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from basic science to liver transplantation"
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OC-01

Predicting Early Recurrence in Hepatocellular Carcinoma: Leveraging Machine Learning for Enhanced Prognosis and Personalized Treatment

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Introduction: Hepatocellular Carcinoma (HCC) recurrence is a significant clinical challenge, especially within the first year following treatment. Early prediction of recurrence is crucial for improved prognosis and personalized treatment strategies.
Aim: This study aims to establish an effective predictive model for early recurrence (i.e., within one-year post-treatment) in naive treatment patients with HCC.
Materials and Methods: Our study encompasses 320 patients, divided into an 80/20 training/test split, with 10-fold cross-validation employed within the training set. Various predictive models including Random Forest (RF), Multilayer Perceptron (MLP), Support Vector Machine (SVM), Logistic Regression (LR), Gradient Boosting, AdaBoost, Naive Bayes, and K-Nearest Neighbors (KNN) were compared. Predictive variables included full blood panels, liver disease etiology, portal hypertension signs, and imaging information.
Results: The most performant model was the RF in both the training (AUC 0.95, Accuracy 90%, Recall 0.97, Precision 0.98, F1. 0.94) and the test (AUC 0.90, Accuracy 88%, Recall 0.94, Precision 0.95, F1. 0.90) sets. The ten features that impacted the most on the model predicted risk were: tumor margin characteristics (smooth vs. irregular), arterial peritumoral enhancement, alpha-fetoprotein, wider nodule diameter (mm), platelet count, previous semestral ultrasound screening, number of nodules, portal vein thrombosis, and presence of portosystemic shunts.
Conclusions: Our study demonstrated the viability and robustness of the RF model in predicting early recurrence of HCC. The identified ten high-impact factors underscore the importance of comprehensive assessments involving clinical, biochemical, and radiological parameters. This model, incorporating tumor characteristics and liver function, allows for early risk stratification of recurrence, highlighting patients who might benefit from more aggressive or tailored treatments post-HCC diagnosis. These findings present a strong foundation for developing a clinical decision support system that could significantly enhance personalized patient management and ultimately improve HCC prognosis. Integrating machine learning models into clinical practice opens promising avenues for advancing the precision medicine paradigm in hepatocellular carcinoma management. Future studies should seek to validate these results in larger, diverse cohorts and explore the potential for incorporating additional dynamic and molecular markers.

doi: 10.1016/j.dld.2023.08.003

OC-02

Sequential systemic treatments for hepatocellular carcinoma: real-life clinical practice data in the time of multiple agents

F. Tovoli [1,2], M. Tonnini [1], R. Mandolesi [1], D.P. Pallotta [1], B. Stefanini [1], R. Chen [1], A. Granito [1,2], F. Piscaglia [1,2]

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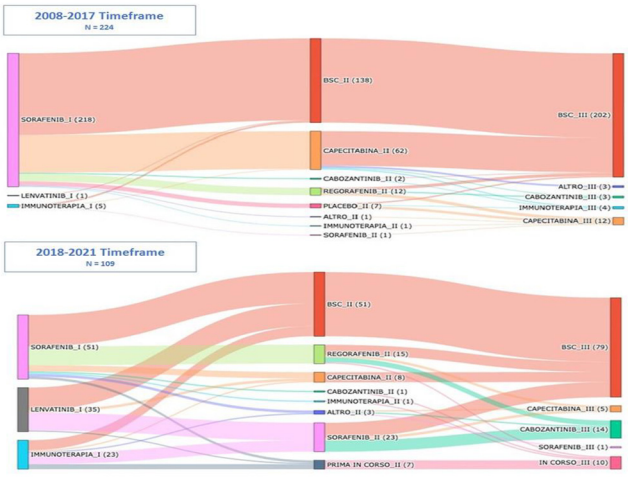
Background: Different drugs became available for prescription for HCC patients in the last 5 years, paving the way for sequential treatments, up to the a third line. Unfortunately, not all patients starting a frontline systemic treatment will became eligible for further treatments, due to failing liver function or performance status (ECOG-PS). The proportion of such patients is ill-defined. Also, baseline factors associated with the eventual elegibility to further lines has not been explored.
Methods: Retrospective analysis of the therapeutic sequences prescribed in our center in the 2008-2021 timelapse. To minimize bias, we divided the groups by historical availability of multiple systemic agents (2008-2017 vs 2018-2021). Patients were considered elegible for further lines in case of ECOG-PS≤2 and Child-Pugh≤B7) at the time of failure of the previous treatment. In the 2008-2017 timeframe, second-line options included clinical trials or metronomic capecitabine.

