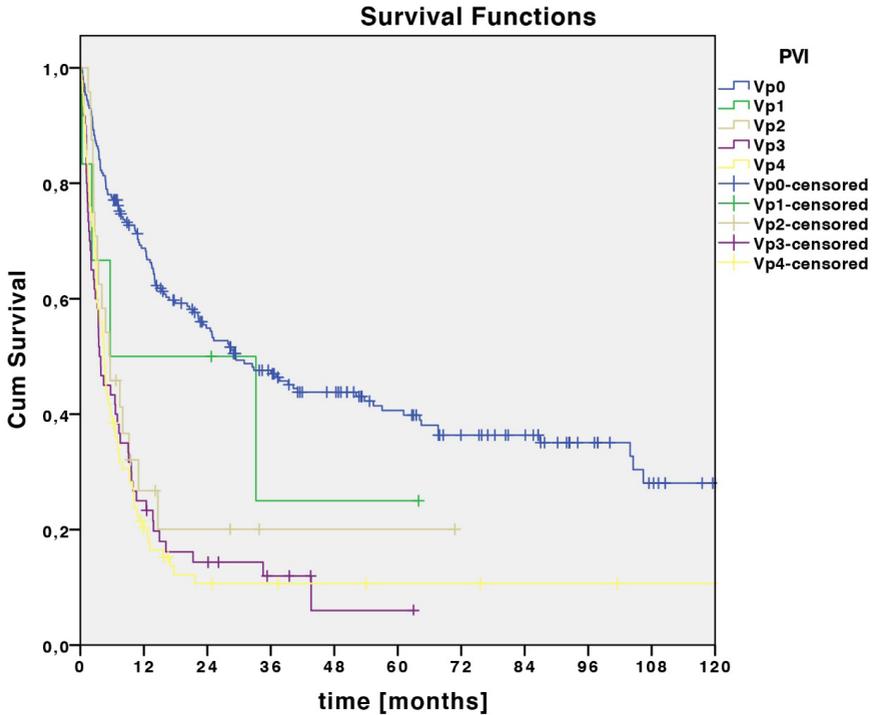
Aims: The aim of this study was to evaluate whether the degree of invasion correlates with an impaired prognosis.

Material and Methods: 407 patients with HCC were extracted from the clinical registry of our tertiary referral center as an ongoing effort to reevaluate the extent of PVI in all patients treated between January 2000 and December 2015. PVI was diagnosed by contrast enhanced computed tomography or magnetic resonance imaging. The extent of PVI was documented using the classification suggested by the Liver Cancer Study Group of Japan ranging from Vp0-Vp4: Vp0=no PVI; Vp1=segmental; Vp2=right anterior or right posterior portal vein; Vp3= right or left portal vein; Vp4=main trunk. Median overall survival (OS) was calculated for each Vp-group.

Results: PVI was present in 186 patients, 221 patients showed no sign of PVI. The patients with PVI were classified Vp1 to Vp4 in 7, 27, 62, and 90 cases. The corresponding median OS yielded 105, 164, 115, and 136 days for Vp1-Vp4, respectively. There was no significant difference between these PVI-subgroups ($p=0.437$). Median OS without PVI was 854 days and was therefore significantly longer compared to the patients with any form of PVI ($p<0.001$).

Conclusions: PVI in patients with HCC is associated with a dismal prognosis. However, the extent of PVI itself has no significant impact – even a minor PVI leads to a very poor prognosis.

Figure:



ePOSTER ABSTRACTS

Disclosure of Interest: None Declared

HEPATOCELLULAR CARCINOMA RECURRENCE AFTER DIRECT ANTIVIRAL AGENT TREATMENT: A EUROPEAN MULTICENTRIC STUDY

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Introduction: Since the introduction of new Direct Antiviral Agents (DAA) for hepatitis C virus, evidence has been published suggesting an increased rate of hepatocellular carcinoma recurrence after DAA therapy.

Aims: The aim of this study is to explore the HCC recurrences after DAA therapy in patients having been treated for HCC in an international multicentric cohort and looking at possible cofactors.

Material and Methods: For this study, a multicentric cohort was built with patients treated in five different centers in Europe: University Hospital Frankfurt, Germany, Inselspital Bern, Switzerland, Erasmus Hospital Brussels, Belgium, University Hospital Leipzig, Germany and Canton Hospital St Gallen, Switzerland. We included patients that have been treated for their HCC prior to DAA therapy with surgical resection, ablation or transarterial (chemo-)embolization and who showed a radiological complete response before starting DAA treatment.

Results: We included a total of 56 patients, 73.2% were men, median age was 61 (48-83), and the mean follow up time was 21.0 months after HCC treatment. HCC recurrence rate of 19% at 1 year and 44% at 2 years after HCC treatment. Anti-HBc positive serology ($p = 0.193$), hepatitis C genotype ($p = 0.970$) were not associated with HCC recurrence.

Patients who had a longer timeframe between HCC treatment and DAA treatment were less at risk of developing a recurrence (HR 0.908, 95% CI 0.857-0.962, p = 0.001).

Conclusions: An international multicentric cohort of HCC patients with complete radiological response before DAA treatment finds a HCC recurrence rate of 19% and 44% at 1 and 2 years, respectively. The timeframe between HCC treatment and DAA therapy is a predictor for recurrences.

Disclosure of Interest: P. Kolly: : None Declared, O. Waidmann: Grant: Conflict with: Medac, Consultant: Conflict with: Bayer, Celgene, Merck Serono, Novartis Oncology, Roche, Other: Conflict with: Travel/congress cost support: Abbvie, Bayer, Celgene, Gilead, Ipsen, Medac, Merck Serono, Novartis Oncology, Teva, J. Vermehren: Sponsored Lectures (National or International): Conflict with: Abbott, Abbvie, BMS, Gilead, Medtronic, Roche, C. Moreno: Grant: Conflict with: Abbvie, BMS, Gilead, Janssen, Roche, Astellas, Consultant: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, Intercept, T. Berg: Grant: Conflict with: Abbvie, Roche, BMS, Gilead, Novartis, Merck/MSD, Janssen, Consultant: Conflict with: Abbvie, Alexion, Bayer, Boehringer Ingelheim, BMS, Gilead, GSK, Janssen, MSD/Merck, Novartis, Roche, Vertex, D. Semela: Consultant: Conflict with: Abbvie, Bayer, BMS, Gilead Science, Intercept, Merck, Sponsored Lectures (National or International): Conflict with: Abbvie, Bayer, Gilead Science, S. Zeuzem: Consultant: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck/MSD, J.-F. Dufour: Grant: Conflict with: Bayer, Consultant: Conflict with: Abbvie, Bayer, BMS, Genfit, Gilead Science, Intercept, Merck, Novartis, Sillagen, Sponsored Lectures (National or International): Conflict with: Abbvie, Bayer, Gilead Science

COMBINATION OF SORAFENIB WITH TRANSARTERIAL CHEMOEMBOLIZATION (TACE) IMPROVES SURVIVAL AS COMPARED TO TACE ALONE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A METAANALYSIS OF 17 STUDIES

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Introduction: The efficacy and safety of transarterial chemoembolization (TACE) plus sorafenib for patients with hepatocellular carcinoma (HCC) have been explored by many studies and meta-analyses, however the results have been controversial.

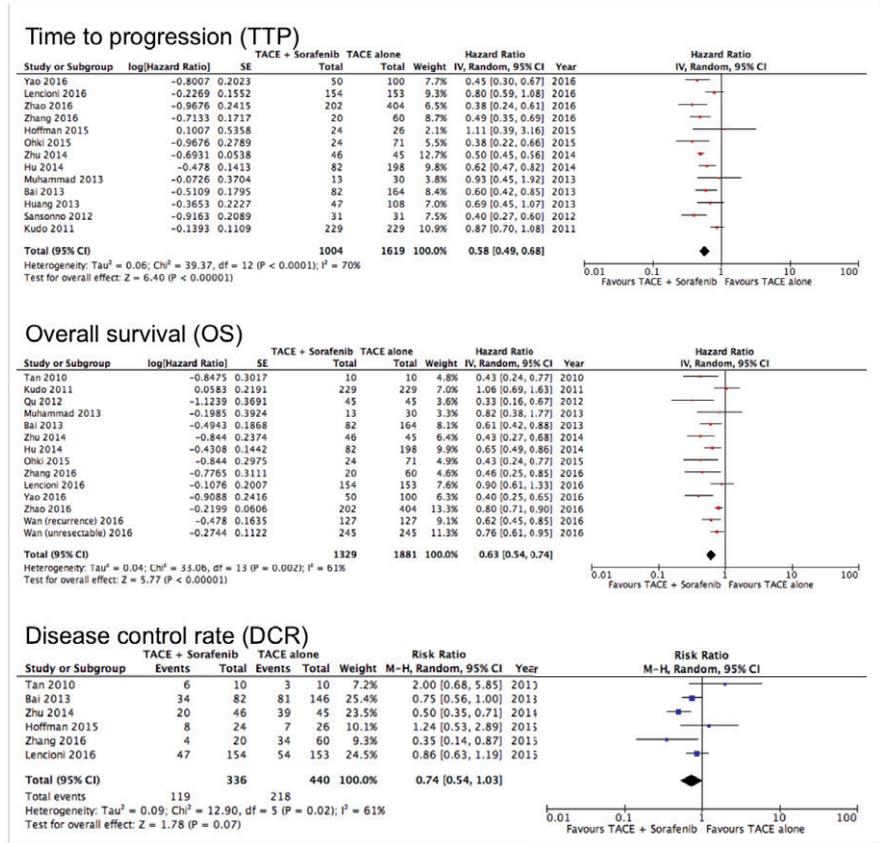
Aims: To perform a meta-analysis of randomized controlled trials and case-controlled studies to evaluate the efficacy and safety of TACE plus sorafenib versus TACE monotherapy in patients with HCC.

Material and Methods: PubMed database was systematically reviewed for studies published in English language, up to November 2016, that compared TACE plus sorafenib with TACE alone. The pooled hazard ratio (HR) with 95% confidence intervals (95% CIs) were calculated for time to progression (TTP), overall survival (OS), disease control rate (DCR), and the incidence of treatment-related adverse events (AEs) using random-effects or fixed-effects model, depending on the heterogeneity between the included studies.

Results: Seventeen trials, including a total of 3477 patients with HCC, were included in this meta-analysis. The pooled results showed that TACE plus sorafenib significantly improved TTP (HR = 0.58, 95% CI: 0.49, 0.68; P < 0.01) and OS (HR = 0.63, 95% CI: 0.54, 0.74; P < 0.01), and marginally improved DCR (RR = 0.74, 95% CI: 0.54, 1.03; P = 0.07). The incidence of treatment-related AEs was higher in the TACE plus sorafenib group.

Conclusions: This meta-analysis confirmed that the combination therapy of TACE plus sorafenib in patients with HCC, significantly improves survival and time to progression. However, the combination therapy was also associated with a significantly increased risk of adverse reactions.

Figure:



Disclosure of Interest: None Declared

RISK OF HEPATOCELLULAR CARCINOMA (HCC) RECURRENCE IN HCV CIRRHOTIC PATIENTS TREATED WITH DIRECT ACTING ANTIVIRALS (DAAs)

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Introduction: Conflicting data exists regarding the impact of Direct Acting Antivirals (DAAs) on early recurrence in successfully treated HCV-related HCC.

Aims: With this aims, we analysed the on-going dataset of RESIST-HCV.

Material and Methods: We evaluated 185 cirrhotic patients with complete radiological response after curative treatment of HCC (mean age 70±9 years, 63.8% males, 41% naïve to antiviral therapy, 156 (84.3%) Child-Pugh A and 29 (1.7%) Child-Pugh B) who completed the treatment between March 2015 and October 2016 in 22 centers of RESIST-HCV. Each physician established DAA regimens and use of Ribavirin. Seventy-nine patients received 12 weeks of therapy, while 106 received a DAA regime of 24 weeks. All patients received HCC surveillance according to the clinical practice policy. The primary endpoint of the analysis was the rate and the time of HCC recurrence from the start of DAAs.

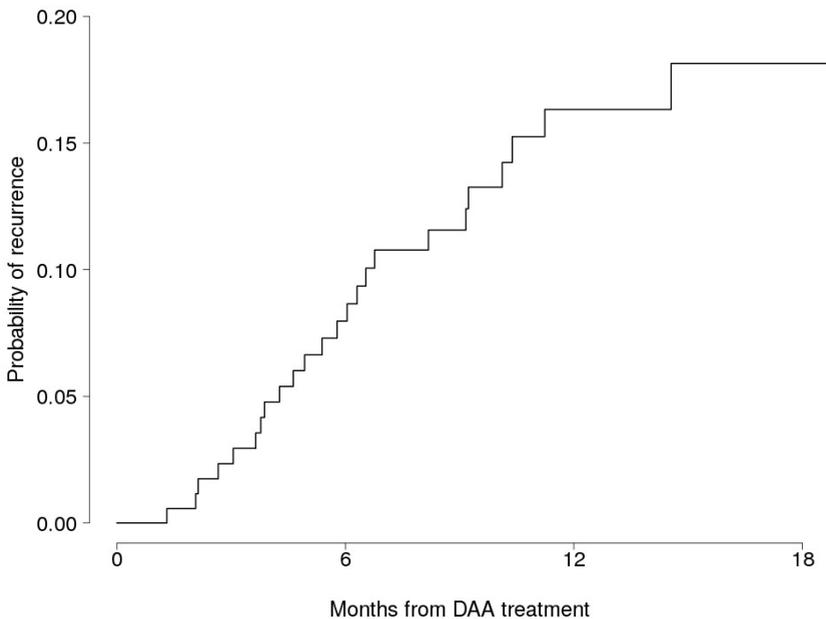
Results: At the end of October 2106, 145 patients (78.4%) completed the DAA regime and 40 were still on treatment. During the follow-up (mean 24 weeks, rang 8-60) 24 patients had a recurrence of HCC with a crude rate of 13%.

Pattern of HCC recurrence was nodular in 83% patients (20/24) and infiltrative in 17% (4/24).

The actuarial probability by Kaplan-Meier method of developing HCC recurrence during follow-up is shown in Fig. 1. The 6 and 12 mo. HCC recurrence rates were 7.9% and 16.3%, respectively. One patient died during follow-up.

Conclusions: In patients with HCV-related successfully treated HCC DAAs does not increase the risk of HCC recurrence. Moreover, potential benefit of DAA on preservation of liver function, resulting in a lower cirrhosis-related mortality and a greater change of receiving curative treatments, should improve survival of patients with HCV-related HCC who achieved complete radiological response after curative treatment.

Figure:



Disclosure of Interest: None Declared

RADIOLOGICAL ASSESSMENTS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA FOLLOWING TRANSARTERIAL CHEMOEMBOLIZATION: CAN INITIAL RESPONSE INDEPENDENTLY PREDICT THE SURVIVAL REGARDLESS OF TUMOR LOAD?

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Introduction: Whether the initial response assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST) can reliably predict the survival in hepatocellular carcinoma (HCC) patients following repeated transarterial chemoembolization (TACE) has been controversial. This may be because difference in tumor load between published studies and tumor load may play a pivotal role in response evaluation.

Aims: The aim of our study was to investigate the prognostic value of mRECIST response in patients with different tumor load.

Material and Methods: A total of 350 patients with intermediate stage HCC and preserved liver function treated with TACE were enrolled. Response to therapy was based on mRECIST criteria. Spline-based analysis was used to define the best cutoff value of tumor load in terms of size and number. Kaplan–Meier and Cox regression analyses were used to explore differences in OS between mRECIST responders and mRECIST non-responders.

Results: Spline-based analysis revealed that the best cutoff value of tumor size was 7 cm and that of 2 for tumor number. On this basis, tumor load was stratified into two groups: a total of 158 patients with 7 cm or less in size and 2 or less in number were assigned to low-tumor load group; Another 192 patients were assigned to high-tumor load group. In low-tumor load group, difference in median survival between responders and non-responders was statistically significant (37.8 versus 22.5 months, P 0.001) and mRECIST responders had a 57% risk reduction when compared to non-responders. Multivariable Cox regression

analysis showed that mRECIST response was an independent predictor of survival. In high-tumor load group, no significant statistic difference in median survival was observed between mRECIST responders and non-responders (20.9 versus 10.0 months, P=0.123); Multivariable Cox regression analysis showed that the initial mRECIST response was not an independent predictor of survival (Table 1).

Conclusions: Response evaluation should be further stratified by the tumor load. The initial mRECIST response strongly predicts the survival only in those patients with low-tumor load, not in patients with high-tumor load.

Figure:

Table 1. Prognostic significance of mRECIST response in low- and high-tumor load subgroups

Variables	Number of patients	Median survival (Months)	Univariate analysis		*Multivariate analysis	
			HR (95% CI)	P	HR (95% CI)	P
Low-tumor load group						
Responders	113	37.8	0.43 (0.28, 0.66)	<0.001	0.41 (0.27, 0.63)	<0.001
Non-responders	45	22.5	Reference		Reference	
High-tumor load group						
Responders	98	20.9	0.77 (0.56, 1.07)	0.125	0.80 (0.54, 1.17)	0.243
Non-responders	94	10.0	Reference		Reference	

mRECIST, modified Response Evaluation Criteria in Solid Tumors; HR, hazard ratio; CI, confidence interval.

* The HR was adjusted by variables of age, sex, ECOG score, α -fetoprotein, albumin, aspartate aminotransferase, and total bilirubin in multivariate Cox regression analysis.

Disclosure of Interest: None Declared

METRONOMIC CAPECITABINE AS SECOND-LINE SYSTEMIC TREATMENT FOR HEPATOCELLULAR CARCINOMA

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Introduction: Metronomic Capecitabine (MC) is a well-tolerated systemic treatment showing promising results as second-line therapy in patients with hepatocellular carcinoma (HCC).

Aims: To test the efficacy and safety of MC as second-line therapy in HCC patients who progressed under sorafenib or did not tolerate this drug.

Material and Methods: Eighty-five patients undergoing MC were compared to 60 patients treated with best supportive care (BSC) after Sorafenib discontinuation. The two groups were compared for demographic and clinical features. In order to minimize differences between groups, a propensity score model was performed. A multivariate regression analysis was conducted to detect independent prognostic factors.

Results: Patients undergoing MC showed better performance status, lower tumor burden, lower prevalence of portal vein thrombosis, and better BCLC stage. Median (95% CI) survival was 9.9 (6.7-13.0) months in MC and 4.8 (3.8-5.8) months in BSC patients ($p=0.001$). This benefit was confirmed in patients matched with the propensity analysis [11.6 months (5.9-17.3) vs. 4.2 months (2.4-6.0), $p=0.003$]. The cause of Sorafenib discontinuation and MC were independent prognosticators. Capecitabine achieved better results in patients who stopped Sorafenib for adverse events than in those who progressed



[17.6 months (15.8-19.5) vs. 8.4 months (5.2-11.5), $p=0.002$]. Treatment toxicity was low and easily manageable with dose modulation.

Conclusions: Metronomic Capecitabine may be an efficient and safe second-line systemic therapy for HCC.