Results: This study included 333 patients (n=224 and n=109 in the older and most recent timeframe, respectively). The elegibility to second (51.0 vs 38.4%, p=0.040) and third (20.2 vs 9.8%, p=0.019) line treatments increased in the latest years, with different prescription patterns (Figure). Macrovascular invasion (OR 0.62, 95% CI 0.39-0.99), Child-Pugh B7(OR 0.05, 95% CI 0.16-0.98), and ECOG-PS>0 (OR 0.30, 95% CI 0.16-0.55) at the start of the frontine treatment decreased the likelyhood of being eligible for further lines. Similar results were found for the elegibility to third line treatments. Both regorafenib [15.0 months, HR 0.60(0.40-0.88)] and cabozantinib [12.8 months, HR 0.44(0.23-0.87)] increased the post-frontline survival compared to metronomic capecitabine (6.5 months).
Conclusion: A relevant proportion of patients who started a frontline treatment after 2017 became eligible for further systemic treatments. ECOG-PS 0, Child-Pugh A, and absence of macrovascular invasion identified the patients who were most likely to receive multiple treatments.



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OC-03

The impact of the onset of Hepatocellular Carcinoma on the natural history of cirrhosis

A. Martini, E. Libralesso, A. Baroni, P. Guerra, S. Cagnin, S. Incicco, N. Zeni, R. Gagliardi, V. Calvino, M. Tonon, C. Gambino, P. Pontisso, S. Piano, P. Angeli

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Introduction: Hepatocellular Carcinoma (HCC) is a leading cause of cancer related death and the large majority of HCC occur in the setting of chronic liver disease. Nevertheless, its impact on development of decompensating events, such as ascites, hepatic encephalopathy (HE), portal hypertension related bleeding (PHB), and episodes of further decompensation (refractory ascites, spontaneous bacterial peritonitis [SBP] and hepatorenal syndrome [HRS]) in patients with cirrhosis has not yet been investigated.
Aim: to investigate the role of HCC in the development of decompensating events in patients with cirrhosis.
Materials and Methods: 876 patients with cirrhosis were consecutively evaluated in the Outpatient clinic (CMP) of the Padua Teaching Hospital, and followed up until death and/or liver transplantation (258 patients developed HCC, 618 patients without HCC during follow-up). Demographic, clinical, and laboratory data were collected, and patients were evaluated at least every 6 months between January 2000 and December 2022. The median follow-up time was 33 months. The primary outcome was the development of decompensating events after the diagnosis of HCC. HCC was considered as a time-varying covariate for the statistical analysis.
Results: Patients with HCC had a higher risk of developing a decompensating event as a whole (adjusted hazard ratio [aHR] =3.07; p<0.001), as ascites (aHR= 2.78; p<0.001), HE (aHR=1.70; p=0.002) and PHB (HR=1.78; p=0.021). As far as further decompensation patients with HCC were at higher risk of developing refractory ascites (aHR 3.73; p<0.001), but not SBP (p=0.50) and HRS (p=0.09). Among patients with HCC, ALBI Grade was an accurate score to identify patients at higher risk of liver complications (p<0.001), and mortality (p=0.029). The first treatment of HCC (surgical or locoregional therapy) reduced both the risk of decompensation (p=0.005) and that of mortality (p<0.001).
Conclusions: The occurrence of HCC is associated with a high risk of decompensation and further decompensation in patients with cirrhosis.

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OC-04

Efficacy of nivolumab monotherapy in cirrhotic patients with advanced hepatocellular carcinoma: a single-center retrospective study

F. Frigo [1], P. Carucci [1], A. De Giorgi [1], G.P. Caviglia [1], P. Pochettino [2], E. Rolle [1], M. Scaldaferri [3], F. Cattel [3], E. Castellana [3], A. Risso [1], G. Saracco [1], S. Gaia [1]

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Introduction: Nivolumab, an anti-PD-1 monoclonal antibody, showed promising results as a monotherapy for advanced HCC, but lacked a statistically significant survival benefit over sorafenib.
Aim: To evaluate the efficacy and OS of nivolumab as monotherapy in cirrhotic patients with advanced HCC who are ineligible for other treatments.
Materials and methods: Our retrospective, single-centre study included 22 cirrhotic patients with advanced HCC treated off-label with nivolumab between September 2019 and April 2023. Enrolled patients had disease progression or intolerance to prior TKI therapy and were not eligible for local therapy or other systemic therapies. Outcomes measured were OS, radiological response (RR), defined as stable disease, complete or partial response, and biological response (BR), defined as a ≥ 25% decrease in AFP blood level from baseline.
Results: 22 patients were included: 73% male, median age 64.5 years (range: 30-80), 91% BCLC-C, 82% Child-Pugh A, 94% received prior lines of treatment. The median duration of treatment was 3.5 months (range: 0.4-36.9). OS was 7.8 months (95%CI 4.7-14.2; range 1.1-34.1). RR at 3 months was achieved in 8 patients and maintained in 6 patients at 6 months. BR at 3 months was achieved in 6 patients.

OS was significantly associated with RR (p 0.002) and BR (p 0.0001) at 3 months. Median OS in patients with RR at 3 months was 27.7 months (95%CI 4.7-27.7) versus 6.4 months (95%CI 3.2-9.1) in patients with progression (p 0.0003). At baseline, better performance status (p 0.031), presence of metastatic lymph nodes

(p 0.040) and lower disease burden (p 0.009) correlated with improved OS. Grade 3-4 AEs occurred in 5 patients.
Conclusions: Nivolumab monotherapy in HCC patients with no other therapeutic option showed acceptable efficacy, with OS exceeding 6 months in 68% of patients. RR and BR at 3 months predicted longer survival (median OS 27.7 and 27.9 months, respectively). Nivolumab showed a manageable safety profile.

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OC-05

Comprehensive characterization of viral integrations in HBV-infected intrahepatic cholangiocarcinomas

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Chronic hepatitis B virus (HBV) infection is associated with an increased risk of intrahepatic cholangiocarcinoma (ICC) development. However, there is no direct evidence of a causal relationship between HBV infection and ICC. In this study we attempted to determine the landscape and mechanisms of HBV integration of HBV-infected iCCA (HBV-iCCA) tumours.
Methods We conducted a high-throughput HBV integration sequencing (HBIS) analysis on tumour specimens from 13 HBV positive patients with ICC (3 HBsAg-positive and 10 with occult HBV infection, OBI) and 8 paired non-tumour liver tissues to study HBV integration sites.
Results: A total of 15.247 HBV integration sites were detected in the 13 patients studied, 12.785 in tumours and 2462 in non-tumour tissues, with no significant differences between HBsAg- and OBI-positive patients. All patients studied showed HBV integrations, with an average of 983.5 and 307.7 integration sites per tumour and non-tumour sample, respectively ($P<0.01$). HBV integration sites were annotated to analyse their distribution in distinct genomic elements. Integrations were more frequent in coding region ($P<0.0001$), LTR ($P<0.01$), LINE ($P<0.0001$), and SINE ($P<0.0001$) in tumours than non-tumour samples. Characterization of breakpoints in the HBV genome revealed accumulation of integration of the Enh1/HBx/ENH2 genomic sequences in tumours ($P<0.0001$) than non-tumour tissue samples, whereas HBV breakpoints were significantly enriched at level of the preS/S gene in non-tumour tissues ($P<0.0001$). To elucidate the mechanisms of HBV integration, the presence of microhomology (MH) sequences between nuclear DNA and HBV DNA integrants at level of integration sites was investigated. We found that almost all the HBV integration sites detected showed the presence of MH sequence (range 3bp-15bp).
Conclusions: HBV integration occurs at high frequency in both tumour and adjacent non tumour tissues of patients with ICC and HBV infection (both in cases with overt and occult HBV infection), showing significantly higher insertion rates in tumours. Furthermore, our data strongly indicate the involvement of MH-mediated mechanism in HBV integration, which could be triggered by the genomic instability/fragility near the integration sites