Disclosure of Interest: None Declared

COMPARATIVE ANALYSIS BETWEEN PATIENTS WHO DEVELOPED HEPATOCELLULAR CARCINOMA AND WERE TREATED FOR HCV USING DIRECT ACTING ANTIVIRALS: DE NOVO VERSUS RECURRENCE LESIONS

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Introduction: A recent appearance of direct-acting antivirals (DAAs) led to a surge in, management of Hepatitis C virus (HCV) patients even with advanced liver disease situations. Nowadays, a large proportion of HCV treated patients are already cirrhotic with retained possibility to develop HCC even after complete cure from HCV.

Aims: We aimed to study tumoral differences between patients who developed HCC post HCV treatment either as a recurrence post confirmed complete ablation (before their management with DAAs) or as denovo appearance of HCC lesions.

Material and Methods: We retrospectively analyzed 89 patients who presented to our HCC multidisciplinary clinic with HCC lesions after their HCV management using sofosbuvir-based regimens. Forty-five patients gave a history of complete ablation of focal lesions before intake of DAAs and were confirmed according to international guidelines for management of HCC. Another 44 patients developed de novo lesions post DAAs treatment. Both groups of patients were compared as regards their baseline characteristics, tumor-related criteria, their response to sofosbuvir-based therapy for HCV therapy as well as their response to ablation methods for HCC lesions.

Results: Both groups showed no significant difference as regards their baseline characteristics (age, gender, Child-Pugh score and performance status). No differences were detected in their response to DAAs (P=0.5) even when we sub-analyzed their response according to the different lines of sofosbuvir-based therapy. Concerning tumoral factors, no significant difference was present between groups according to; number (P=0.9), site (P=0.2) and size of lesions (P=0.39). However, time elapsed between the end of DAAs

management and first diagnosis of the presence of focal lesions was significantly longer in denovo group (15.22±16.39 months) versus recurrence group (6.76±5.1 months) (P=0.008). In addition, response to ablation was significantly better in de novo lesions compared to HCC recurrence (P=0.03).

Conclusions: Although de novo HCC lesions significantly developed later than recurrence lesions in patients treated for HCV using sofosbuvir-based therapy, their response rates were significantly better. No differences were detected between both groups in their response to DAAs and their tumoral characteristics.

Figure:

		HCC recurrence after DAA N=45	HCC de novo after DAA N=44	P value
Age, years		57.76 ± 6.52	58 ± 6.85	0.9
Male gender		35 (77.8%)	36 (81.8%)	0.6
Child score	A	35 (77.8%)	36 (81.8%)	0.6
	B	10 (22.2%)	8 (18.2%)	
Response to DAAs*	Responder	29 (64.4%)	31 (70.5%)	0.5
	Non responder	4 (8.9%)	4 (9.1%)	
	Relapser	12 (26.7%)	7 (15.9%)	
Time to detection of HCC, months, mean ± SD		6.76 ± 5.1	14 ± 16.02	0.008
Ablation method for HCC	TACE	23 (51.1%)	19 (43.2%)	0.2
	MWA	4 (8.9%)	11 (25%)	
	PEI	0	1 (2.3%)	
	Resection	2 (4.4%)	0	
	TACE + MWA	1 (2.2%)	1 (2.3%)	
	Supportive	15 (33.3%)	12 (27.3%)	
Response to HCC treatment	Complete	15 (33.3%)	27 (61.4%)	0.02
	Partial	8 (17.8%)	3 (6.8%)	
	Not treated	22 (48.9%)	14 (31.8%)	

TACE: transarterial chemoembolization, MWA: microwave ablation, PEI: percutaneous ethanol injection

Disclosure of Interest: None Declared

LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA > 5 CM

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Introduction: Management of hepatocellular carcinoma (HCC) larger than 5 cm is still debated.

An unfavourable prognosis in which morbidity rates range from 25% to 50% and mortality rates from 0% to 8% are described in patients with lesions of ≥ 10 cm, these patients are often deemed to be non-amenable to surgery.

Aims: The aim of our study was to compare morbidity and mortality after the surgical resection of HCC according to the nodule size.

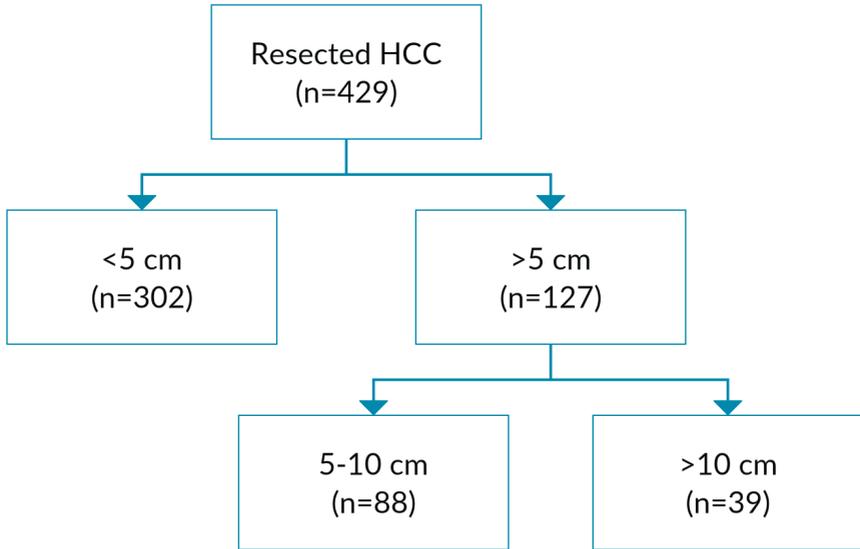
Material and Methods: Since 2001, 429 liver resections for HCC were performed in our institution. We divided the cohort into two groups, 88 patients in group 1 patients with HCC diameter from 5 to 10 cm and 39 patients in group 2 with HCC diameter ≥ 10 cm. (figure 1)

Results: The HCC nodule was associated with an underlying liver disease with similar rates in the two groups. In 17% and 17,9% for HBV infection for group 1 and 2 respectively; in 43,2% and 30,8% for HCV infection; in 4,5% and 7,7% for alcohol. In 30,7% of cases in the first group and in 35,9% of cases in the second group the HCC grew into a healthy liver. ween the two groups ($p=0,595$).

In 30,7% of cases in the first group and in 35,9% of cases in the second group the HCC grew into a healthy liver. A major liver resection was performed in 36,3% of cases in group 1 versus 66,6% in group 2 ($p=0,001$). In 2 cases for the first group and in 10 cases in the second group a laparoscopic approach was performed. Median operative time was higher in group 2 ($p=0,001$). The median postoperative hospital stay was similar in the two groups ($p=0,897$). The postoperative morbidity was not different between the two groups ($p=0,595$).

Conclusions: The tumour size does not contraindicate a surgical resection of HCC even in patient with HCC ≥ 10 cm.

Figure:



Disclosure of Interest: None Declared

APOLIPOPROTEINS ALTERATIONS IN HEPATITIS C ASSOCIATED HEPATOCELLULAR CARCINOMA: COULD THEY SERVE AS A DIAGNOSTIC TOOL?

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Introduction: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. Poor survival rate of HCC patients is largely attributed to their diagnosis in a late incurable stage. Novel non-invasive biomarkers for screening and diagnosis of HCC are highly needed

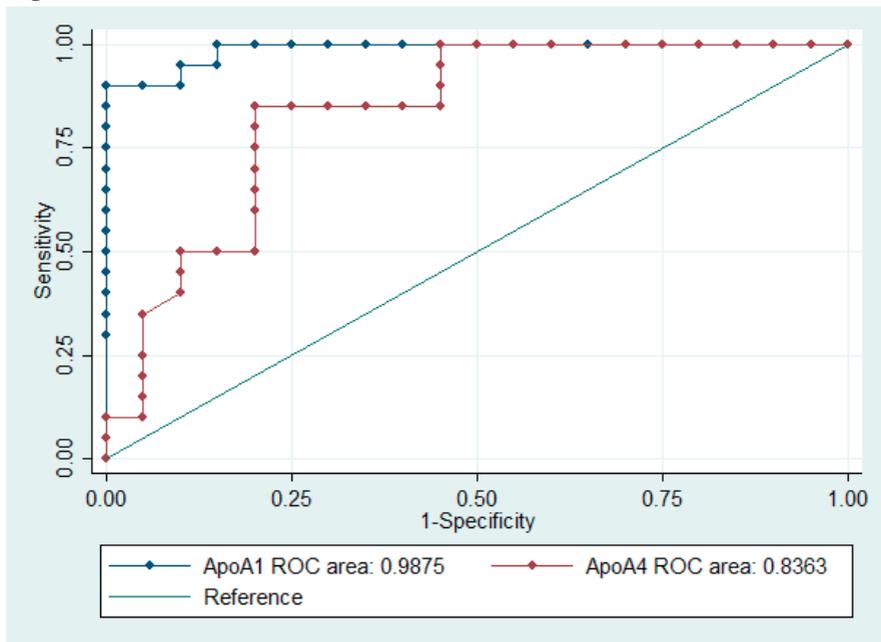
Aims: Evaluation of circulating Apolipoprotein A1 (Apo-A1) and apolipoprotein A4 (Apo-A4) as potential markers for HCC screening and diagnosis.

Material and Methods: A prospective case-control study was conducted on 60 adult patients of both sex within the spectrum of HCV-related chronic liver disease including HCC. In addition to 20 healthy control individuals. Patients were stratified into 3 equal groups each of 20; chronic hepatitis C (CH), post-hepatitis C cirrhosis (LC) and HCC. All patients and controls have undergone full clinical assessment and lab investigations in addition to evaluation of serum Apo-A1 and Apo-A4 levels by ELISA

Results: High levels of circulating Apo-A1 and Apo-A4 were detected in HCC patients compared to patients with LC (212.12 ± 101.24 mg/dl Vs. 30.25 ± 12.71 mg/dl) and (19.00 ± 4.13 mg/dl Vs. 11.22 ± 6.63 mg/dl) respectively. Receiver operator characteristics (ROC) curve showed that for diagnosis of HCC, a cutoff of 78.6 mg/dl for Apo-A1 yielded 90% sensitivity and 100% specificity with 100% PPV and 86.96% NPV (C statistics =0.99) and a cutoff of 16.5 mg/dl for Apo-A4 yielded 85% sensitivity and 80% specificity with 80% PPV and 80% NPV (C statistics =0.84) (Figure 1). Furthermore, within HCC group, Apo-A1 was significantly higher in patients with small HCC (>2cm) than those with large tumors (319.23 ± 108.58 mg/dl vs. 185.35 ± 82.47 mg/dl respectively, p-value 0.01). Lower Apo-A1 level correlated significantly with the occurrence of pylethrombosis (188.18 ± 86.45 mg/dl vs. 347.83 ± 71.33 mg/dl respectively, p-value 0.007).

Conclusions: Apo-A1 and Apo-A4 are novel biomarkers for HCC screening and diagnosis with a special discriminative ability for Apo-A1 for those with small tumors as well as those with pylethrombosis.

Figure:



Disclosure of Interest: None Declared

MICROWAVE ABLATION OF LARGE HCCS BY SIMULTANEOUS MULTIPLE ANTENNAE INSERTION: LONG TERM FOLLOW-UP

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Aims: We report long term results of microwawe ablation (MWA) with simultaneous insertion of multiple antennae in the treatment of large Hepatocellular Carcinoma (HCC).

Material and Methods: Between October 2008 and december 2015, 46 cirrhotics (33 class A, 13 class B Child-Pugh) with a HCC nodule >3 cm (range:3.2-7.0cm; mean:4.5cm) underwent MW ablation in a single session by one or more simultaneous insertion of multiple 13-gauge-MW-antennae (Evident MWantenna, Covidien, USA; SynchroWave. MicroThermX® microwave-ablation system, Terumo, Belgium, Europe). 28 patients were not eligible for surgery, 18 refused surgical therapy (liver transplantation or hepatic resection). All patients underwent intra operative contrast enhanced ultrasound (CEUS) to detect residual viable tumor, in order to treat it in the same session by reinsertion of 2-3 MW antennae in the tumor. Efficacy of ablation was definitely assessed with three-phase computed tomography (CT) after one month. After treatment, scheduled follow-up entailed US every 3 months and CT every 6 months for 2 years and every 12 months thereafter.

Results: 10 and 24 patients underwent a single insertion of 2 and 3 synchronous antennae, respectively. 12 patients underwent 2 insertions of 3 antennae in the same session. Post-treatment-CT showed complete necrosis in 41/46 (89%) patients. Major complication occurred in 4 patients: severe hemoperitoneum, treated with blood transfusion, 2 superinfection of large necrotic ablation areas and 1 severe liver failure. Minor complications were: self limiting Right pleural effusion in 3 cases, and pain requiring i.v. pain killers in 12 cases. Follow-up ranged from 18 to 78 months (mean: 32 months). During follow-up, local recurrence occurred in 9/46 (19%) within 3 to 24



months (median 12 months). Recurrences in other liver segments occurred in : 42/46 (91%) within 6 to 36 months (mean 15 months). Extrahepatic bone metastasis from HCC were observed in 1 patient 24 months after treatment. 19/46 patients (41%) died within 18 – 60 months (mean 30 months). Death occurred for tumor progression in 11 (69% of deaths, 30% series), decompensation of cirrhosis in 4, hemorrhage from esophageal varices in 3 and hemorrhagic stroke 1 patients, respectively. 27 patients (59%) are alive at 18 – 78 months (mean 32 months).

Conclusions: Aggressive ablation of large HCC by simultaneous insertion of multiple MW antennae is safe and seems to result in patients' survivals comparing with surgery and small HCC ablation.

Disclosure of Interest: None Declared

CAN HEPATIC RESECTION BE ADVOCATED OVER THE TRANSARTERIAL CHEMOEMBOLIZATION FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA?

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Introduction: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of cancer-related death. The European Association for Study of the Liver (EASL) recommends the transarterial chemoembolization (TACE) as the first line treatment for HCC patients with intermediate stage (stage B) while hepatic resection is recommended for HCC patients with stage A. Multiple clinical studies have investigated whether the hepatic resection might achieve better survival than the TACE in HCC patients. However, results of these studies are controversial.

Aims: The aim of this meta-analysis is to provide class one evidence about the survival rate following hepatic resection compared with the TACE for patients with HCC.

Material and Methods: We searched PubMed for clinical studies comparing the TACE with hepatic resection for patients with HCC. Overall survival rate, 1- and 5- year survival rates, and 30-day mortality rate were pooled as RR in a random effect model meta-analysis. Subgroup analysis was performed to stratify the survival rate according to HCC stage and the status of portal vein tumor thrombus.

Results: Seventy-three studies (with a total of 21944 patients) were pooled in the final analysis. The overall survival rate favored the hepatic resection group than the TACE group RR 0.35, 95% CI [0.29 to 0.43]. Similarly, the one-year and five-year survival rates favored the hepatic resection group than the TACE group (RR 0.92 and RR 0.74, respectively). The incidence rate of mortality within 30 days from the procedure was higher in the hepatic resection group than TACE group (2.8% vs. 1.3%), however, this difference was not statistically significant. Stratification analysis showed that hepatic resection achieved better survival rate than the TACE in all HCC subgroups (1) patients with stage A (RR 0.44, 95% CI [0.36 to 0.55]), (2) patients beyond stage A (RR 0.28,

95% CI [0.19 to 0.39]), and (3) patients with portal vein tumor thrombus (RR 0.49, 95% CI [0.39 to 0.62]).

Conclusions: Our meta-analysis provides class one evidence that hepatic resection achieves better survival rate than the transarterial chemoembolization for patients with HCC within stage A and beyond stage A of the Barcelona Clinic Liver Cancer staging.

Disclosure of Interest: None Declared

PLATELET-COUNT INFLUENCES SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Current evidence suggests that a normal platelet function is essential for cancer progression and metastasis. Blocking the purinergic P2Y₁₂ receptors on platelets with ticagrelor e.g. inhibited metastasis and improved survival in a murine model of cancer. To date, no information on the influence of platelets on hepatocellular carcinoma (HCC) is available.

Aims: We hypothesized that irrespective of functional platelet blocking cancer progression in HCC could depend on platelet-count and aimed to analyse the correlation with survival.

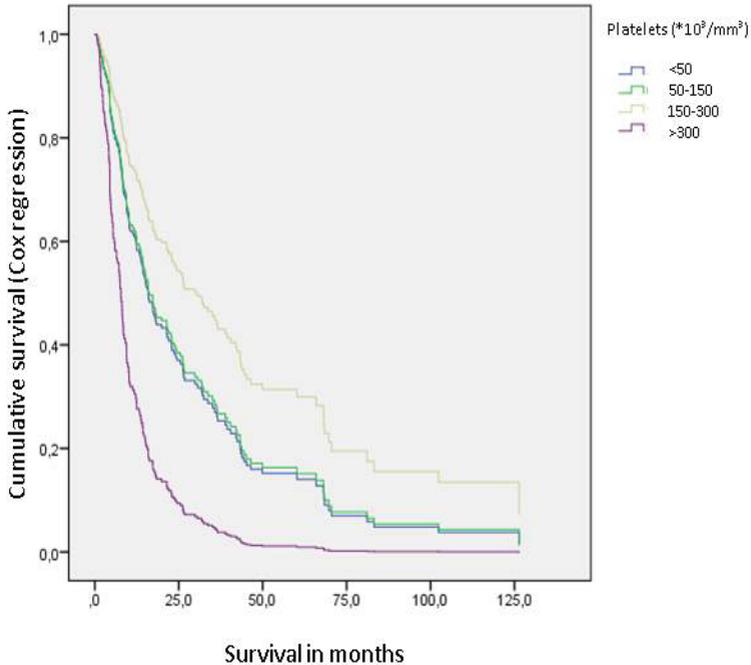
Material and Methods: We retrospectively analysed data of subsequent patients of mostly Caucasian descent from 2005 to 2014 with proven HCC. Patients were categorised according to the platelet count (I: <50, II: 50-150, III: 150-300 and IV: >300*10³/mm³). We compared survival in the different groups and analysed the contribution of other prognostic factors including BCLC stage and presence of cirrhosis. Descriptive statistics and a Cox-regression model were performed using SPSS.

Results: 299 HCC patients (mean age 66.0+/-10.2 years) were included. 83.3% were male, 72.2% had a proven diagnosis of liver cirrhosis. BCLC stages ranged from 0 to D (0: 3.7%, A: 25.8%, B: 40.5%, C: 24.1%, and D: 5.7%). Metastasis and portal vein invasion were observed in 19.7% of the patients. Treatment of HCC generally followed the BCLC algorithm (resection 27.8%, RFA 7.0%, transplant 4.7%, TACE 49.2%, SIRT 7.7% Sorafenib 33.1%). Median survival in the total cohort was 17.2 months (mean 26.9+/-30.0 months). Considering platelet-counts, group IV (n=36) had the shortest survival (median 5.4 months). Median survival in the other groups was 21.4 months (I), 15.9 months (II), and 29.8 months (III), respectively, with statistically significant differences between groups. Differences in survival according to platelet count were comparable within the individual prognostic groups of BCLC (A-C) and Child-Pugh stages (A-C). In

a Cox-regression model including age, sex, cirrhosis, and BCLC stage survival differences between platelet groups were highly significant ($p < 0.00$ – $p = 0.038$).

Conclusions: Patients with hepatocellular carcinoma and platelet-counts $>300 \times 10^3/\text{mm}^3$ have a shorter survival compared with patients with lower counts. Given a confirmation of these findings in other cohorts, platelet counts may be incorporated into adapted prognostic scores for HCC patients. Future research will have to elicit underlying mechanisms and confirm a putative benefit of platelet inhibition in platelet counts $>300 \times 10^3/\text{mm}^3$.

Figure:



Disclosure of Interest: None Declared

THE FUNCTIONAL LIVER TESTS (ICG, HBS, 13-METACITIN) IN LIVER CANCER PATIENTS: WHICH IS THE BEST?

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Introduction: Postoperative liver failure is the major cause of mortality and morbidity after partial liver resection, and develops as a result of insufficient remnant liver function. Therefore, accurate preoperative assessment of the future remnant liver function is mandatory in the selection of candidates for safe partial liver resection.

Aims: The aim of study was to sum up our experience on the most clinically relevant and novel liver function tests used for the assessment of hepatic function before liver surgery.

Material and Methods: ICG-test, methacetin breath test and 99mTc-technephyt hepatobiliary scintigraphy (HBS) were performed prior to major resection in 30 high-risk patients with liver tumors, including 15 patients with hepatocellular carcinoma. Liver function determined with HBS was compared with methacetin breath and ICG test by unified scale.

Results: Passive liver function tests, including biochemical parameters and clinical grading systems, are not accurate enough in predicting outcome after liver surgery. Dynamic quantitative liver function tests such as the ICG test is more accurate as it measures the elimination process of a substance that is cleared and metabolized almost exclusively by the liver. However, this test only measure global liver function. Nuclear imaging techniques such as 99mTc- technephyt hepatobiliary scintigraphy can measure both total and future remnant liver function, and potentially identify patients at risk for postresectional liver failure. Meanwhile, 13C-methacetin breath test measures the microsomal capacity of the liver. In fact, a strong positive association ($r\ 0.73$, $p<0.01$) was found between 13C-methacetin breath test determined with 99mTc-technephyt hepatobiliary scintigraphy, a positive moderate uphill relationship between results of ICG & breath test ($r\ 0.53$, $p<0.01$) and ICG& HBS ($r\ 0.6$, $p<0.01$)



Conclusions: As there is not one test that can measure all components of liver function, liver functional reserve remains to be estimated from combination of quantitative liver function tests. Presently, combination of ^{99m}Tc - technophyt HBS, ICG and ^{13}C -methacetin breath test seems to be the most valuable liver function estimate, as its can measure multiple aspects of liver function in specifically the future remnant liver.

Disclosure of Interest: None Declared

ALPHA FETOPROTEIN – A USEFUL TOOL FOR FOLLOW-UP OF INTERFERON-FREE TREATED CIRRHOTIC PATIENTS WITH DE NOVO HEPATOCELLULAR CARCINOMA AFTER SVR

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Introduction: The risk of hepatocellular carcinoma (HCC) development decreases after obtaining sustained virological response (SVR) in patients treated with pegylated interferon and ribavirin. In DAA era, with very high SVR rates in patients with compensated and decompensated liver cirrhosis, this effect was expected to be even more pronounced.

Aims: The aim of our study was to evaluate the early occurrence and recurrence of HCC in cirrhotic patients treated with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin.

Material and Methods: We analyzed 284 consecutive patients with HCV liver cirrhosis genotype 1b treated with 3D and ribavirin regimen and followed for 6 months. Twenty patients had treated HCC and documented imaging without recurrence prior to initiation of antiviral therapy.

Results: 3D regimen induced SVR in 99.3% of patients. During 6 months of follow-up, HCC was detected in 10 patients (3.5%): 4 patients out of 20 patients with previous HCC (20%) and 6 out of 264 patients (2.3%) without previous HCC. Nine patients with de novo or recurrent HCC had SVR, only one was nonresponder and developed de novo HCC. Patients with recurrent or de novo HCC had a median age of 63years, 58.6% were males, 96.6% were with HCC intraMilan, predominantly one nodule in 82.8%, with a median maximum size of the nodule of 2.5cm. The median time to recurrence or de novo HCC was 3.2 months. According to BCLC classification 24.1% of patients were stage 0, 69% were stage A and 6.9% were stage B. There was a significant difference regarding AFP value between patients with de novo HCC and those without HCC de novo at the end of antiviral therapy (121.1 ± 96.8 vs 6.3 ± 0.5 ng/ml, $p=0.03$). In the group without HCC de novo, AFP value decreased significantly between initiation and the end of the antiviral therapy (26.1 ± 8.3 vs 6.3 ± 0.5 ng/ml, $p=0.02$).



Conclusions: All cirrhotic patients with SVR following DAA therapy should be screened for de novo HCC as well as surveilled for recurrent HCC in patients with previous HCC prior to antiviral therapy every 3 months after the end of antiviral therapy. Association of AFP monitoring during antiviral therapy can increase the diagnostic accuracy in these patients with early stages of HCC.

Disclosure of Interest: None Declared

PROGNOSTIC FACTORS FOR SURVIVAL OF BCLC-C STAGE HEPATOCELLULAR CARCINOMA PATIENTS ACCORDING TO PREVIOUS TREATMENTS: A REAL-LIFE EXPERIENCE

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Introduction: BCLC-C stage hepatocellular carcinoma (HCC) includes a wide spectrum of tumor and patients' characteristics. Prognostic analyses have included a majority of patients without previous treatments, thus being far from the real-life setting.

Aims: To assess prognostic factors for survival of patients affected by BCLC-C stage HCC in a real-life setting, according to the previous treatment history.

Material and Methods: Caucasian cirrhotic patients with BCLC-C stage HCC consecutively evaluated by the HEPATOCATT multidisciplinary group were included in the analysis. Pre-treatment (Child-Pugh score, performance status (ECOG), number and maximum size of lesions, vascular invasion, metastases, the combination of vascular invasion and extrahepatic spread, alfafetoprotein (AFP) levels) and post-treatment (the number of treatments after the progression to BCLC-C stage and disease control (DC) considering stable+partial+complete response as the best treatment outcome) variables were considered as prognostic factors. The analysis was adjusted for sex and age.

Results: 116 patients were included in the analysis, 60 (51.7%) received at least one previous treatment before the progression to BCLC-C stage (previously treated (T)), whereas the remaining 56 patients did not receive any previous therapy (never treated (U)) (Table 1). U patients had a worse liver function, larger tumors, more frequent vascular invasion and higher AFP levels.

Median survival was 13.8 mo (95%CI 11.2-22.1) for T and 13 mo (95%CI 8.2-25.7) for U patients ($p=0.845$). In T subjects, the coexistence of vascular invasion and extrahepatic spread was the only pre-treatment variable associated with a worse outcome at univariate and multivariate analysis (HR 2.197, 95%CI 1.12-4.3, $p=0.022$. Median survival: 12.8 mo vs. 16.3 mo) (Table 1). In U patients, AFP>200 was the only independent predictor of worse outcome (HR 7.46, 95%CI 1.18-47.29; $p=0.033$. Median survival: 5 mo vs. 13.9 mo). As expected, DC was associated with a better survival in both T and U groups (T: HR 0.363, 95%CI 0.15-0.83, $p=0.017$, median survival 13.4 mo vs. 10.7mo; NT: HR 0.15, 95%CI 0.05-0.45; $p=0.0007$, median survival 35.1 mo vs. 4.2 mo).

Conclusions: In patients with BCLC C HCC, the coexistence of both vascular invasion and metastases in previously treated subjects and high levels of AFP in never treated patients are pre-treatment predictors of poor patients' outcome.

Figure:

Table 1

	Pts' characteristics			Survival analysis TREATED pts		Survival analysis UNTREATED pts	
	Treated pts (60)	Untreated pts. (56)	p-value	Univariate	Multivariate	Univariate	Multivariate
Age>=65	36(60%)	34(60.7%)	0.943	0.462	-	0.575	-
Sex	51(85%)	43(76.7%)	0.373	0.664	-	0.231	-
ECOG			0.234	0.160	-	0.015	ECOG1 vs 0: $p=0.144$; ECOG2 vs 0: $p=0.055$
Child-Pugh score (A/B)	51(85%)/ 9(15%)	35(62.5%)/ 21(37.5%)	0.010	0.741	-	0.651	-
N nodules (1/2-3/>3 or infiltrating)	16(26.6%)/ 13(21.7%)/ 30(50%)	22(39.3%)/ 8(14.3%)/ 25(44.7%)	0.293	0.522	-	0.571	-
Size (max. cm)	22(36.7%)	31(55.3%)	0.048	0.558	-	0.0001	0.187
Vascular invasion	20(33.3%)	30(53.6%)	0.044	0.064	-	0.123	-
Metastases	11(18.3%)	8(14.3%)	0.735	0.113	-	0.888	-
Vascular invasion+ Metastases	27(45%)	31(55.3%)	0.352	0.0217	HR 2.197 (95%CI 1.12-4.3; $p=0.022$)	0.181	-
AFP>200	8(13.3%)	20(35.7%)	0.014	0.52	-	0.0001	HR 7.46 (95%CI 1.18-47.29; $p=0.033$)
N treatments post-BCLC C (none/singl e/multiple)	11(18.3%)/14 (23.3%)/ 35(58.3%)	11(19.7%)/ 21(37.5%)/ 24(42.9%)	0.110	0.013	0.085	0.461	-
DC	23(38.3%)	21(37.5%)	1	0.017	HR 0.363 (95%CI 0.15-0.83; $p=0.017$)	<0.0007	HR 0.15 (95%CI 0.05-0.45; $p=0.0007$)

Disclosure of Interest: None Declared

HEPATOCELLULAR CARCINOMA RECURRENCE RATE IN HCV INFECTED PATIENTS TREATED WITH DIRECT ANTIVIRAL AGENTS. A SINGLE CENTER EXPERIENCE

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Introduction: In the last few years many HCV patients with previous diagnosis of hepatocellular carcinoma (HCC) have been treated with direct antiviral agents (DAAs) for HCV infection. However there are conflicting data on HCC recurrence rate after DAAs therapy.

Aims: Aim of this study was to prospectively evaluate the rate of HCC recurrence following sustained virological response (SVR) by DAAs.

Material and Methods: From April 2015 to September 2016 we consecutively enrolled HCV infected patients previously treated for HCC at Liver Unit of Cardarelli Hospital. All patients had a free-disease survival from HCC of at least 6 months before starting antiviral therapy. The efficacy of HCC therapy was evaluated according to mRecist criteria at CT or MRI. Radiological evaluation was carried out within 30 days from the start of therapy. All patients underwent DAAs therapy, selected on an individual basis according to the recommendation issued by the Italian association of the study of the liver

Results: A total of 71 patients were enrolled. Among them, 42 patients had available data on SVR status and were considered for the analysis. There were 21 males (58.3 %) and 15 females. The median age of the patients was 73 years (range:52-85). The median follow up was 12 months after the beginning of treatment (range: 6-18 months). Genotype distribution was as follows: 36 patients infected with genotype 1 (85.7%), 5 with genotype 2 and 1 patients with genotype 3. SVR was achieved in 38/42 patients (90.5%). HCC recurrence was observed in 11/38 patients with SVR (28.9%). The median time for recurrence was 9 months from the start of therapy with a range of 1-13 months; with 2 patients who showed recurrence during therapy. Among the patients who did not achieve SVR, 1/4 showed HCC recurrence after 10 months from end of treatment.



Conclusions: Treatment with DAAs are highly effective with a SVR of about 90% even in patients with advanced liver disease. Nonetheless, in patients with previous history of HCC, the eradication of HCV did not reduce the risk of short and medium term recurrence.

Disclosure of Interest: None Declared

ALKALINE PHOSPHATASE LEVELS CAN IMPROVE PREDICTION FOR HEPATOCELLULAR CARCINOMA IN DECOMPENSATED NONCHOLESTATIC CIRRHOTIC PATIENTS

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Introduction: Liver Cirrhosis is a major risk factor for hepatocellular carcinoma and all societies recommend surveillance. In addition to the routine surveillance, ultrasound and alpha-fetoprotein can be complemented by alkaline phosphatase levels.

Aims: The aim of this study is to assess the effectiveness of ALP measurement in HCC surveillance.

Material and Methods: In this retrospective analysis, all patients with decompensated cirrhosis, who received surveillance through ultrasound, alpha-fetoprotein and Alkaline-Phosphatase measurements between Jan 2012 to Jan 2014 were followed up until February 2015. The performance effectiveness of surveillance using ultrasound, alpha-fetoprotein and Alkaline-Phosphatase in hepatocellular carcinoma was compared.

Results: Overall, 1004 patients were followed for a period of 1 year. Forty five patients developed hepatocellular carcinoma. The difference in Alkaline-Phosphatase values in patients with and those without hepatocellular carcinoma showed significant difference right from 9 months before the actual diagnosis of HCC ($P < 0.0001$). This abnormality predicted HCC much earlier than Ultrasound, alpha-fetoprotein and transaminases. The sensitivity of Alanine-aminotransferase, Aspartate-aminotransferase, Alkaline-phosphatase, alpha-fetoprotein and alkaline-phosphatase+alpha-fetoprotein at diagnosis of hepatocellular carcinoma was 91%, 96%, 42%, 51% and 66% while specificities were 31%, 22%, 83%, 98% and 84% respectively. However, when ultrasound was combined with Alkaline-phosphatase and alpha-fetoprotein levels altogether the sensitivity and specificity becomes 100% and 83% respectively.



Conclusions: The complementary use of alkaline-phosphatase greatly improved the sensitivity for hepatocellular carcinoma detection in patients with decompensated cirrhosis.

Disclosure of Interest: None Declared

META-LEARNING ANALYSIS TO FIND THE BEST PREDICTIVE ALGORITHM FOR PREDICTION OF HEPATOCELLULAR CARCINOMA OUTCOME IN A COHORT OF 1200 HCV-RELATED PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is the second most common neoplasm in Egypt due to the highest prevalence of hepatitis C virus (HCV). The prediction of prognosis and treatment outcome with HCC is complex with the underlying liver cirrhosis in the majority of patients. There is no worldwide consensus on the use of any HCC staging system. Data mining is a method of predictive analysis which can explore tremendous volumes of rich information found in electronic health records to discover hidden patterns and relationships.

Aims: to develop a non-invasive algorithm for prediction of the outcome of curative and palliative treatment options for HCC. This algorithm should be economical, reliable, easy to apply and acceptable by domain experts.

Material and Methods: This cross-sectional study included 1200 HCV-related HCC patients attending HCC multidisciplinary clinic, Kasr Al-Aini hospital, Cairo University between years 2009- 2016. Using the data mining analysis, we constructed Reduced Error Pruning (REP) decision tree algorithms then we applied Auto-WEKA to select the best classifier out of 39 algorithms.

Results: REP-tree algorithm was able to predict the outcome of HCC management with recall (sensitivity) 0.658 and precession (specificity) 0.653 using only routine data. The correctly classified Instances were 854 (65.8%), and the incorrectly classified Instances were 444 (34.2%). Out of 31 attributes, liver decompensation was selected by the REP-tree as the best predictor of HCC outcome (root node) followed by the decision of treatment. To a less extent Serum albumin, creatinine, bilirubin, AFP, focal lesion and spleen size are

simple variables that have the prospect to support outcome prediction either alive or dead, without imposing extra costs for additional examinations. When Auto-WEKA was applied, the Random subspace classifier was selected as the best predictive algorithm with recall (sensitivity) 0.750 and precession (specificity) 0.752. The correctly classified Instances were 974 (75.04%), and the incorrectly classified Instances were 324 (24.9%) that was better than REP-tree.

Conclusions: Data mining analysis and meta-learning explores data to discover hidden patterns, trends and improves the accuracy of prediction of HCC outcome either alive or dead through utilizing simple laboratory data. Liver decompensation and treatment decision were the most decisive variables. The Random subspace classifier is more accurate than REP-tree in predicting the outcome.

Figure:

Reduced Error Pruning Tree

```

Clinical decompensation = Yes
| Decision = TACE : Dead (70/23) [45/6]
| Decision = supportive : Dead (40/3) [15/2]
| Decision = microwave : Alive (20/9) [6/2]
| Decision = hepatectomy : Dead (5/1) [2/1]
| Decision = combined : Dead (19/6) [7/2]
| Decision = sorafenib : Dead (13/1) [9/2]
| Decision = RFA : Dead (13/1) [5/1]
| Decision = PEI : Dead (1/0) [0/0]
| Decision = Transplantation : Dead (0/0) [1/0]
Clinical decompensation = no
| Decision = TACE : Alive (302.44/87) [152.44/40]
| Decision = supportive
| | Alb < 2.45 : Dead (26.18/5.18) [12/7]
| | Alb >= 2.45 : Alive (95/46) [48.18/21]
| Decision = microwave
| | Crea < 0.45 : Dead (4/0) [1/1]
| | Crea >= 0.45
| | | Crea < 1.35
| | | | AFP < 18.7 : Alive (63.09/4.54) [38.19/10]
| | | | AFP >= 18.7
| | | | | F.L size < 3.75 : Alive (37.64/7) [12/3]
| | | | | F.L size >= 3.75
| | | | | | Spleen = enlarged
| | | | | | | AFP < 1656.5 : Alive (6.34/0.34) [3/0]
| | | | | | | AFP >= 1656.5 : Dead (2.11/0) [2/0]
| | | | | | | Spleen = average : Dead (7/1) [1/1]
| | | Crea >= 1.35
| | | | Alb < 3.45 : Dead (6/0) [1/0]
| | | | Alb >= 3.45 : Alive (2/0) [1/0]
| Decision = hepatectomy : Alive (14.02/3) [6.02/0]
| Decision = combined
| | Bil.T < 0.69 : Dead (3/0) [4/0]
| | Bil.T >= 0.69 : Alive (43.07/10) [24.07/10]
| Decision = sorafenib : Alive (32.05/12) [10.05/6]
| Decision = RFA : Alive (22.03/11) [13.03/6]
| Decision = PEI : Alive (13.02/5) [8.02/1]
| Decision = Transplantation : Alive (5.01/1) [6.01/1]

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Disclosure of Interest: None Declared

LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA, ARE WE GOING TO DISMISS THE TRADITIONAL APPROACH?

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Introduction: Minimally invasive surgery has recently demonstrated results comparable to traditional surgery for recurrence-free or overall survival, even in cirrhotic patients. Laparoscopic liver resection (LLR) is gaining a central role for the treatment of hepatocellular carcinoma (HCC).

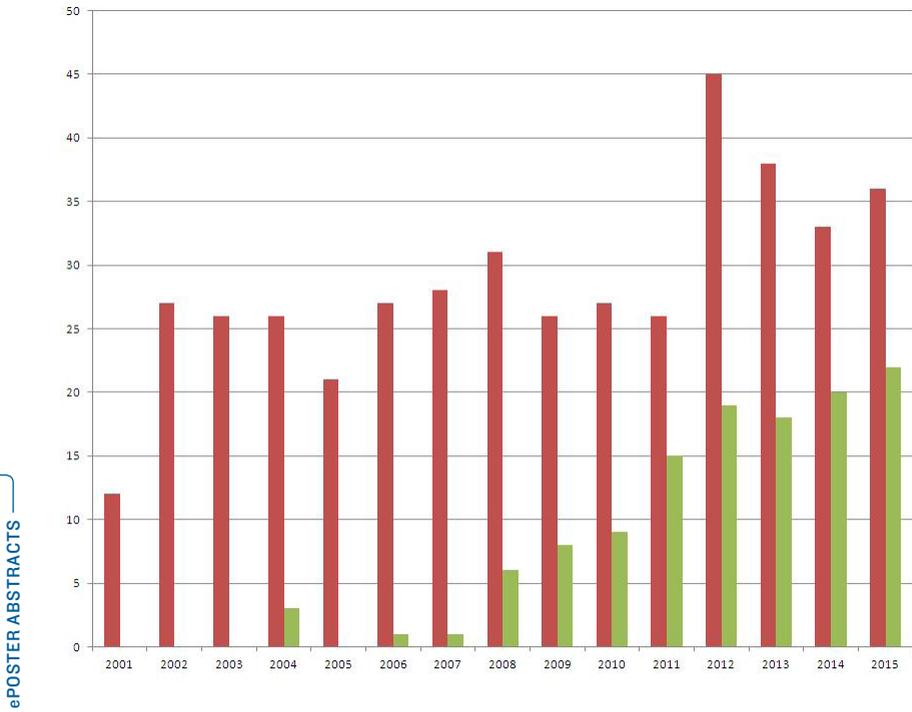
Aims: The aim of our study is to analyze the evolution of traditional and minimally invasive liver resection for HCC in our Center since 2001.

Material and Methods: Between 2001 to December 2015, 1463 liver resections were performed. Of them 429 were hepatocellular carcinoma. We divided the cohort into two groups: Group 1, patients between 2001 and 2007 and Group 2 patients between 2008 and 2015.

Results: 429 cases were included into this study. In group 1 we performed 42 major hepatectomies (25,3%) and 124 minor hepatectomies (74,7%). In group 2 we respectively performed 49 (18,6%) major hepatectomies and 214 (81,4%) minor hepatectomies. We had no difference between the two groups for major or minor surgery ($p=0.09$). In group 1, 3% of patients and 44,5% in group 2 were treated by LLR. Nonetheless, of the 44,5% of laparoscopic resections in the second group only 1 major resection was performed. We observed an improvement of morbidity between the two groups ($p<0,001$), and of mortality with 3,6% in group 1 versus no mortality in group 2.

Conclusions: Laparoscopic approach in HCC is gaining more place even in patients with cirrhosis. Minor resection should be always performed with a minimally approach. Major LLR in these patients are still selected cases. In our experience, the traditional surgical approach has yet a place for the major resection in patients with HCC

Figure:



Disclosure of Interest: None Declared

ALPHA-FETOPROTEIN (AFP) LEVELS BEFORE AND AFTER SUSTAINED VIROLOGICAL RESPONSE WITH DIRECT-ACTING ANTIVIRALS (DAAs) IN PATIENTS WITH LIVER CIRRHOSIS DUE TO HEPATITIS C VIRUS (HCV)

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Introduction: Cure of HCV infection with IFN reduces AFP levels and high levels of AFP after SVR increase the risk of developing HCC.

Aims: To analyze AFP levels after SVR obtained with DAAs in patients with liver cirrhosis due to HCV.

Material and Methods: We analyzed 188 patients with HCV cirrhosis who obtained SVR after DAAs treatment. Most patients were male (66.5%), mean age 58±19 yrs; 48.9% were infected with genotype 1b, 53% had esophageal varices, 20% a previous episode of decompensation, and 16% were coinfecting with HIV. In all cases, basal AFP levels (AFP-TT) were compared with those observed at the time of SVR (AFP-SVR). The influence of different demographic, clinical and analytical variables on AFP levels was analyzed.

Results: AFP-TT levels were 16.0±42.6 (0.9-530) and AFP-SVR were 5.3±4.7 (1.1-37.1) ng/ml ($p < 0.001$), with an average decrease of 10.6±42.3 ng/ml. AFP-SVR was higher than AFP-TTO in 27 patients (increase of 3.1±6.7 ng/ml), equal in 3 and lower in 158 (decrease of 13.2±45.7 ng/ml). Comparing AFP-TTO and AFP-SVR, the proportion of patients with AFP > 10 was 37.2% and 7.9%; between 5-10, 25% and 26% and <5, 37.8% and 65.9% respectively ($p < 0.001$). Levels of AFP-TTO > 10 ng/ml were related with higher levels of ALT (113.7±78.2 vs. 70.6±53.3, $p < 0.001$) and AST (107.8±56.3 ($P < 0.001$), with the presence of steatosis in ECO (20% vs. 13%, $p = 0.03$) and with the absence of previous decompensation (88.6% vs. 74.6%; $p = 0.05$). There was no relationship with sex ($p = 0.22$), age ($p = 0.75$), HCV genotype ($p = 0.1$), baseline platelet count ($p = 0.79$) or albumin ($p = 0.13$), presence of varices ($p = 0.73$), HIV ($p = 0.09$) or diabetes ($p = 0.26$). AFP-RVS levels were not related with any of the variables analyzed.

During the follow-up, 4 patients developed CHC (3 to 12 months from SVR), 3/15 (20%) with AFP-SVR > 10 and 1/173 (0.57%) with AFP-SVR ≤ 10 ng/ml (p=0.001).

Conclusions: SVR obtained with DAAs significantly reduces AFP levels. While high levels of AFP before treatment are related with the degree of necroinflammatory activity and with the presence of liver steatosis, this relationship is lost at the time of SVR. Although further monitoring is required, high AFP levels (>10ng/ml) at the time of SVR may be a marker of risk for the development of HCC, as is the case after IFN treatment. Since after SVR most patients have normal AFP levels, this marker may gain a role in the early diagnosis of HCC in patients with HCV cirrhosis in the DAAs era

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COMBINED TREATMENT, TRANSARTERIAL CHEMOEMBOLIZATION AND RADIOFREQUENCY ABLATION IN PATIENTS WITH ADVANCED HCC

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Introduction: Hepatocellular carcinoma (HCC) is the fifth most common cancer, and the third most common cause of cancer-related death worldwide. Various loco-regional treatments are offered including RF and TACE to treat HCC. We compared these modalities with the combined treatment (TACE+RF) in the treatment of HCC larger than 3 cm and smaller than 5 cm.

Aims: To compare the feasibility and benefit of combined therapy (TACE+RF ablation) versus TACE or RF alone in the treatment of HCC larger than 3 cm and smaller than 5 cm

Material and Methods: During 3 years, 150 consecutive patients with HCC larger than 3 cm and smaller than 5 cm were divided into 3 groups, group (1) 50 HCC patients underwent TACE, group (2) 50 HCC patients underwent RF ablation and group (3) 50 HCC patients received combined therapy with TACE followed by RF ablation after 1 month. Mean age was 57 years, 94 (62.7%) were males. Follow up with Triphasic CT was performed after 1 month then every 3 months for 1 year.

Results: After 1 month, complete response was detected in 27 cases (54%) in group (1), 22 cases (44%) in group (2) and 50 cases (100%) in group (3), partial response in 8 cases (16%) in group (1), 5 cases (10%) in group (2) and progressive disease in 15 cases (30%) in group (1) and 23 cases (46%) in group 2. Recurrence rate after 1 year was 38 cases (72%) in group (1), 40 cases (80%) in group 2 and 9 cases (18%) in group 3. Disease free survival rate at 12 months was 12 cases (24%) in group 1, 10 cases (20%) in group 2 and 41 cases (82%) in group 3.

Conclusions: Combined therapy (TACE+RF ablation) in HCC larger than 3 cm and smaller than 5 cm is better than TACE or RF ablation alone concerning the recurrence rate and disease free survival rate.

Disclosure of Interest: None Declared

TREATMENT-STAGE MIGRATION MAXIMIZES SURVIVAL OUTCOMES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH SORAFENIB: AN OBSERVATIONAL STUDY

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Introduction: Sorafenib (SOR) is an effective first-line therapy in patients with Barcelona Clinic Liver Cancer (BCLC) C hepatocellular carcinoma (HCC). The efficacy of SOR after failure to curative or loco-regional therapies is not based on randomized controlled trials and efficacy is extrapolated from studies in advanced disease, which however carries a more adverse course.

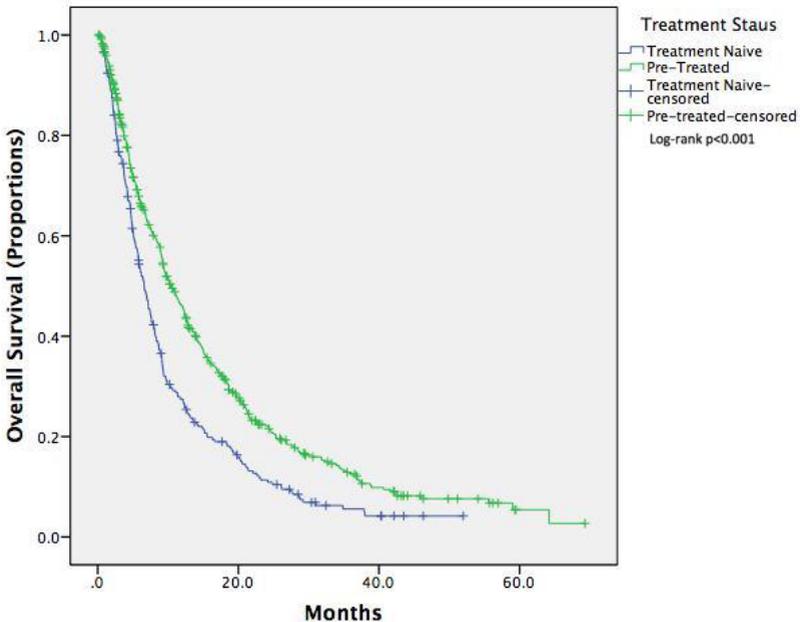
Aims: We compared outcomes of patients who received SOR as first-line therapy with those treated at disease progression after curative or loco-regional therapy failure.

Material and Methods: From a multi-center cohort of 790 patients from Europe (n=483, 61%) and Asia (n=307, 39%) a total of 265 (34%) were treatment naïve (TN) whereas 525 (66%) had been pre-treated (PT) with at least 1 line of therapy including TACE (n=416, 79%), RFA (n=170, 32%) and resection (n=149, 28%). Commonest causes of SOR discontinuation were progressive disease in 456 patients (58%) or unacceptable toxicity in 149 (19%). Primary endpoint was overall survival (OS) from the date of SOR commencement with prognostic factors analyzed using Kaplan-Meier and Cox regression analysis.

Results: Median OS was 9 months for the entire cohort (95%CI 8.2-9.7), median SOR duration was 2.8 months (IQR 5.4). PT patients had better Child Pugh (CP) class (CP A n=283, 57%) than TN (n=117, 47%, $p<0.001$) and lower BCLC stage (BCLC A-B n=158, 33% vs. 55, 23% $p=0.003$). Median OS was shorter in TN (6.6 months 95%CI 5.7-7.5) compared to PT (10.4 months, 95%CI 9.1-11.7 $p<0.001$). The prognostic impact of prior treatment for HCC (HR 1.4 95%CI 1.2-1.7, $p<0.001$) was preserved in a multivariate Cox regression model adjusted for baseline BCLC (HR 1.7 95%CI 1.4-2.1 $p<0.001$), alpha-fetoprotein >400 ng/ml (HR 1.8 95% CI 1.5-2.1, $p<0.001$) and CP class ($p=0.24$). PT patients were more likely to receive further active anticancer treatment after SOR than TN (n=105/369, 29% vs n=14/158, 9% $p<0.001$).

Conclusions: In this observational study SOR treatment conferred a better OS in PT compared to TN patients suggesting biologic heterogeneity in these patient subgroups, a finding that may facilitate drug development and interpretation of trials. The improved survival outcomes in pre-treated patients justifies BCLC-stage treatment migration to maximize survival outcomes after failure to curative or loco-regional therapies.

Figure:



Disclosure of Interest: None Declared

DROP-OUT RATE DUE TO HCC PROGRESSION IS NOT AFFECTED BY HCV ERADICATION WITH DAAS IN PATIENTS AWAITING LIVER TRANSPLANTATION

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Introduction: The loss of intrahepatic immune-surveillance, due to viral-eradication with Direct-Antiviral Agents(DAAs), may be associated with increased recurrence of HCC in HCV patients who previously achieved complete-response.

Aims: Data on the impact that this may have in terms of drop-out in HCV-HCC patients awaiting liver transplantation (LT), are lacking.

Material and Methods: All HCV-HCC patients listed for LT between 01/2015-05/2016, and successfully treated with DAAs achieving SVR, were retrospectively evaluated (cases). For each patient clinical, serological, virological data and HCC characteristics were taken into account. A group of untreated patients listed for HCV-related cirrhosis and HCC, with similar HCC-characteristics were also enrolled(controls).

Results: Forty-nine patients were enrolled (23cases/26controls); HCC characteristics at time of LT-listing were comparable between the 2 groups: median HCC nodules number was 2 (range0-4) in cases group vs 2 (range0-6) in controls (p=NS); median nodules total diameter was 22mm (range0-65) in cases group vs 22mm (range0-53) in controls (p=NS). Median follow-up was 7 months (range4-19) in cases group vs 5 months (range3-19) in controls group, during which 2/23 (8.7%) and 1/26 (3,8%) drop-out events due to HCC-progression between cases and controls were respectively registered (p=NS). Comparing radiologic images at the beginning and end of FU, no significant differences in terms

of radiologic-progression were highlighted (p=NS). 8/23(35%) patients treated with DAAs and 13/26 (50%) controls underwent LT, and histopathological analysis of HCC performed on explanted liver showed no differences in terms of median number of HCC nodules [5 (range1-14) vs 3 (range0-14), p=NS] and median maximum diameter [26mm (range10mm-65mm) vs 28mm (range0mm-80mm), p=NS], tumor differentiation [G3-HCC% 13%vs15%, p=NS] or microvascular invasion [cases% 38%vs23%, p=NS]. During post-LT FU 1/8 DAAs treated patient (11%) and 1/12 control(8.3%) experienced HCC-recurrence(p=NS).

Conclusions: Viral eradication doesn't seem to be associated with increased risk of drop-out due to neoplastic disease-progression in HCV-HCC patients awaiting LT. Therefore, DAAs treatment can be safely offered to this patients population.

Disclosure of Interest: None Declared

HOW OFTEN PATIENTS TREATED WITH SORAFENIB FOR HEPATOCELLULAR CARCINOMA MIGHT RECEIVE SUBOPTIMAL DECISIONS ABOUT TREATMENT DURATION? AN ANALYSIS OF THE INTEROPERATOR VARIABILITY AND SOURCE OF ERRORS IN TUMOR RESPONSE ASSESSMENT

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Introduction: The role of imaging is pivotal in the setting of therapy with Sorafenib for hepatocellular carcinoma (HCC), as the decision to stop treatment in the absence of relevant adverse events is mainly based upon the imaging findings. Imaging assessment involves subjective human judgment and may suffer errors, whose risk might theoretically also be affected by the response criteria adopted.

Aims: To clarify whether and to which extent clinical decisions in HCC may become affected by operators variability in the real life practice.

Material and Methods: All patients with HCC who received sorafenib in our Centre between 2008 and 2015 were scrutinized for this retrospective study. All radiological images of the eligible patients were evaluated separately by 3 radiologists with different experience in liver imaging (Operator 1 > 10 years; Operator 2: 5 years; Operator 3: 2 years). Each operator expressed his assessment of response according to each of the following criteria: Response Evaluation radiological Criteria In solid Tumors (RECIST) 1.1, modified RECIST (mRECIST), Response Evaluation Criteria In Cancer of the Liver (RECICL).

Results: The overall response concordance between the more expert operators was good, irrespective of the criteria (RECIST 1.1:k=0.840;mRECIST:k=0.871;RECICL:k=0.819),

but still imperfect. The concordance between the less expert operator and each of the two more experienced colleagues was lower, especially with RECICL (OP1 $k=0.519$; OP2 $k=0.591$). The most evident discordance was in target lesion response assessment, with expert operators disagreeing mostly on lesion selection and less expert operators on lesion measurement. Instead, new lesions assessment yielded a fairly high concordance between the expert operators ($k=0.856$), which remained good between the less skilled and each of the expert operators (OP1: $k=0.725$; OP2: $k=0.699$).

Conclusions: Worryingly, decision on whether a patient with HCC is responder or progressor under Sorafenib may be variable among operators, meaning that some patients may continue or stop treatment simply based on which operator is on duty or which criterion is adopted. Reproducibility of response criteria is good between operators with at least 5-year experience in liver imaging. Instead, reproducibility in the instance of less expert operators is overtly lower, particularly using the RECICL. It is strongly advisable that patients undergoing sorafenib treatment are evaluated by experienced radiologists, using mRECIST or RECIST1.1 to minimize variability.

Disclosure of Interest: None Declared

FREQUENCY OF COMPLETE PATHOLOGICAL NECROSIS OF HCC IN EXPLANTED LIVERS: RADIOEMBOLIZATION WITH RESIN VS DRUG ELUTING BEADS WITH DOXORUBICIN

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Introduction: Complete pathological necrosis is associated with significant lower post-transplant recurrence of HCC than incomplete response.

Aims: To identify complete pathological necrosis (CPN) in explanted liver in patients with hepatocellular carcinoma who have undergone their last preoperative treatment with either Drug Eluting Beads with Doxorubicin (DEB-TACE) vs radioembolization (RE) with resin spheres prior to orthotopic liver transplantation (OLT).

Material and Methods: From 2013-2016 a total of 41 patients underwent locoregional therapy with either DEB-TACE alone (n=30) or RE alone/RE after failed TACE(n=11) prior to OLT. OLT was performed in 38/41 of patients on the transplant list. The explanted livers were examined histologically for size of the lesion, necrosis, macrovascular invasion and distribution of microspheres in relation to tumor cells.