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OC-06

Metabolic dysfunction and DNA damage of exhausted tumor-infiltrating CD8 T-cells in hepatocellular carcinoma

A. Montali [1], V. Reverberi [2], R. Dalla Valle [1], C. Boni [2], P. Fisicaro [2], A. Vecchi [2], M. Rossi [1], S. Doselli [2], C. Ceccatelli Berti [1], C. Tiezzi [1], I. Montali [1], C. Ferrari [1], G. Missale [1]

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Introduction: CD8 T-cells are the main effectors of the adaptative immune system and are characterized by cytotoxic and regulatory functions, thus constituting the most relevant line of defense against viral infections and tumors. The tumor immune microenvironment is able to release soluble factors or exert other regulatory mechanisms capable of intervening on different immunological pathways.

Functional defects of CD8 T-cell response have been described in HCC showing correlation with disease stage and clinical outcome, however the molecular bases of CD8 cell dysfunction are still not completely known.
Aim: the aim of this study was to define the molecular profile of tumor-infiltrating CD8 T-cells, their metabolic, phenotypic and functional alterations associated with CD8 T-cell exhausted phenotype.
Materials and Methods Results: by comparison with CD8 cells from the non-tumorous counterpart, genomic profiling of tumor-infiltrating CD8 T-cells showed upregulation of several pathways among which hypoxic and oxidative stress response, DNA damage response and TGF-β pathway. We performed phenotypic analysis, staining tumor and liver infiltrating CD8 T-cells for CD103, CD39, PD-1, TIM-3, TIGIT, CXCR6. An enhanced expression of check point molecules such as PD-1, CD-39 and TIM-3 was evident in the tumor. Moreover, infiltrating CD8 cells showed depolarized mitochondrial membrane and higher levels of phosphorylation of the histone H2AX and ATM suggesting dysfunctional mitochondria and DNA damage, in agreement with the genomic profiling of CD8 T-cells.
Conclusions: the discovery of metabolic and functional alterations of tumor infiltrating CD8 T-cells, provides the basis for further investigations aimed at identifying new therapeutic strategies to restore tumor-specific CD8 T cells response in HCC patients.

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OC-07

Dynamic evolution of circulating tumor DNA in patients with hepatocellular carcinoma across tumor stages and treatments