Results: Both groups were similar for age at diagnosis, sex, race, lobar involvement, etiology of cirrhosis and mean tumor size ($p < 0.05$). A total of 69 lesions in 38 patients underwent individual histological analysis. In the DEB-TACE cohort (n= 56 lesions), the mean histological tumor diameter was 1.9 cm [range, 0.3–5.4 cm] with a median necrosis rate of 72%. In the RE cohort (n=13 lesions), the mean tumor diameter was 1.9, [range, 0.6–4.7 cm] with a median necrosis of 100%.

Lesions achieving CPN RE DEB-TACE P-value Frequency of CPN 9/13 (69.2%) 12/56 (21.4%) $p < .005$ Tumor Diameters (mean) 1.8 cm 1.9 cm NS Median time to OLT (months) 8.5 4.5

Conclusions: The use of either RE or DEB-TACE results in a high rate of pathological necrosis. A higher rate of median necrosis and CPN was seen in the RE group. Further prospective studies are needed to validate these findings.

Disclosure of Interest: None Declared

EXTERNAL VALIDATION OF THE HCC-MELD SCORE FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA WAITING FOR LIVER TRANSPLANTATION

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Introduction: We recently described a method for calibrating HCC and non-HCC patients according to survival benefit, and propose that this method has the potential, if externally validated, to restore equity to the organ allocation system.

Aims: The aim of this study is to externally validate this method in a large cohort of US patients.

Material and Methods: We modelled the post-transplantation survival of adult, first-time liver transplant recipients with HCC (n. 9135) or without (n. 25,890) from 2002 through 2013 using Cox proportional hazards regression. We modelled waitlist survival of patients listed for transplantation with HCC (n. 15,605) or without (n. 85,229) using competing risks analysis. MELD-related hazard ratios obtained using these models were included in a Monte Carlo simulation and used to calculate 5-year survival benefit estimations (i.e. the difference between post-transplantation and waitlist life expectancy) in HCC and non-HCC populations.

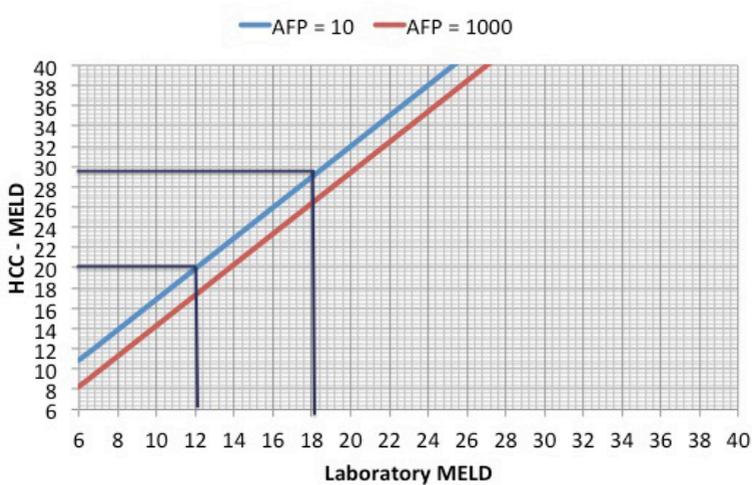
Results: The 5-year survival benefit increased with actual MELD score for patients with and without HCC, ranging from just a few months in patients with low MELD scores (ie, 6-8) to more than 48 months in patients with the highest MELD scores (ie, 36-40). As in the Italian study, the survival benefit of patients with HCC was higher than that of patients without HCC who had the same actual MELD score, irrespective of tumor burden or serum level of α -fetoprotein. Median 5 year transplant benefit was 10.30 months (5.72-45.09) for the non-HCC patients, and 28.54 months (10.66-44.88) for the HCC patients ($p < 0.001$).

Using our previously published method, we obtained the equation “HCC-MELD US” = 1.51 *MELD -logAFP + 2.8 calculating a numerical score for HCC patients, whereby their transplant benefit is equal to that of non-HCC patients with the same numerical value for MELD.

Conclusions: Our proposed method for calibrating HCC and non-HCC patients according to survival benefit was validated in a large US population. On these bases, we think that this method has the potential to restore equity to the organ allocation system.

Figure:

Figure 1. 5-year benefit model, Monte Carlo simulation
Relationship between laboratory MELD, HCC MELD, and AFP



Disclosure of Interest: None Declared

ePOSTER ABSTRACTS

METABOLIC DISORDERS ACROSS HEPATOCELLULAR CARCINOMA IN ITALY

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Introduction: Metabolic disorders, such as obesity and diabetes, are well known risk factors for hepatocellular carcinoma (HCC). Conversely, their impact on the natural history of HCC patients is not established.

Aims: This study aimed at evaluating the impact of metabolic disorders on clinical features, treatment and survival of HCC patients regardless of its etiology.

Material and Methods: We analyzed the Italian Liver Cancer (ITA.LI.CA) database regarding 839 HCC patients prospectively collected from 2009 to 2014. The following metabolic features were analyzed: BMI, diabetes, arterial hypertension, hypercholesterolemia and hypertriglyceridemia. According to these features, patients were divided into 3 groups: 0-1 metabolic features, 2 metabolic features, 3-5 metabolic features.

Results: As compared with patients with 0-1 metabolic features, patients with 3-5 features showed lower percentage of HCC diagnosis on surveillance (p 0.021), larger tumors (p 0.038), better liver function (higher percentage of patients with Child-Pugh A [p 0.007] and MELD<10 [p 0.003]), higher percentage of metastases (p 0.024), and lower percentage of portal vein thrombosis (p 0.010). The BCLC stage and treatment options were similar among the 3 groups, with the exception of a less frequent access to locoregional therapies for BCLC stage B patients with 3-5 features (p 0.012). Overall survival and survival according to BCLC stage and/or treatment did not significantly differ among the 3 groups. Diabetic patients showed a lower survival (p 0.046). Child-Pugh score, BCLC stage, HCC morphology, nodule size and portal vein thrombosis were independent predictors of lead-time adjusted survival.

Conclusions: Our “real world” study, suggests that metabolic disorders shapes the clinical presentation of HCC but do not seem to play a major role in setting the patient survival, except for diabetes.

Disclosure of Interest: None Declared

PREDICTING OUTCOME IN PATIENTS WITH INTERMEDIATE OR ADVANCED HEPATOCELLULAR CARCINOMA RECEIVING SORAFENIB: INFLUENCE OF THE RADIOLOGIST EXPERIENCE ON THE PROGNOSTIC VALUE OF THE DIFFERENT PROPOSED RADIOLOGIC CRITERIA OF RESPONSE

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Introduction: Sorafenib is the standard treatment for patients with advanced hepatocellular carcinoma (HCC). The main clinical endpoint is overall survival (OS), however in clinical practice radiologic imaging assessment is used as a surrogate endpoint. A number of different radiologic criteria of response have been proposed. Currently, there is no agreement on which is the best set of criteria. Further, it has not been clarified whether the experience of the operator in liver imaging might influence the predictive abilities of the adopted criterion.

Aims: To verify whether the predictive value of three different radiologic criteria was influenced by the experience of the operator.

Material and Methods: All patients with HCC who received sorafenib in our Centre between September 2008 and February 2015 were scrutinized for this retrospective study. All radiological images of the eligible patients were evaluated separately by 3 radiologists with different experience in liver imaging (Operator 1 > 10 years; Operator 2: 5 years; Operator 3: 2 years). Each operator expressed his assessment of response according to each of the following criteria: Response Evaluation radiological Criteria In solid Tumors (RECIST) 1.1, modified RECIST (mRECIST), Response Evaluation Criteria In Cancer of the Liver (RECICL).

Radiologic response, dichotomized as disease control (DC) versus progressive disease (PD) was compared with the OS of the patients using log-rank test

Results: A total of 77 Barcelona Clinic Liver Cancer stage B-C patients were evaluated. Median OS was 16.8 months. DC was an independent predictor of the OS, independently from the adopted criteria and from the experience of the operator. However, the hazard ratios (HR) were sensibly different when the more expert operators analyzed the radiologic images and when RECIST 1.1 and mRECIST were the selected criteria (TABLE).

Conclusions: Both RECIST 1.1 and mRECIST appear more appropriate than RECICL to identify responders with long survival among intermediate and advanced HCC patients benefiting from sorafenib. Imaging evaluation by a radiologist with at least a 5-year experience in liver imaging is also pivotal to achieve the best accuracy.

Figure:

Table: Correlations between overall survival and radiologic response (progressive disease versus disease control) according to the different operators and criteria

		RECIST 1.1	mRECIST	RECICL
OPERATOR 1	Median survival (months)	11.13 vs 26.00	10.6 vs 25.30	10.66 vs 23.40
	Hazard ratio (95% CI)	3.25 (1.87-5.64)	3.08 (1.74-5.44)	2.52 (1.45-4.35)
	p	<0.0001	<0.0001	0.0001
OPERATOR 2	Median survival (months)	10.43 vs 25.30	10.43 vs 25.30	10.43 vs 25.30
	Hazard ratio (95% CI)	3.51(1.90-6.48)	3.51(1.90-6.48)	2.96 (1.65-5.29)
	p	<0.0001	<0.0001	<0.0001
OPERATOR 3	Median survival (months)	11.23 vs 23.66	11.23 vs 23.66	11.23 vs 23.66
	Hazard ratio (95% CI)	2.27 (1.37-3.76)	2.16 (1.30-3.57)	2.27 (1.37-3.76)
	p	0.0004	0.0008	0.0004

Disclosure of Interest: None Declared



NON-ALCOHOLIC FATTY LIVER AS GLOBAL BURDEN: A CHANGING TREND OF LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN LATIN AMERICA

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Introduction: Hepatocellular carcinoma (HCC) is currently the second most common cause of cancer related death worldwide with an increasing incidence rate during the last decade. An increasing burden of non-alcoholic fatty liver disease has been recently observed.

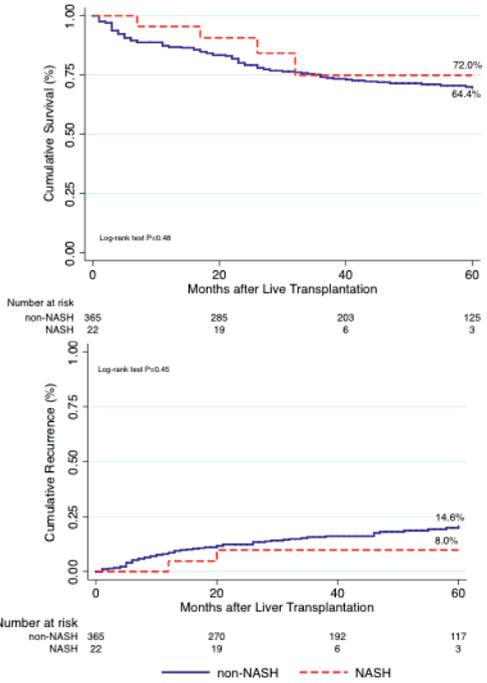
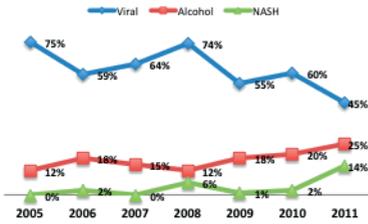
Aims: The aim of this study was to evaluate aetiologies, selection criteria and treatment during transplant waiting list of LT for HCC during the last years in Latin America.

Material and Methods: This study was conducted including a cohort of consecutive adult LT patients between 2005 and 2011 in 17 different LT centres who were prospectively followed up after transplantation. Different periods including years 2005-2006, 2007-2008, 2009-2010 and 2011 were considered.

Results: From a total of 2,761 consecutive adult LT patients, 435 patients with HCC were included. From years 2005 to 2011, there was a change in the underlying aetiologies of HCC. While hepatitis C virus chronic infection was the first cause in 2005-06 (62.5%), decreased to 23% in 2011. Conversely, whereas alcoholic liver disease was mainly stable, non-alcoholic steatohepatitis (NASH) increased from 0-2% in years 2005-2006 to 14% in 2011, accounting for the 3rd leading cause of HCC. Patients with NASH were older and have a trend towards lower serum AFP values at listing. Similar survival and recurrence rates were observed comparing NASH and non-NASH HCC patients. During waiting list, 67% of the cohort was granted with supplementary MELD points. At listing, 81% (n=354), 91% (n=393) and 81% (n=354) of the patients were within Milan, San Francisco and AFP model, respectively. Milan criteria persisted as the gold standard for transplantation per periods; however, during the last years a higher proportion of patients within AFP model were transplanted between years 2005-2006 and 2011 (73.2% vs 88.7%; P=0.03). During the periods considered, the proportion of patients receiving bridging therapies was similar (n=193). Multivariate Cox regression analysis showed that AFP model at listing was independently associated with 5-year HCC recurrence with an adjusted hazard ratio of 2.44 (CI 1.32;4.52).

Conclusions: There is a changing figure regarding aetiologies of HCC in Latin America, including a decreasing HCV and an increasing NASH liver related diseases. Most of the LT centres transplanted patients within MC at listing, although a recent focus on AFP values was observed.

Figure:



Disclosure of Interest: F. Piñero: Grant: Conflict with: National Institute of Cancer. “Asistencia financiera a proyectos de investigación en cáncer de origen nacional III”- INC- Dr M Silva, P. Costa: : None Declared, E. de Ataíde: : None Declared, S. Hoyos: : None Declared, S. Marciano: : None Declared, M. Anders: : None Declared, A. Varón: : None Declared, A. Zerega: : None Declared, J. Poniachik: : None Declared, A. Soza: : None Declared, M. Padilla Machaca: : None Declared, J. Menéndez: : None Declared, R. Zapata: : None Declared, M. Vilatoba: : None Declared, L. Muñoz: : None Declared, M. Maraschio: : None Declared, L. Podestá: : None Declared, L. McCormack: : None Declared, A. Gadano: : None Declared, I. Boin: : None Declared, J. Parente García: : None Declared, M. Silva: Grant: Conflict with: National Institute of Cancer. “Asistencia financiera a proyectos de investigación en cáncer de origen nacional III”- INC- Dr M Silva

LIVER STIFFNESS AND SERUM FIBROSIS BIOMARKER VARIATIONS AFTER DAAs TREATMENT: PREDICTIVE ROLE IN HCC DEVELOPMENT IN CIRRHOTIC PATIENTS

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Introduction: Direct acting antivirals (DAAs) are an effective treatment in HCV patients since SVR is achieved in more than 90% of the patients after 12-24 months. However, HepatoCellular Carcinoma (HCC) development risk does not seem to reduce in SVR patients after DAAs-treatments. Recently, it has been suggested that liver stiffness measurement (LSM) by Fibroscan [Echosens®] can predict the HCC risk in liver cirrhosis patients.

Aims: The aim of our study was to evaluate the role of LSM and clinical parameters as predictors of HCC development in patients treated with DAAs.

Material and Methods: In 110 HCV-related cirrhotic patients (F4 >12.5 kPa) before (BL) and at the end of treatment (EOT) with DAAs, TE and laboratory tests were performed. AST to platelet ratio test (APRI) and Fibrosis-4 score (FIB4) were also assessed. Patients were followed-up for one years after EOT. LSM variation was expressed as percentage (%). Uni and multivariate logistic regression analysis was used to identify prognostic factors for HCC development after DAA.

Results: Twelve (12) patients developed HCC after DAA treatment. LSM, APRI Test and FIB4 score significantly ($p < 0.001$) reduced from BL to EOT. The median percentage variation between EOT and BL (DELTA% EOT-BL) was -24.4% (IQR -40% -14%). Factors associated with increased HCC development after DAAs treatment (p -value < 0.05) at univariate analysis were reported on Table

	Univariate model		
	OR	95% CI	p-value
Age	0.995	0.95- 1.05	0.834
Sex	0.794	0.25- 2.54	0.698
MELD Score	1.337	1.07- 1.68	0.011
Child-Pugh	3.699	1.69- 8.11	0.001
Child-Pugh (A;B;C)	7.667	1.39- 42.37	0.020
GOV	4.727	1.01- 22.13	0.049
History of HCC	8.500	1.51- 47.91	0.015
Liver Transient Elastography BL	1.033	0.98- 1.09	0.200
Liver Transient Elastography EOT	1.082	1.03- 1.14	0.002
Liver Transient Elastography EOT (median cut-off =13.6 kPa)	3.906	1.02- 14.89	0.046
Delta% EOT-BL	12.577	1.56-88.97	0.011
Delta % EOT-BL (median cut-off=-24.4%)	15.721	1.69- 36.75	0.009
APRI Test BL	1.351	0.99- 1.84	0.076
APRI Test EOT	6.701	1.94- 23.20	0.003
FIB-4 Score BL	1.284	1.02- 1.53	0.033
FIB-4 Score EOT	1.425	1.12- 1.82	0.005

At multivariate model only Child-Pugh Score (OR=5.3214; 95% CI=1.943-14.571) and DELTA%EOT-BL (OR=24.8287; 95% CI=2.117-291.63) were independent predictors of HCC development (p-value<0.05).

Conclusions: Our preliminary result indicates that in cirrhotic HCV-related patients treated with DAAs a reduction of less than 24.4% DELTA%(EOT-BL) LSM, together with Child-Pugh Score can predict HCC development. Further studies are needed on a larger population to confirm our data.

Disclosure of Interest: F. Ravaioli: : None Declared, G. Mazzella: : None Declared, P. Andreone: Consultant: Conflict with: Roche, MSD, Janssen Cilag, AbbVie,Boehringer, Ingelheim, Gilead Sciences, Intercept, BMS, Other: Conflict with: Roche, MSD, Gilead Sciences, BMS, S. Brillanti: Grant: Conflict with: Novartis, Gilead Sciences, Other: Conflict with: Gilead Sciences, Janssen, MSD, G. Verucchi: Consultant: Conflict with: AbbVie, Gilead Sciences, BMS, Sponsored Lectures (National or International): Conflict with: AbbVie, Gilead Sciences, BMS, MSD,, F. Conti: : None Declared, F. Buonfiglioli:

: None Declared, I. Serio: : None Declared, M. L. Bacchi Reggiani: Consultant: Conflict with: AbbVie, Gilead Sciences, BMS, Sponsored Lectures (National or International): Conflict with: AbbVie, Gilead Sciences, BMS, MSD,, G. Marasco: : None Declared, A. Colecchia: : None Declared, D. Festi : : None Declared

TELOMERASE ACTIVITY: A VALUABLE MARKER OF HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CIRRHOTIC HEPATITIS C PATIENTS

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Introduction: The ability to maintain functional telomeres may be one mechanism that allows cancer cells to grow in vitro for decades. Telomerase reactivation is necessary to preserve many cancer types including hepatocellular carcinoma (HCC) and is considered a good biomarker for cancer detection. Studies that explore telomerase activity (TA) and the relative telomerase activity (RTA) in cirrhotic hepatitis C (HCV) patients and risk of HCC development are lacking.

Aims: The aim of the present work was to verify the value of telomerase activity in early detection of HCC development in cirrhotic HCV patients.

Material and Methods: TA was investigated in 50 patients; 25 patients were cirrhotic HCV patients without HCC (group I) and 25 cirrhotic HCV patients with HCC (group II). Besides, 25 apparently healthy volunteers were included as a control group (group III). TA was assessed in the peripheral blood polymorph nuclear cells using Telo TAGGG telomerase PCR ELISA ^{PLUS} kits. Group I were followed up for 6 months and screened for HCC development.