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Background: Circulating tumor DNA (ctDNA) is a promising non-invasive biomarker in cancer management. We aimed to assess the dynamic evolution of ctDNA in patients with hepatocellular carcinoma (HCC).
Methods: 832 plasmas collected in 173 patients with HCC and 56 patients with chronic liver diseases without HCC were studied. We evaluated the quantity of cell free DNA (cfDNA) and search for mutations in *TERT* promoter (*TERT*p.), *CTNNB1*, *TP53*, *PIK3CA* and *NFE2L2* by ultra-deep next generation sequencing and for *TERT*p. by digital droplet PCR.
Results: Among the 173 HCC patients (82% male, median age 63y), 73% had cirrhosis. Among the 776 plasmas of patients with HCC, 502 were collected in patients with an active HCC (aHCC), 158 24 hours after a locoregional treatment (H24) and 116 in patients with a past history but without active HCC at sampling (iHCC). Median cfDNA quantity was higher in aHCC than iHCC (0.27 vs 0.16 ng/µL, $p<0.001$). Within the 502 aHCC plasmas we identified mutations in 46% of them: *TP53* (29%), *TERT*p. (27%), *CTNNB1* (13%), *PIK3CA* (0.4%) and *NFE2L2* (0.2%). CfDNA mutation rate increased across tumor stages (16% BCLC 0,25% BCLC A, 42% BCLC B and 58% BCLC C; $p<0.001$). The presence of mutations, particularly in the *TERT*p. and *TP53*, was associated with OS-RFS/PFS, both when considering all plasma samples and in the analysis of various treatment subgroups. Regarding H24 plasmas an increase in cfDNA level (0.19 before vs 0.63 after, $p<0.001$) and in mutation rate (31% vs 44%, $p<0.001$) was observed. Finally, a total of 179 plasmas in 50 patients treated by atezolizumab/bevacizumab were analyzed. Baseline cfDNA mutations were observed in 49% of cases. Mutations in cfDNA observed at baseline disappeared in all patients with a response at 12 weeks. In contrast, persistence of mutations under treatment was significantly associated with progression ($p=0.005$).
Conclusion: Circulating tumor DNA offers dynamic information about tumor biology representing a non-invasive tool potentially useful to guide HCC clinical management.

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OC-08

Inhibition of the Extracellular Signal-Regulated Kinase ERK5 induces an increased expression of the Epidermal Growth Factor receptor and sensitizes hepatocarcinoma cells to gefitinib

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Background: Hepatocellular Carcinoma (HCC) is the most common form of liver cancer and a top cause of cancer death. Despite its relevance, molecular targeted therapy for the treatment of this malignancy are not available, and additional therapeutic targets need to be identified. The extracellular signal-regulated kinase 5(ERK5) is a member of the Mitogen-Activated Protein Kinases family highly expressed in hepatocytes, and its gene has been shown to be amplified in hepatocellular carcinoma (HCC). It has been previously reported that ERK5 regulates the development and growth of HCC.
Aim: We investigated the possible interplay between ERK5 and epidermal growth factor receptor (EGFR).
Methods: Two hepatocellular carcinoma cell lines, Huh7 and HepG2, were used. ERK5 knock down (KD) was performed using lentiviral vectors encoding shRNA for the ERK5 gene
Results: ERK5 silencing resulted in increased gene expression levels of the EGFR in Huh7 cells. In both Huh7 and HepG2 cells ERK5 knock down induced an increase in EGFR expression at the protein. Accordingly, downstream signals including AKT phosphorylation were upregulated. In addition, in ERK5-KD HCC cells, an inreased nuclear translocation of the EGFR, compared to control cells, was observed. Combined exposure to ERK5 (JWG-071; XMD-892) and EGFR (gefitinib) was more effective than single treatments in reducing cell viability in both cell lines.
Conclusion: We have elucidated an adaptive mechanism that results from the treatment of HCC cells with ERK5 inhibitors. Combined treatments targeting ERK5 and EGFR could provide an effective strategy to overcome this escape mechanism, and may contribute to the identification of additional therapeutic options for the treatment of HCC.

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OC-09

Liver transplantation for metastatic colorectal cancer after optimal systemic treatment (COLT trial): feasibility and safety data

V. Mazzaferro [1,2], M. Maspero [2], F. Pietrantonio [3], F. Di Benedetto [4], M. Vivarelli [5], G. Tisone [6], L. De Carlis [7], R. Romagnoli [8], S. Gruttadauria [9], M. Colledan [10], U. Baccarani [11], G. Torzilli [12], C. Sposito [1,2], on behalf of the COLT trial investigators

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Introduction: Liver transplant (LT) is a promising therapeutic option for patients with liver metastases from colorectal cancer (CRLM). The COLT trial is a prospective multicenter parallel

trial that compares the outcomes of LT with chemotherapy alone (Triplete trial) in patients with unresectable CRLM.
Aim: To assess the feasibility and the short term outcomes of the LT arm of the COLT trial.
Materials and Methods: Inclusion criteria were unresectable CRLM, CEA < 50 ng/mL, response to maximum 2 cycles of chemotherapy, previous radical resection of the primary colorectal tumor, T stage < T3, N stage < N2, RAS and BRAF wild type. After central multidisciplinary discussion, patients were prospectively enrolled in the COLT trial and subsequently enlisted for LT in their referral Center. LT was performed as per local standards as well as subsequent immunosuppressive regimen.
Results: From November 2018 and June 2023, 34 patients were enrolled at 10 participating Centers. From the time of formal enrolment, 5 patients (14.7%) were excluded from LT: 2 patients for intrahepatic progression and 2 for extrahepatic progression on waiting list, 1 for peritoneal diffusion at explorative laparotomy. Six patients are still on waiting list, and 23 underwent LT within a median waiting time of 46 days (IQR: 25-74). One patient needed re-LT for primary non-function, and subsequently died for multiorgan failure. The remaining 22 patients had a median post-LT hospital stay of 10.5 (IQR:8-20) days and experienced postoperative complication (DCC > II) in 18%. The readmission rate at 90 days was 9%. Within a median follow-up of 17 months, 10 patients experienced tumor recurrence and 14 patients are alive without evidence of disease
Conclusions: Liver transplant confirms is feasible and safe in the setting of CRLM. There is a significant rate of dropout despite short waiting time, underlying the need of strict selection criteria and ongoing treatments while on waitlist.

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OC- 10

Impact of ISO score on oncological outcomes and survival in liver transplant candidates with hepatocellular carcinoma

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Introduction: Liver transplantation (LT) is the most efficacious curative treatment for hepatocellular carcinoma (HCC) patients. The waiting list (WL) prioritization criteria determine patient outcomes. Since 2015, the Italian Score for Organ Allocation (ISO) has been used in Italy to prioritize patients on the WL, introducing a specific policy for HCC.
AIM: To assess the impact of ISO-score on WL dropout, HCC recurrence, and patient survival in LT candidates with HCC.
Materials and Methods: We retrospectively analyzed all consecutive LT candidates with HCC at our Hospital from 2013 to 2020, comparing the impact on different outcomes in 2 groups: those patients prioritized before (group A, 2013-2015) and after (group B, 2016-2020) ISO score implementation.
Results: During the study period, 378 LT candidates with HCC were included: 261 patients underwent LT, 42 patients (11%) died before LT, and 57 patients (15%) were removed for HCC progression, during a median follow-up of 49 months. The intention-to-treat (ITT)-survival rates at 1- and 3-years were significantly lower in group A compared to group B (85% and 71% vs 89% and 85%, respectively, p=0.009). HCC recurrence rate at 3 years was significantly higher in group A compared to group B (19.5% vs. 8%, respectively, p=0.008) with similar waiting time in the two groups (median: 6 months, IQR 2-14). The dropout rate was not significantly different in the two groups (30% group A vs 25% group B, p=ns). At the same time, the disease-free survival 3 years after LT was significantly lower in group A vs group B (80% vs 92%, respectively, p=0.009). Explant pathology and AFP levels at LT were comparable in the two groups.
Conclusion: Implementing ISO score improved ITT-survival of LT candidates with HCC in a single center cohort. This improvement seems mainly related to a lower post-LT HCC recurrence rate than to a significant change in dropout rates.