Results: TA was positive in 20% of group I patients, 68% of group II patients and none of controls. RTA was significantly higher in group II than in groups I and III ($z=-3.13$ and -4.81 respectively) ($p=0.002$ and 0.00 respectively). In HCC patients, the mean RTA was significantly higher in patients with larger tumors > 3 cm in diameter ($f=15.83$) ($p=0.001$). Also, those with portal vein thrombosis had significantly higher RTA than those without ($f=11.18$) ($p=0.003$). Significant positive correlation was observed between RTA and BCLC classification for HCC patients ($r=0.47$) ($p=0.03$).

After 6 months of follow up 3 patients in group I died (2 TA positive and 1 negative) and 6 patients developed HCC. At the beginning of the study, 3 patients from those who developed HCC were TA negative with their RTA levels of (-0.08, 0.02 and 0.34 respectively) that increased after 6 months to (2.65, 2.79 and 0.61 respectively) making them positive. The other 3 patients who developed HCC were TA positive from the start and also increased.

ROC curve analysis showed that at a cut off value of 0.85 RTA showed 60% sensitivity, 80% specificity, 75% PPV, 66.6% NPV and 72% efficacy to detect HCC occurrence. Odds ratio for developing HCC in cirrhotic patients with positive TA is 15 and they are at significantly increased risk of HCC development 4.5 times than those with negative TA ($p=0.018$).

Conclusions: Positive TA as well as rising RTA could be used as a valuable predictor of early HCC development in cirrhotic HCV patients.

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DRUG-ELUTING BEAD TRANSARTERIAL CHEMOEMBOLIZATION VERSUS CONVENTIONAL TACE IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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Introduction: DEB-TACE is a new locoregional treatment for unresectable hepatocellular carcinoma (HCC). However, the benefits of DEB-TACE versus conventional transarterial chemoembolization (TACE) still unclear.

Aims: To compare the safety, tumor response, tumor recurrence and survival rate in patients with HCC treated with DEB-TACE versus cTACE

Material and Methods: During 2 years, 200 consecutive patients with HCC were divided into 2 groups, group (1) 100 HCC patients underwent DEB-TACE and group (2) 100 patients with HCC underwent cTACE. Mean age was 56.5 years, 130 (65%) were males. Follow up was done after 1 month then every 3 months for 24 months

Results: No significant differences were detected in local and overall tumor response and also no significant differences were observed concerning the tumor recurrence during the 2 years follow up. The 1 year survival rate in group (1) was 84.6 % and 80.3% in group (2) and the 2 years survival rate was 54.4% in group (1) and 51.8 % in group (2) with no significant differences. The post-TACE syndrome was more in group (2) compared with group (1) with p-value < 0.05

Conclusions: DEB-TACE and cTACE have the safe effect regarding the tumor response, recurrence rate and overall survival rate; however DEB-TACE has an advantage with less post-TACE syndrome than cTACE

Disclosure of Interest: None Declared

VALIDATION OF THE ALBI GRADE AS A SUBSTITUTE FOR THE CHILD-PUGH CLASS IN THE BCLC CLASSIFICATION OF HEPATOCELLULAR CARCINOMA AND OF THE ADDITIONAL VALUE PROVIDED BY THE NEUTROPHIL-TO-LYMPHOCYTE RATIO

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Introduction: It has been suggested that the Albumin-Bilirubin (ALBI) grade may conveniently substitute the Child-Pugh score in the Barcelona Clinic Liver Cancer (BCLC) classification of hepatocellular carcinoma (HCC). In a recent meta-analysis, the inflammatory marker Neutrophil-to-Lymphocyte Ratio (NLR) was identified as a major prognostic factor for HCC patients, possibly qualifying for incorporation into prognostic models of HCC (Oncotarget 2016; doi: 10.18632/oncotarget.9942).

Aims: Our aims were a) to validate the prognostic performance of ALBI based BCLC in comparison to that of Child-Pugh based BCLC, and b) to assess the putative role of NLR as a covariate (at the proposed cut-off = 2.8) with either system.

Material and Methods: A single center series of N.=311 HCC patients (N.=230 males, median age at diagnosis 70 years) was studied. Overall survival was calculated from the time of radiological diagnosis to the time of death or last follow-up. This set of data was divided randomly into two subsets: the first (N = 156; 83 events) was used as a training set, the second (N =155; 88 events) as a validation set. To compare the predictive ability of different Cox proportional hazards models, we calculated the Somers'D coefficients with relative confidence limits and p-values, using the Stata statistical software package, rel. 13.1 (StataCorp, College Station, TX, USA).

Results: In the training set, the time at risk was 87,634 days, with a median survival time of 652 days (IQR, 270-1504 days); in the validation set, the corresponding figures were 88,498 and 652 days (IQR, 210-1481), respectively. The ratio between the incidence rates in the two sets was 0.952 (95%CI, 0.697-1.300). The Table presents hazard ratios,

Somers'D coefficients and corresponding 95% confidence intervals for the models either including the Child-Pugh based BCLC or the ALBI based BCLC, with/without NLR as covariate, both in the training and the validation set. The p values refer to a) contribution of each variable to the model; b) comparisons between the Somers'D coefficients attributable to each model.

Conclusions: Incorporating the ALBI grade into the BCLC classification qualifies as a validated (although not more performant) alternative to the use of the Child-Pugh score. Adding NLR as a covariate refines prognostic performance more consistently when used in conjunction with the Child-Pugh based BCLC rather than with the ALBI based BCLC.

Figure:

Training set (N.=156)					
Predictors in the model	Hazard ratio	P value(s)	<u>Somers'D</u>	95%CI	P value
Child-Pugh based BCLC	2.46	<0.001	0.456	0.358-0.553	0.400
ALBI based BCLC	1.65	<0.001	0.424	0.323-0.525	
Child-Pugh based BCLC/NLR	2.40/1.38	<0.001/<0.001	0.514	0.407-0.620	0.439
ALBI based BCLC/NLR	1.53/1.32	<0.001/0.001	0.488	0.384-0.591	
Validation set (N.=155)					
Predictors in the model	Hazard ratio	P value(s)	<u>Somers'D</u>	95%CI	P value
Child-Pugh based BCLC	2.41	<0.001	0.516	0.408-0.623	0.447
ALBI based BCLC	2.56	<0.001	0.533	0.432-0.633	
Child-Pugh based BCLC/NLR	2.29/1.19	<0.001/0.031	0.544	0.434-0.653	0.483
ALBI based BCLC/NLR	2.42/1.16	<0.001/0.074	0.561	0.461-0.662	

Disclosure of Interest: None Declared

VALIDATION OF LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS) VERSION 2014

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Introduction: Liver Imaging Reporting and Data System (LI-RADS) attempts to standardize the interpretation of liver lesions detected at computed tomography (CT) and magnetic resonance (MR) in cirrhotic patients on surveillance for hepatocellular carcinoma (HCC), stratifying them on the probability of HCC (categories LR3, LR4 and LR5 as intermediate probability, probably and definitely HCC, respectively).

Aims: The aim of our study is to assess the diagnostic accuracy of LI-RADS categories.

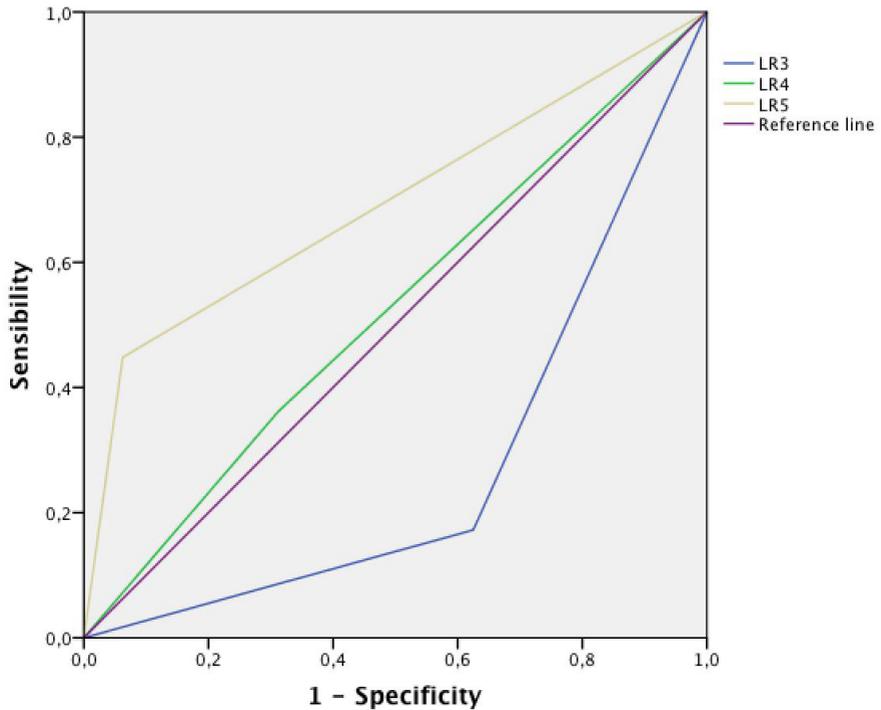
Material and Methods: We retrospectively reviewed CT and MR images of 47 patients consecutively submitted to liver resection or transplantation for HCC from January 2015 to June 2016. Three radiologists, with different experience in liver cancer, reviewed the images. Liver lesions were detected and classified according to LI-RADS (LR3=21, LR4=26, LR5=27). Sixteen lesions belonged to categories LRT that refers to HCC treated with loco-regional approaches. Each lesion was compared with histological sample (reference standard). Diagnostic accuracy was assessed with receiver operating curve analysis and defined by area under the curve and 95% confidence interval. Continuous values are expressed as mean and standard deviation, categorical variables as number and percentage.

Results: CT or MRI were performed 1.7 ± 1.2 months before surgical procedure. Ninety liver lesions (diameter 22.8 ± 19.2 mm) were detected at imaging: 66 were histologically proven HCC and 24 were negative for malignancies. HCC was confirmed in 11/21 (52.4) lesions classified as LR3, in 21/26 (80.8) classified as LR4 and in 26/27 (96.3) classified as LR5. HCC was also confirmed in 8/16 (50.0) LRT lesions, despite no signs of disease recurrence at imaging. After removing LRT observations the overall diagnostic accuracy of each LIRADS category were: LR3=0.274 (0.121-0.426), LR4=0.525 (0.366-0.684), LR5=0.693 (0.564-0.822). Sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV) progressively increased across categories: LR3 (17.2%,

37.5%, 52.4%, 11.3%), LR4 (36.2%, 68.7%, 80.8%, 22.9%), LR5 (44.8%, 93.7%, 96.3%, 31.9%).

Conclusions: In cirrhotic patients a liver lesion categorized as LR5 can be confidently diagnosed as HCC as shown by the high specificity and PPV. However, the low sensibility implies that a relevant number of neoplastic nodules are eventually missed. Moreover, a high proportion of HCC are still detected among LR3 categories. These findings highlight the urgent need of further refinements of imaging features emerging from LI-RADS.

Figure:



Disclosure of Interest: None Declared

RECURRENT HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION: VALIDATION OF A PATHOLOGICAL RISK SCORE ON EXPLANTED LIVERS TO PREDICT RECURRENCE

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Introduction: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide. A curative treatment option is liver transplantation in selected patients, although recurrence occurs in 8-20% of patients for which prognosis tends to be quite poor. An HCC recurrence risk score was developed by Parfitt et al. in 2007 which stratified patients into low, intermediate or high risk of recurrence based on explant pathology.

Aims: The aim of this study was to validate this risk score in a cohort of patients with HCC who have undergone liver transplantation.

Material and Methods: We retrospectively evaluated 124 patients over a ten year period that underwent liver transplantation for HCC at the London Health Sciences Center. Using explanted pathology reports, each patient was stratified according to the HCC recurrence risk score. Within our cohort of patients, we determined the 1, 3, 5, and 7 year rates of HCC recurrence. Z test was used to compare recurrence in our cohort and that from Parfitt et al. 2007

Results: Out of 124 consecutive liver transplants for HCC, recurrence occurred in 15 patients (12%). Mean follow-up was 3.2 years with 86% of patients within Total Tumor Volume (TTV), 62% within University of California San Francisco (UCSF) criteria, and 49% within Milan criteria on explanted pathology. 10 (8%), 21 (17%), and 93 (75%) patients were stratified into high, intermediate, and low risk of recurrence, respectively. At one year of follow-up, HCC recurrence occurred in 67% of patients considered high, 20% in intermediate, and 5% in low risk. At 7 year follow-up, recurrence occurred 80%, 25%, and 5% for high, intermediate, and low risk, respectively. From a validation perspective low ($p=0.62$) and intermediate risk ($p=0.14$) were consistent with Driman et al. 2007 but high risk recurrence rates ($p=0.00$) were not consistent possibly due to a small sample size.



Conclusions: The HCC recurrence risk score is an effective method to risk stratify patients post liver transplant based on explanted pathology. A tailored surveillance strategy then could be implemented for early detection and potentially early curative or adjuvant therapy to improve long-term survival.

Disclosure of Interest: None Declared

VALIDATION OF THE RISK PREDICTION MODELS STATE-SCORE AND START-STRATEGY TO GUIDE TACE TREATMENT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Several scoring systems that guide patients' treatment regimen for Transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC) have been introduced, but none have gained widespread acceptance in clinical practice.

Aims: The purpose of this study is to externally validate the Selection for TrAnsarterial chemoembolization TrEatment (STATE)-score and START-strategy (i.e., sequential use of the STATE-score and Assessment for Retreatment with TACE [ART]-score).

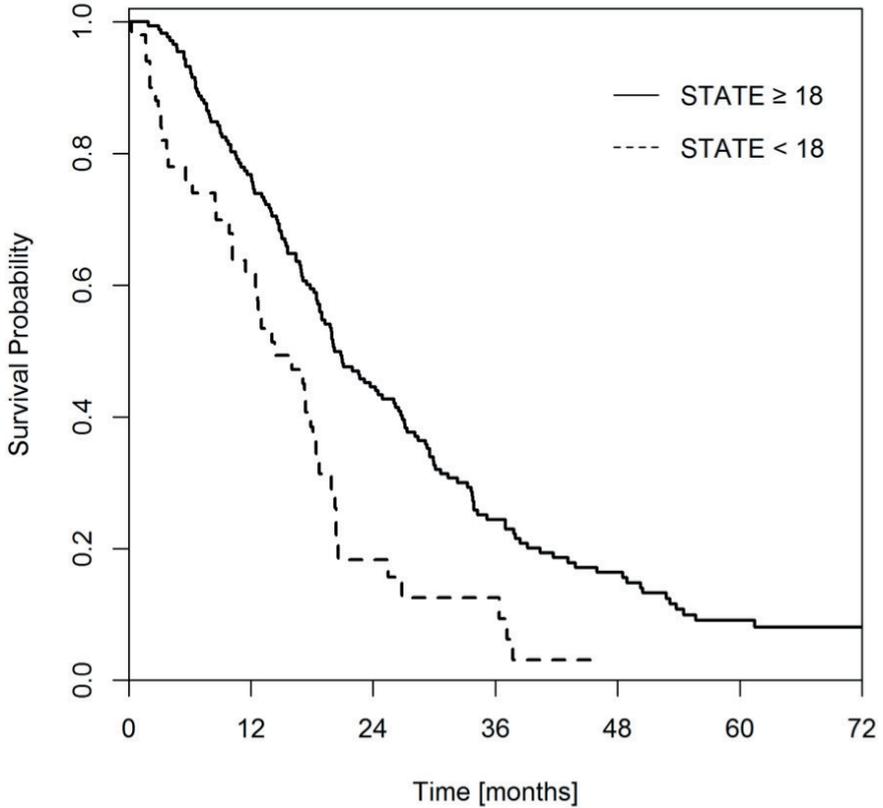
Material and Methods: From 01/2000 to 09/2015, 933 patients with HCC underwent TACE at our institution. All variables needed to calculate the STATE-score and implement the START-strategy were determined. STATE comprised serum albumin, up-to-seven criteria, and C-reactive protein (CRP). ART comprised an increase in aspartate aminotransferase, the Child-Pugh-score, and a radiological tumor response. Overall survival was calculated and multivariate analysis performed. In addition, the STATE-score and START-strategy were validated using the Harrell's C-index and integrated Brier score (IBS).

Results: The STATE-score was calculated in 228 patients. Low and high STATE-scores corresponded to median survival of 14.3 and 20.2 months, respectively. Harrell's C was 0.558 and IBS 0.133. For the STATE-score, significant predictors of survival were up-to-seven criteria ($p=0.006$) and albumin ($p=0.022$). CRP values were not predictive ($p=0.367$). The ART-score was calculated in 207 patients. Combining the STATE-score and ART-score led to a Harrell's C of 0.580 and IBS of 0.132.

Conclusions: The STATE-score was unable to reliably determine the suitability for initial TACE. The START-strategy only slightly improved the predictive ability compared to the ART-score alone. Therefore, neither the STATE-score nor START-strategy alone provide sufficient certainty for clear-cut clinical decisions.

Figure:

Kaplan-Meier estimates by STATE category



# at risk		0	12	24	36	48	60	72
TE ≥ 18	178	135	73	34	22	10	7	
TE < 18	50	30	7	4	0	0	0	

Disclosure of Interest: None Declared



THE ROLE OF SPLEEN STIFFNESS MEASUREMENT AS PREDICTOR OF HCC RECURRENCE AFTER CURATIVE RESECTION IN CIRRHOTIC PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is a frequent complication in patients with chronic liver diseases and one of the most common malignancies worldwide. Liver resection is the gold standard treatment option for patients with solitary tumors; however, tumor recurrence complicates 70% of cases of hepatic resection at 5 years. Recently it has been demonstrated that the degree of portal hypertension (PH) measured by HVPG is directly correlated with the risk of developing hepatocellular carcinoma. We recently documented that spleen (SSM) and liver (LSM) stiffness measurement are accurate non-invasive markers of portal hypertension in cirrhosis.

Aims: The aim of our study was to identify the role of SSM and LSM as predictors of HCC recurrence after curative resection.

Material and Methods: One hundred and fifty-seven (157) patients with HCC who underwent curative resection between 2008 and 2014 were prospectively enrolled to assess early (<12 months) and late (>24 months) recurrence. The results of LSM and SSM assessed with TE (Fibroscan®, Echosens, Paris) together with clinical and histological data were collected before surgery and their association with early or late recurrence was assessed by uni and multivariate logistic regression analysis.

Results: Forty-nine (49) patients with early and 22 with late HCC recurrence were identified during follow-up period. At univariate analysis, early recurrences were associated with etiology, number of nodules, HCC diameter and grading, infiltrated resection margins and satellitosis. Multivariate analysis showed that only viral (HCV, HBV) etiology, tumor diameter and margin infiltration were independently associated with early recurrence

with an area under the curve (AUC) of 0.73. At univariate analysis late recurrence was associated only with SSM ($p=0.0027$) with an AUC of 0.70.

Conclusions: Early HCC recurrence is associated with HCC clinical and pathological features; late recurrence was best predicted by the assessment of SSM, thus suggesting a role of portal hypertension in the development of HCC late recurrence.

Disclosure of Interest: None Declared

IS GENDER A DISCRIMINATING FACTOR FOR HEPATOCELLULAR CARCINOMA PRESENTATION, MANAGEMENT AND OUTCOME? RESULTS FROM THE ITALIAN LIVER CANCER DATABASE

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Aims: To analyze gender differences in epidemiology, management and survival among hepatocellular carcinoma (HCC) patients in a large Italian database.

Material and Methods: Data of 6449 cases of naïve HCC, diagnosed between January 1987 and December 2014 and included in the ITA.LI.CA. (Italian Liver Cancer) database were analyzed using SPSS software.

Results: Female gender was significantly ($p < 0.05$ or less) associated with: 1) older age at diagnosis (71, range 32-95 vs 67, 17-93); 2) more HCV-related and less HBV-related, alcohol-related and metabolic-related liver disease; 3) higher prevalence of cirrhosis (95.9% vs 92.8%) and comorbidities (62.3% vs 59.4%). Conversely, Child-Pugh class at HCC diagnosis did not differ between genders.

Women were more frequently diagnosed with HCC under surveillance (62.6% vs. 53.0%, $p < 0.001$), while incidental or symptomatic diagnoses were more frequent in men. Therefore, HCC was more frequently single in women (60.6% vs. 48.1%, $p < 0.001$), while multifocal, infiltrative or massive tumour were more common in men.

The prevalence of Barcelona Clinic Liver Cancer (BCLC) stages showed gender differences in stages A (women: 43.0%, men: 37.9%, $p < 0.001$) and B (women: 15.4%, men: 20.9%, $p < 0.001$).

Women underwent more frequently ablative treatments in BCLC stages 0/A (52.4% vs. 46.2%, $p = 0.009$) and C (33.1% vs. 18.9%, $p < 0.001$), while in BCLC stage 0/A surgical treatments were more frequently performed in men. In the remaining BCLC stages, treatment prevalences did not significantly differ between genders.

The median follow up was 22 months (range 0-294). Overall survival tended to be longer in women (38 months, 95% CI 34.8-41.2 vs 34 months 95% CI 32.2-35.8; $p = 0.06$).



When segregated by BCLC stage, no survival differences were observed, except for stage C, in which women survived longer (25 months, 95% CI 20.7-29.3 vs 17, 95% CI 15.4-18.6, $p < 0.001$).

Conclusions: As compared to male, women diagnosed with naïve HCC are older, more frequently HCV-infected, and with an earlier tumour stage, due to a more extensive use of surveillance.

HCC management is affected by gender in early and advanced tumour stages, in which women undergo more ablative treatments than men. Moreover, in early stages men receive more surgical treatments than women.

Despite an earlier diagnosis, women show an only marginally longer overall survival. In BCLC C stage, female gender is associated with a prognostic advantage.

Disclosure of Interest: None Declared

TRANSARTERIAL CHEMOEMBOLIZATION COMBINED WITH SORAFENIB FOR INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA: A WINDOW OF TUMOR BURDEN FOR SURVIVAL BENEFIT

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Introduction: The benefit of combining transarterial chemoembolization (TACE) and sorafenib (TACE-S) over TACE alone in intermediate stage of hepatocellular carcinoma (HCC), a highly heterogeneous patient population, remains a controversial issue.

Aims: Therefore, we aim to investigate how the treatment outcome changes as the tumor burden varies and find the subset of patients appropriate for TACE-S.

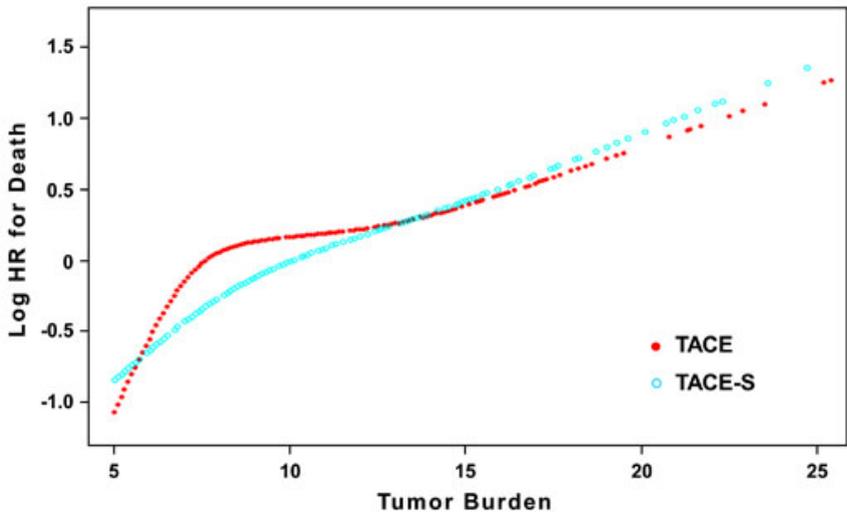
Material and Methods: From January 2009 to December 2015, 616 consecutive intermediate HCC patients with preserved liver function (Child-Pugh \leq B8) and well performance status (ECOG score \leq 1) underwent TACE alone (n=394) or TACE-S (n=222). Tumor burden is defined as the algebraic sum of tumor size [cm] and number, based on which we divide the intermediate stage of HCC. In the entire cohort and different subsets of patients, the Cox regression analyses were separately used to evaluate the superiority of TACE-S to TACE in improving overall survival (OS) and time-to-tumor progression (TTP).

Results: During a median follow-up of 16 months, 443 patients (71.9%) had died. In multivariate analysis, there was no significant difference between TACE and TACE-S in improving OS (adjusted hazard ratio [HR] 0.88, p=0.196); however, the concomitant administration of sorafenib statistically prolonged TTP compared with TACE alone (adjusted HR 0.75, p=0.007). With the cut-off value of seven and twelve for tumor burden, the included patients were divided into three groups with low, moderate and high

tumor burden. For patients with moderate tumor burden, TACE-S significantly improved OS compared to TACE (adjusted HR 0.68, $p=0.013$), whereas no significant differences with respect to OS were observed in patients with low or high tumor burden (adjusted HR 0.77, $p=0.132$ and 0.77, $p=0.132$, respectively).

Conclusions: Compared with TACE alone, TACE-S significantly prolongs TTP but not OS in the whole cohort of intermediate HCC patients. Notably, a significant improved OS is observed in the subset of patients with 7-to-12 tumor burden. Consequently, there might be a window of survival benefit based on intrahepatic tumor burden, and further prospective, multicenter studies are needed.

Figure:



Disclosure of Interest: None Declared

LONG TERM RESULTS OF TREATMENT OF INTERMEDIATE HCC IN CIRRHOSIS USING HIGH-POWERED MICROWAVES: A PROSPETTIVE, MULTICENTER STUDY

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Introduction: AASLD and EASLD guidelines recommend only TACE in treatment of intermediate HCC in cirrhosis.

Aims: The aim of the present study was to report our results in the treatment of intermediate HCC in cirrhotic patients using new high-powered microwaves for percutaneous ablation under Ultrasound guidance.

Material and Methods: From January 2010 to December 2014, 277 cirrhotics with intermediate HCC seen in our 6 Institutes were prospectively asked to undergo MWS percutaneous ablation instead of TACE. 215 patients (162 males, mean age 70 y; 149 Child A, 66 Child) accepted MWS ablation and composed the study group. 109 patients had a single nodule (diameter range 5.3 – 8.2 cm, mean 6.4 cm) [group A]; 70 patients had 2 nodules (diameter range 3-6 cm, with at least one nodule > 5 cm) [group B] and 36 patients had 3 -5 nodules (diameter range 1.5 – 6.7 cm with at least one nodule > 5 cm) [group C]. No patient had ascites or portal venous thrombosis or extrahepatic spread of HCC. In patients with single nodule (Group A), one-two sessions were scheduled; for

group B patients from 2 to 3 sessions were scheduled and for group C patients up to 4 session were scheduled. Percutaneous ablation was performed using high powered MWS device (100-180 watt), at 2450 MHZ, under US guidance. Ten possible factors affecting survival were analyzed.

Results: All patients but one were treated according to the scheduled protocol. The complete ablation rates were 83% for the first ablation and 100% for the second ablation for 3-5cm lesions. The complete ablation rates were 64 % for the first ablation and 86% for the second ablation for 5 – 8.2 cm lesions. One patient (Child A; 80 years; HCC diameter 6 cm ; one session) died for haemoperitoneum. Apart this case, no major bleeding, liver rupture, or liver abscesses occurred. The 1, 3 and 5-year survival rates were 89, 81, 60, 40 and 21%, respectively. At univariate analysis, age, number of tumors, diameter of HCC, number of insertions and pre-ablation bilirubin were independent factors for survival. At multivariate analysis only bilirubin and number of insertions were independent factors in predicting survival.

Conclusions: High powered percutaneous US guided MWS ablation of intermediate HCC in cirrhotic patients is safe and effective in this stage of cancer disease. Our data indicate that percutaneous ablation using the new high- powered MWS should have long term survival similar to TACE in the treatment of intermediate HCC in cirrhosis.

Disclosure of Interest: None Declared

ADHERENCE TO HEPATOCELLULAR CARCINOMA GUIDELINES IN FIELD-PRACTICE: PROGETTO EPATOCARCINOMA CAMPANIA

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Introduction: Currently, the Barcelona Clinic Liver Cancer (BCLC) algorithm and the EASL guidelines are the standard systems for clinical management of HCC. Data on adherence to these therapeutic paradigms are scarce.

Aims: The aim of this field-practice study is to provide a description of HCC patients in Southern Italy, and to evaluate the adherence to therapeutic guidelines and its impact on patients' survival.

Material and Methods: We analyzed the region-wide Italian database PROGETTO EPATOCARCINOMA CAMPANIA, which includes data of HCC patients, prospectively collected from 2013 to 2015, in 15 regional centers. At baseline, demographic, clinical, biochemical, and imaging data were recorded.

Results: Overall 1008 patients with a first HCC diagnosis were enrolled. Concerning the modality of treatment, 712 (70.6%) patients were treated with standards of care according to the BCLC stage, while 296 (29.4%) were treated with non-standardized procedures. The comparison of the 2 groups showed that patients treated with non-standardized procedures had lower percentage of diagnosis on surveillance programs, worse liver function, higher percentage of AFP levels > 200 ng/ml, less early HCC stage, less frequency of HCC single nodule, higher percentage of largest nodule > 5 cm, and higher percentage of portal vein thrombosis and metastases. The multivariate analysis showed that the adherence to treatment guidelines was independently associated only to the BCLC stage and to the presence of neoplastic thrombosis. Mean overall survival according to adherence to treatment guidelines was higher in adherent patients than non adherent (35.5 vs 31.9 months, $p < 0.0001$).

Conclusions: Adherence to guidelines in field-practice was high in early- and end-stage HCC patients, but it was poor in intermediate and advanced patients. This may be due to the large heterogeneity of intermediate-stage patients, and to the limited use of sorafenib in advanced-stage patients. Strategies to improve adherence and stratification of HCC patients are required.

Disclosure of Interest: None Declared

MODIFIED ALBI-T SCORE AS A PROGNOSTIC MODEL IN THE EVALUATION OF EGYPTIAN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: ALBI score eliminates the need for the subjective variables required in the CTP grade. The addition of tumor characteristics from TNM classification resulted in ALBI-T score. ALBI grade 2 showed a wide range of patients, Ogasawara sub classification of ALBI grade 2 classifies patients more precisely.

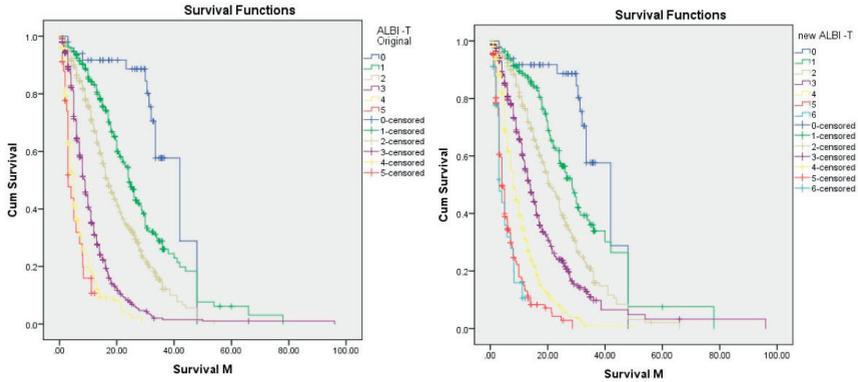
Aims: In this study we propose a modification to the ALBI-T score by adding Ogasawara sub-classification of ALBI score.

Material and Methods: We accrued data from the HCC clinic at National Liver Institute, Menoufia University. We had access to a data set of a cohort of 1910 patients diagnosed with HCC and fulfilled the inclusion criteria. Patients were followed up from the time of diagnosis to the date of death or date of data collection if they remained alive. Modified ALBI-T was obtained through using new grading of ALBI score (grade 1 to 4 instead of grade 1 to 3) obtained through Ogasawara sub-classification of ALBI grade 2 and using it in calculating ALBI-T score.

Results: For 1910 patients, the mean age was 57 years, 1575 were males. At presentation, 50.6% were CTP A, 36.1% were CTP B and 13.4 % were CTP C. Most of patients were ALBI grade 2 (63.2%), 17.8 % were ALBI grade 2A while 45.5% were ALBI grade 2B. ALBI grade 1 & 3 were 12% & 24.7% respectively. The overall median survival was 13 months; the median survival was better in patients with ALBI grade 1 than ALBI 2 & 3 (28.6, 14 and 5.8 months respectively, $P < 0.001$). Moreover, the median survival for ALBI grade 2A patients was better than ALBI 2B (18.6 vs. 13 months respectively, $P < 0.001$). ALBI-T grades 0 & 1 patients had better median survival than those of ALBI-T grades 2, 3, 4 & 5 (42, 24.4, 17, 8.9, 5 and 3 months respectively ($P < 0.001$)). On adding the ALBI sub classification proposed by Ogasawara, the modified ALBI-T showed significant improvement in the median survival. Modified ALBI-T grades 2, 3, 4, 5 and 6 to be 28.6, 20.9, 13.9, 8 and 4 months respectively. (Figure)

Conclusions: Modified ALBI-T classifies patients with HCC more precisely than ALBI-T score.

Figure:



Disclosure of Interest: O. Elshaarawy: Grant: Conflict with: Euroscicon, A. Gomaa: : None Declared, A. Elkhatieb: : None Declared, M. Elhelbawy: : None Declared, N. Allam: : None Declared, A. Alsebaey: : None Declared, E. Rewisha: : None Declared, I. Waked: Sponsored Lectures (National or International): Conflict with: Jansen, Glead, Abbvie & Pharco

TRANSARTERIAL CHEMOEMBOLIZATION PRIOR TO LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA – A SINGLE-CENTER EXPERIENCE

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Introduction: Liver transplantation (LT) is a curative treatment option for patients with hepatocellular carcinoma (HCC) and liver cirrhosis.

Aims: The aim of this study is to present our results using transarterial chemoembolization (TACE) in HCC patients before LT.

Material and Methods: A retrospective analysis was performed on data of patients with HCC who were treated with at least one TACE followed by LT between 2010 and the end of 2016. Demographic, etiological, laboratory and histological characteristics, as well as waiting time (WT) on list for LT were reviewed.

Results: In total period 197 patients with HCC underwent LT. Among them 28 patients with HCC were treated with TACE prior to LT. Because of insufficient data, 25 patients were included in this study. Majority of patients were male (76%), the mean age at the time of LT was 61 ± 5.3 years with the mean body mass index (BMI) of $28 \pm 4,38$ kg/m². Leading etiology of liver disease was alcohol (60%), followed by viral hepatitis (24%). 96% patients were classified in stage A or B according to the Barcelona Clinical Liver Cancer classification. The median of a serum α -fetoprotein concentration was 14.30 (1.30-13527.0) μ g/L with the mean MELD score 12 ± 4 before LT. In 60% patients one cycle of TACE was preformed while the rest of study patients undergone 2 or more cycles. The median of WT on the list was 16 (1-354) days. Before entering the pre-transplant TACE protocol, 7 patients assumed to meet and 18 to exceed the Milan criteria. According to the surgical specimens (SS), 11 patients met and 14 exceeded the MC. On the histopathological examination the median number of tumor lesions were 3

(1-11) with sum of lesions 72 (10-300) mm. Vessel microinvasion was observed in 52, 8% and macroinvasion in 8% patients. After a median follow up of 21 (3-74) months overall survival is 88%. 4 patients developed recurrent HCC after LT. There was no statistical significant difference between survival and HCC recurrence in patients in and out of MC according to SS ($p=0.39$ and $P=0.79$ respectively).

Conclusions: Even though TACE was performed with intention to downstage or as a bridge therapy before LT, more than 50% patients exceed MC after TACE. Nevertheless, there was no significant difference in survival nor HCC recurrence when comparing them to patients who meet MC. Current high donor rate in Croatia provides HCC patients short WT on the list for LT.

Disclosure of Interest: None Declared

TRANSIENT ELASTOGRAFY CAN PREDICT THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN HEPATITIS C CIRRHOTIC PATIENTS

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Introduction: Hepatitis C virus (HCV) is one of the main causes of cirrhosis worldwide. Furthermore, as the degree of fibrosis increases, there is a greater risk of developing hepatocellular carcinoma (HCC). Transient Elastography (TE) is a non-invasive tool that stratifies the degree of fibrosis.

Aims: The aim of this paper is to determine the stiffness values that may identify risk groups for HCC, comparing with clinical non-invasive liver serum markers (MELD, APRI, FIB-4).

Material and Methods: A cohort of 100 consecutive hepatitis C patients was included between 2011 and 2016 with a minimum baseline liver stiffness of 12 kPa. These patients were evaluated with laboratory tests, endoscopy, Doppler ultrasound and TE, as well as MELD, APRI and FIB-4 scores. We used the Lausen's test to find the best cut-off point for HCC occurrence and the logrank test, Kaplan-Meier estimates and C-statistic test to better evaluate performance of each method over time.

Results: The mean age was 57.6 ± 10.6 , and 52% were female (N=52). Eighteen (18) patients developed HCC. Median time from baseline to diagnosis of HCC was 2.6 years (range, 0.02 – 4.74). The predictor cut-off points of HCC occurrence: TE 21.1 kPa ($p=0.0083$), MELD 6.8 ($p=0.004$), APRI 1.63 ($p=0.022$) and FIB-4 5.6 ($p=0.0061$) (Table 1). The highest index for the first 6 months was FIB-4, and for over three years it was TE, for which performance progressively improved (Figure 1). A combination of TE and FIB-4 achieved the best rates over 5 years of follow-up on the cumulative incidence curve (46.5%) (Figure 2).

Conclusions: 1. Non-invasive liver fibrosis evaluation methods (serum markers and mechanical) can be used to predict greater risk of developing HCC in selected HCV cirrhotic patients with elevated baseline TE (>12 kPa). 2. TE was the best non-invasive method of predicting the risk of an HCC event, with a cut-off of 21.1 kPa during long-term follow-up. 3. The combination of TE + FIB-4 was the best predictor of HCC incidence over 5 years.

Figure:

Figure 1. Cumulative Incidence curves of HCC in HCV pts with a cut-off value 21.1 kPa in Transient Elastography, $p=0.0083$.

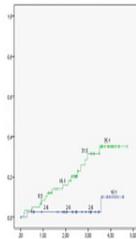


Figure 2. Cumulative Incidence curves of HCC in HCV pts with a cut-off values 21.1 kPa in Transient Elastography and FIB-4 > 5.6, $p=0.0014$.

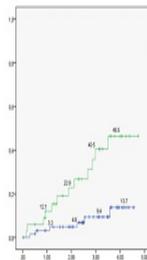


Table 1. Cut-off points and C-statistic test of HCC incidence.

Variable	Cut-off point	C statistic			
		0.5 year	1 year	2 years	3 years
TE	21.1	0.5344	0.6167	0.6556	0.6862
MELD	6.8	0.607	0.604	0.6772	0.658
APRI	1.63	0.6737	0.593	0.6321	0.6226
FIB-4	5.6	0.7842	0.7028	0.6924	0.675
TE + FIB-4		0.6667	0.6676	0.6921	0.6916

Disclosure of Interest: None Declared

RISK FACTORS FOR HEPATOCELLULAR CARCINOMA IN A LARGE COHORT OF PATIENTS AFFECTED BY PRIMARY SCLEROSING CHOLANGITIS