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OC- 11

Hepatitis D virus-associated hepatocellular carcinoma, characteristics and outcome: An Italian Liver Cancer (ITA.LI.CA) study

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Introduction: Chronic hepatitis D virus (HDV) infection is a severe and progressive disease, often leading to end-stage liver disease and hepatocellular carcinoma (HCC). The course of HDV disease is more severe and progressive than that of chronic hepatitis B virus (HBV) mono-infection. Comprehensive and contemporary data pertaining to large populations of patients with HDV infection and HCC are missing.
Aim: To compare characteristics, management and outcome of HCC patients with HDV/HBV vs HBV infection.
Materials and Methods: The Italian Liver Cancer (ITA.LI.CA) registry was analyzed to extract the characteristics of 107 patients with HCC and HDV/HBV positivity (HBV/HDV). Data were compared to patients with HCC and HBV infection alone (n=588). Clinical characteristics, modality of HCC diagnosis, tumor stage, treatment, and survival were analyzed and compared.
Results: Patients with HBV/HDV infection had worse liver function [MELD score: 11 vs 9, <0.0001; Child-Pugh-Turcotte score: 7 vs 5, <0.0001] compared to HBV patients. Diagnosis of HCC was more frequent during surveillance in patients with HBV/HDV (72.9% vs 52.4%, p=0.0002), and these patients had smaller median HCC size (2.2 vs 3.0 cm, p<0.0001). HBV/HDV patients with were more frequently staged as Milan-IN (47.3% vs 32.7%, p=0.005). Curative therapies (54.7%) were administered equally among the two patient groups, although liver transplantation was much more frequent in HBV/HDV patients (36.4% vs 9.5%), while the opposite was observed for surgical resection (8.4% vs 20.1%, <0.0001). Lastly, a trend towards longer survival in HBV/HDV patients was observed (50.4 vs 44.4 months, p = 0.106).
Conclusions: In HBV/HDV patients, HCC is diagnosed more frequently during surveillance, resulting in a less advanced cancer stage, despite a more deranged liver function than patients with HBV alone. Thus, HBV/HDV patients have the “double-benefit” of liver transplantation, with a positive influence on survival.

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OC- 12

Impact of laparoscopic liver resection for access to the waiting list of a single regional liver transplant center in southern Italy: entry and dropout flows' analysis

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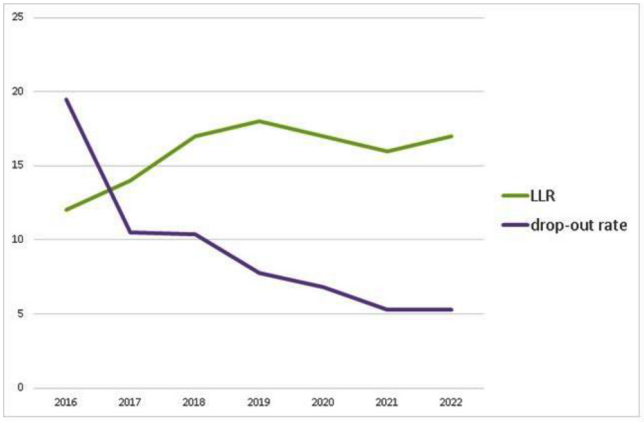
Introduction: Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and both liver resection (LR) and liver transplantation (LT) are considered potentially curative options.
Aims: We aimed to explore the impacting role of minimally invasive approach on entry and drop-out flows waiting list of a single regional center for LT in southern Italy with a very low deceased donation rate.
Materials and Method Results: We retrospectively analyzed our experience performed during a 7-year period between January 2016 and February 2023 in patients treated for end-stage-liver-disease (ESLD) and/or with surgically unresectable early and intermediate stage HCC. Linear correlation was used to evaluate dependence between the number of laparoscopic LR (LLR) treatments for HCC on the following flows of enrollments on the waiting list during the study period:-Enrollments present at the beginning of the year.-Enrollments that took place during the year, the Intention-To-Treat (ITT, present at the beginning of the year+admissions during the year).-Registrations present at the end of the year, and waiting for transplants for transplanted patients. There were 282 HCC patients treated with a first-line approach of LLR ($n = 116$) or open LRs ($n = 166$), with an incremental number of LLR per months. Considering the number of LLR and the rate of drop-out of ITT population and the number of enrolled patients per year, we observed a strong inverse linear correlation (rho=-0.82,p=0.023**). (Figure 1)**
Conclusions: Minimally invasive surgical therapies for HCC has a specific impact on drop-out percentage of overall ITT population, and waiting time for transplants for transplanted HCC patients.