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Introduction: Primary sclerosing cholangitis (PSC) patients are at risk of biliary tract cancer [cholangiocarcinoma (CCA) 5-10% of patients, gallbladder cancer (GBC) 2-4% of cases] and colorectal cancer (CRC). It has been suggested that the risk of developing hepatocellular carcinoma (HCC) may be lower in patients with PSC than in other causes of liver disease. There are no specific recommendations for HCC surveillance in this population.

Aims: Our aim was to report the incidence of HCC in a large single centre cohort of PSC patients and consider the potential risk factors for HCC in this population.

Material and Methods: A retrospective analysis of the PSC database of our tertiary centre was performed, excluding patients with incomplete data.

Demographics, type, location (intra/extrahepatic), duration and severity of PSC, IBD type and duration, prevalence of biliary tract cancers, HCC and CRC, pharmacological treatment, duration of follow-up (FUP) and outcome were recorded. FUP and patients-years at risk calculation started at time of PSC diagnosis. FUP was censored at occurrence of HCC, liver transplant (LT), death or last FUP.

All the abovementioned variables were correlated with the incidence of HCC. Cox proportional hazard model was used for risk analysis.

Results: 281 patients followed-up between 1988 and 2016 were included. Patient's characteristics are summarized in Table 1. Eighty-two (29%) patients underwent LT/death. Eleven (3.9%) developed HCC (1 incidental on explant), 13 (4.6%) CCA, 2 (0.7%) GBC, 2 (0.7%) pancreatic cancer, 11 (3.9%) CRC. All HCC occurred in cirrhotic patients. The only variable significantly associated to the development of HCC at the

univariate analysis was the presence of cirrhosis ($p=0.003$). Statistical significance was not maintained on Cox regression ($p=0.161$, HR 0.020).

Incidence of HCC was 0.6% for the 1756 years FUP covering the entire cohort, 1.1% with regard to the 996 patient-years with cirrhosis.

Conclusions: In our cohort, incidence of HCC was low, as has been previously observed. Presence of cirrhosis was the only variable associated to HCC development, but risk proportion is unclear. Given the low incidence of HCC in this population, it further questions whether a strategy of surveillance for HCC in PSC patients with cirrhosis is justified.

Figure:

Table 1. Characteristics of the study population.

Total number of patients, n (%)	281 (100)
Male sex, n (%)	181 (64)
Age, mean (SD)	48 (16)
Age at diagnosis, mean (SD)	41 (16)
Time from PSC diagnosis, median months (range)	57 (6-413)
Large-duct PSC, n (%)	249(88.6%)
Small duct PSC, n (%)	16 (5.7%)
Overlap syndromes, n (%)	16(5.7%)
Cirrhosis, n (%)	158 (56.2%)
IBD, n (%)	195(69.3%)
UC, n (%)	167 (59.4%)
CD, n (%)	22 (7.8%)
IC, n (%)	6 (2.1%)
UDCA treatment, n (%)	146 (59.8%)
Pre-LT AZA, n (%)	52 (18.5%)
Pre-LT steroids, n (%)	51 (18.1%)

Abbreviations: SD, standard deviation; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IC, indeterminate colitis; UDCA, ursodeoxycholic acid; LT, liver transplant; AZA, azathioprine.

Disclosure of Interest: None Declared

MULTI-OPERATIONAL SELECTIVE COMPUTER-ASSISTED TARGETING OF HEPATOCELLULAR CARCINOMA – PRECLINICAL RESULTS

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Introduction: The benefits of combining local ablation and transarterial chemoembolization (TACE) against monotherapy alone for treatment of early and intermediate stage hepatocellular carcinoma (HCC) were shown previously. However, practical implementation of a combined treatment approach and precise placement of ablation probes remain challenging.

Aims: In this work, we propose a technique termed MOSCAT of HCC, and report accuracy and efficiency in a porcine model. The system combines intraarterial electromagnetic (EM) tracking for referencing with computer-assisted navigation of ablation probes.

Material and Methods: An EM tracked reference sensor was designed and integrated into a standard vascular catheter. The modified catheter was placed via inguinal access into an intrahepatic artery at different distances to an intrahepatic tumour model. Percutaneous targeting of the tumour with an EM tracked ablation probe was performed using computer-assisted navigation technology. Targeting accuracy was assessed as total positioning error (TPE, Euclidean distance) and measured when directly aiming for the intrahepatic reference sensor (baseline targeting) and when aiming at defined distances relative to the sensor (offset targeting, accounting for the expected offset distance between the tumour and the sensor when placed in peritumoural feeding vessels). Time effort for sensor placement and navigated targeting were measured.

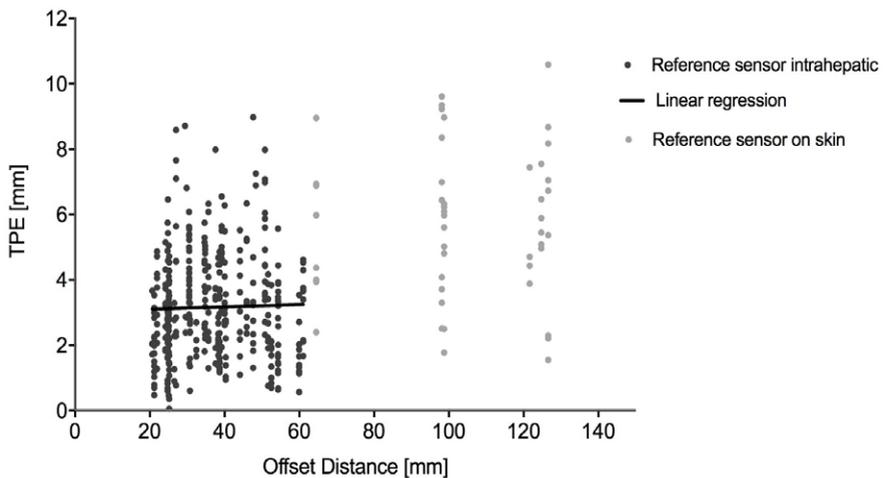
Results: A total of 505 targeting attempts were performed in 6 swines (90 baseline, 415 offset attempts). Mean TPE for baseline targeting was 2.6 ± 1.6 mm, representing basic accuracy when using this navigation technology for in-vivo targeting. Mean TPE for offset

targeting with the reference sensor closest to the tumour model was 3.1 ± 1.6 mm (mean distance sensor to tumour centre 28.7 mm, n=139). No significant correlation between offset distance and targeting accuracy was observed ($r=0.03$, $p=0.62$, Figure 1), as long as the sensor was placed intrahepatically. However, targeting errors increased when placing the sensor externally on the skin (TPE= 5.6 ± 2.3 mm, $p<0.01$). Mean time for placement of the EM-tracked sensor was 6.5 ± 3.8 min, and for navigated targeting 13.6 ± 1.1 sec.

Conclusions: The MOSCAT technique allows accurate and efficient targeting of intrahepatic lesions, while operating in the available real-time angiographic imaging space, in an animal model. It might represent a simple minimal invasive approach for combined TACE and ablative treatment of HCC lesions in a single treatment session.

Figure:

Fig. 1: Targeting Accuracy according to Offset Distance



Disclosure of Interest: None Declared

IS SARCOPENIA A PREDICTOR OF OUTCOME IN PATIENTS WITH HCC TREATED WITH SORAFENIB?

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Introduction: Sarcopenia has been associated with poor outcomes in hepatocellular carcinoma (HCC).

Aims: This retrospective study investigated the relationship between survival of patients with advanced HCC receiving Sorafenib and sarcopenia.

Material and Methods: From 2008 to 2015, 118 consecutive sorafenib treated HCC patients (70±5 years, 97 males, 83% Child Pugh A). Muscle mass was assessed as psoas muscle thickness at lumbar level (L3) on CT scan normalized for height (TPMT/h) according to Durand's score. To validate this score we measured TPMT/h in a group of healthy controls matched for age and sex.

Results: Mean TPMT/h was lower in HCC patients than in controls (19.05±4.30 vs 20.37±4.30 mm/m, p=0.02). However, when subdividing cases and controls according to sex and age (decades), TPMT/h was lower only among male patients (19.66±4.15 vs 21.12±4.00; p=0.013), aged 55-64 years (20.47±3.40 vs 22.98±3.36; p=0.017). Median overall survival (OS) of HCC patients was 11.6 months [IC95% 9.2-14 months; male 10.9 (8.2-13.6), female 13.39 (6.9-19.7)]. Using the mean TPMT/h value minus two standard deviation of healthy subjects (13,12 mm/m) to define the lower normal limit, the rate of sarcopenic patients was too low (5,2%) to perform reliable analyses. Therefore, we analyzed the impact of muscle waste subdivided in percentiles (tertiles, quartiles, decreasing percentiles until 10th) on Sorafenib outcomes and no association was found with OS, treatment duration, dose reduction necessity and adverse events.



Conclusions: In contrast with a previous study using another method to assess muscle mass (Hiraoka A et al, Hepatol Res. 2016), no association was found between sarcopenia and outcomes of patients with advanced HCC treated with sorafenib. More studies are needed to evaluate whether and/or in which patients the muscle waste impacts on sorafenib outcomes.

Disclosure of Interest: None Declared

TEMPORARY SUSPENSION OF SORAFENIB BY ADVERSE EFFECTS IS ASSOCIATED WITH LONGER SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Several studies have assessed if the off-target effects of sorafenib (SOR) predict antitumoral efficacy. An indirect way of measuring the effectiveness of SOR could be the study of dose changes motivated by such adverse effects, most severe handled with temporary suspension (TS).

Material and Methods: Unicentric prospective cohort of consecutive patients treated with SOR. Only patients with compensated cirrhosis Child \leq B7 and ECOG-PS \leq 1 were included. Patients were evaluated at 2, 4, 8, 12 weeks and every 8 weeks. Initial dose 800 mg in all cases, modified according to tolerance. Patients have unscheduled visits whenever necessary. Prognostic value of baseline clinical/analytical variables, vascular and dermatologic adverse effects in the first quarter, maintenance dose, modifications and temporary suspensions (TS) due to adverse effects have been analyzed.

Results: From JUL-07 to DEC-14, 142 patients included, followed until 28-OCT-16. Most of them Child A5 (n=94), ECOG-PS 0 (n=110), BCLC-C (n=102). Median duration of SOR was 8 months (95%CI 6.3-9.7). Median survival 14 months (95%CI 10.2-17.9). At univariate analysis, statistically significant baseline variables were AFP $p < 0.001$; ECOG $p < 0.001$; BCLC $p < 0.001$. In addition, arterial hypertension at 1ST month, dermatologic adverse events at 3RD month and TS were $p = 0.072$, $p = 0.079$ and $p = 0.016$, respectively. Median time from the beginning of SOR to TS was 1 month, median duration of TS was 7 days.

At the multivariate analysis, independent predictors of overall survival were baseline BCLC stage B vs C ($p = 0.003$; HR 0.502, 95%CI 0.319-0.791), ECOG-PS 0 vs 1 ($p = 0.001$; HR 0.467, 95%CI 0.302-0.722) and TS yes vs no ($p = 0.028$, HR 1.500, 95%CI 1.045-2.153).

Within BCLC-C those ECOG-PS 1, n = 32, have a median survival 5 months, 95%CI 2.228-7.772 versus ECOG-PS 0, n=70, median survival 14 months, 95%CI 8.960-19.040; p <0.001.

In the overall cohort, those who did not required TS (n=77) maintained SOR during less time (median 6 months, 95%CI 3.871-8.129) than those who needed it (n=65), median 15 months, 95%CI 8.473-21.527), p=0.001. They also had lower survival (median 11 months, 95%CI 8.140-13.860) than those who needed TS (median 18 months, 95% CI 15.464-20.536), p=0.016.

Conclusions: The temporary suspension of SOR by an adverse effect is an indicator of increased survival independently of baseline BCLC stage and symptoms. This reinforces the need for close monitoring to not discourage treatment maintenance in patients experiencing drug-related adverse events.

Disclosure of Interest: C. Rodríguez-Escaja: : None Declared, M. de Jorge Turrión: : None Declared, A. Castaño García: : None Declared, E. Rubio Díaz: : None Declared, M. González-Diéguez: Sponsored Lectures (National or International): Conflict with: Abbvie, Gilead, C. Alvarez-Navascués: Consultant: Conflict with: Bayer, Sponsored Lectures (National or International): Conflict with: Abbvie, Gilead, V. Cadahía-Rodrigo: : None Declared, M. Rodríguez: Consultant: Conflict with: Abbvie, Gilead, Bayer, Bristol, Sponsored Lectures (National or International): Conflict with: Abbvie, Gilead, MSD, Bristol, M. Varela Calvo: Consultant: Conflict with: Bayer, Sponsored Lectures (National or International): Conflict with: Bayer, Gilead, Abbvie

STEREOTACTIC IMAGE-GUIDANCE FOR PERCUTANEOUS LOCAL ABLATION OF HEPATOCELLULAR CARCINOMA

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Introduction: Local ablation strategies become increasingly important in the treatment of hepatocellular carcinoma (HCC), and minimal invasive and precise targeting approaches are needed. In order to address the remaining challenge of precise targeting of intrahepatic lesions and to optimize the accuracy of needle placement, advanced image-guided navigation technology has been introduced for a percutaneous approach and is now entering the clinical setting.

Aims: Our aim was to analyse safety and efficiency of percutaneous stereotactic image-guided microwave ablation (PIMA) for HCC at our institution.

Material and Methods: Selection criteria were early and intermediate stage HCC including patients listed for transplantation. PIMA was performed by an interdisciplinary team of surgeons and radiologists using Computed tomography (CT)-guidance with needle trajectory planning applying landmark-based registration, precise needle placement by using an aiming device and immediate imaging control over both intrahepatic needle positions and post-ablation zones. Interventions are performed in general anesthesia using jet-ventilation to optimize registration accuracy.

Results: Since January 2015, sixty PIMA have been performed for a total of 90 HCC lesions. In these 53 individual patients, 13 (25%) were women. The majority of patients was BCLC 1 (64%) with a median size of the tumor of 15.5 mm. Fourteen patients had previous liver resections or a liver transplantation. Thirty-eight patients had 1 lesion, 17 had 2 lesions, 4 had 3 lesions and 1 had 4 lesions ablated during one intervention. The median length of stay was 2 days. Within 30 days, no major or liver-specific complications occurred, three patients had minor (grade 1 and 2) complications. Local recurrence occurred in 11/90 lesions (12.2%) at three months. Seventy-five % of these recurrences or incomplete ablations were successfully re-ablated, while 25% recurred with a diffuse intrahepatic progression, as assessed in MRI imaging.



Conclusions: With the described technique, precision and accuracy of needle positioning can be enhanced, while providing support for a wide range of needle trajectories in a minimal invasive setting. PIMA represents a precise and safe local treatment strategy for early and intermediate HCC. Notably, patients with lesions close to the major blood vessels, the diaphragm or the heart, can be offered a curative treatment approach in case they do not qualify for resection or transplantation or cannot be treated by conventional ablation approaches.

Disclosure of Interest: None Declared

EVIDENCE-BASED TWO-AND-SEVEN CRITERIA BASED ON TUMOR NUMBER AND SIZE BEST HELP TO PREDICT SURVIVAL OF PATIENTS WITH INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA TREATED WITH TRANSARTERIAL CHEMOEMBOLIZATION

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Introduction: Tumor burden have a great impact on prognosis of hepatocellular carcinoma(HCC) treated with transarterial chemoembolization (TACE), and it frequently weighted by up-to-seven criteria, which were originally developed from the setting of liver transplantation. The criteria of tumor burden based on data of TACE is urgent needed

Aims: We aim to derive novel criteria of tumor load from landscape of TACE to improve survival prediction

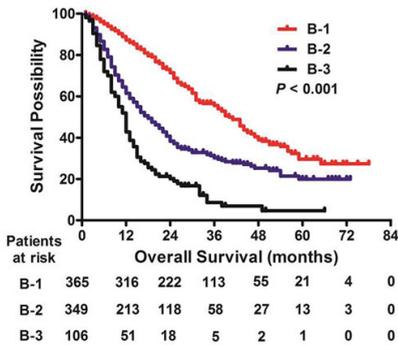
Material and Methods: We retrospectively enrolled 1515 treatment-naïve HCC patients with intermediate-stage HCC and well-preserved liver function underwent TACE during January.2010 to December.2014 from 24 Chinese centers, which were randomly divided into training (12centers, N=820) and validation cohort(12centers, N=695). Cox regression analysis was used to determine prognostic factors, smoothing splines were used to determine the nature of the relationship between tumor burden and mortality, then we developed the criteria. We also analyzed discrimination of these criteria and compared with other criteria.

Results: Tumor size(Ts) and number(Tn) consistently were significant factors in multivariable analysis in training cohort and multivariable analysis of selected variables from whole cohort. Risk of death was correlated with increasing size and number, the effect of size is line, whereas, for tumor number, the effect tend to reach a plateau in both cohorts, with adjustment of confounding factors. Two-and-Seven criteria was developed and could classify the intermediate-stage patients into three sub-stage, ie, B-1: $Tn \leq 2, Ts \leq 7$ cm; B-2: $Tn \leq 2, Ts > 7$ cm or $Tn > 2, Ts \leq 7$ cm, but exceeding Milan criteria; B-3: $Tn > 2, Ts > 7$ cm, with statistical difference in overall survival (40 months, 18.5months, 12.1 months for B-1, B-2 and B-3 sub-stage in training cohort; 41.2months, 25.3 months, 10.1 months for validation cohort respectively, $p < 0.001$). These criteria provided better discriminative ability than up-to-seven and 4 and 7 criteria in both cohorts, and consistently in sub-group analysis of whole cohort.

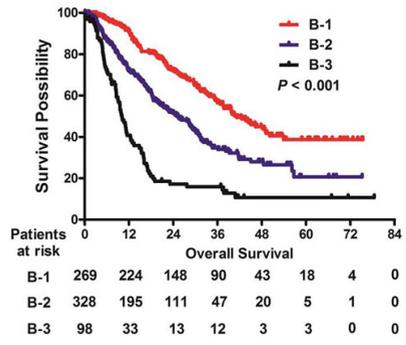
Conclusions: Two-and-Seven criteria offered a simple, validated, evidence-based objective method with higher discriminative ability in predicting overall survival of patients

with intermediate-stage HCC underwent TACE and should be in considerations for the further clinical trails and treatment-decisions making.

Figure:



Kaplan-Meier curve of OS for B1-B3 sub-stage (training cohort)



Kaplan-Meier curve of OS for B1-B3 sub-stage (validation cohort)

Disclosure of Interest: None Declared

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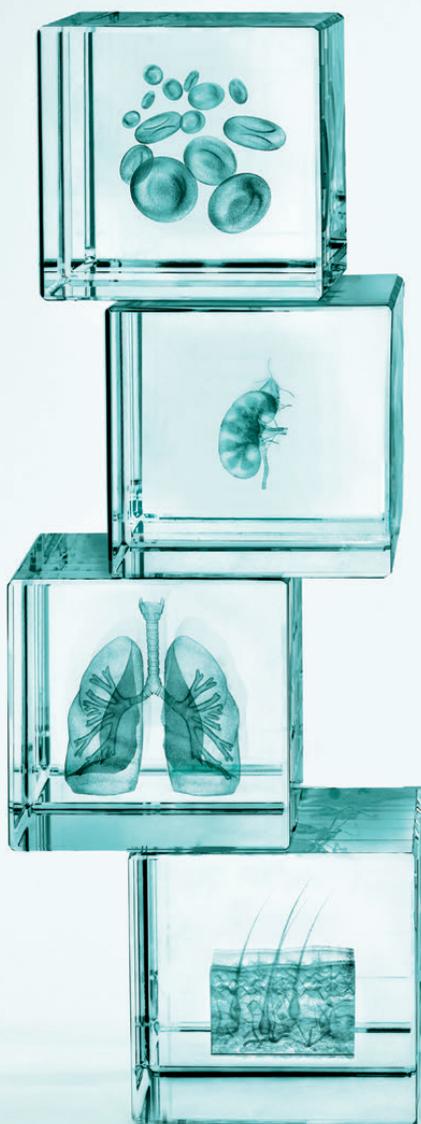
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