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Thursday Posters: Monothematic Conference of the Italian Association for the Study of the Liver – A.I.S.F. (Padua, September 28th-29th 2023)

T-01

Tracing anti-cancer immunity in patients undergoing liver transplantation for HCC after downstaging with immunotherapy

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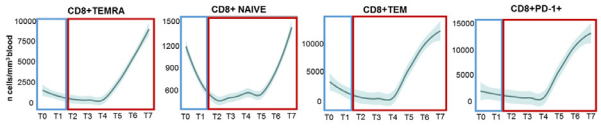
Introduction: Hepatocellular carcinoma (HCC) patients treated with combinatorial immunotherapy (CIT) including anti-angiogenics and immune checkpoint inhibitors (atezolizumab and bevacizumab) can achieve tumor downstaging and become eligible to liver transplantation (LT). While CIT may increase the risk of graft rejection, LT-associated immunosuppression may exert detrimental effects on anti-tumor immunity.
Aim: Patients with intermediate-advanced HCC downstaged to accepted LT criteria, underwent circulating anti-tumor cell immunomonitoring. Here we show the behaviour of memory and effector T cell subsets during treatment, during the washout phase, at early and late post-LT follow-up, with the aim of uncovering immune responses that regulate tumor immunosurveillance.
Material and Methods: Four HCC patients undergoing LT after CIT downstaging (median 120 days on treatment) followed by a 2 month (median 70.5 days) wash-out phase underwent peripheral blood sampling at different time points (end of treatment, during the wash-out phase and up to 5 months after LT). High resolution flow cytometry was performed on whole blood to quantify cells expressing lymphoid markers, with particular regards to CD8+ memory and effector T cell subsets.
Results: Flow cytometry data show that CIT induced a boost of naïve, effector memory (TEM) and terminally differentiated effector memory (TEMRA) T cells that decreases rapidly within the first 30 days of the wash-out phase with a further reduction at early post-LT time points (3-7 days) because of the enhanced immunosuppressive regimen. Nevertheless, within the first month and even more at a five-month post-LT follow-up, most of the effector and memory T cell subsets encompassing anti-tumor responses, regain levels even higher than on-treatment values.
Conclusions: The post-liver transplant regaining of anti-tumor immune cell levels, despite immunosuppression, at levels higher than on-CIT treatment, justifies further investigation in the field and suggests a possible role of organ transplantation as an endogenous adjuvant to aid in adaptive immune responses.

Figure 1. Trend of effector and memory T cell subsets at different time points



During the wash-out phase (blue box), circulating TEMRA, naive, TEM, PD1+CD8+ T cells and T reg decreased rapidly suggesting a quick loss of anti-tumor immune effects in the periphery at treatment discontinuation. After transplantation (red box), this kinetics of cell modulation was maintained and further exacerbated at early time points (T2-T4, i.e. 3, 7 and 14 days post-LT, respectively) as a possible consequence of the enhanced immunosuppressive therapy. At later post-LT time points (T5-T7, i.e. 30 days, 3 and 5 months after LT), most effector T cell subsets recovered or even exceeded the on-treatment levels, revealing a possible rebound and enhanced effect.

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T-02

Impact of digital hepatological network on the referrals of HCC patients: Preliminary results

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Introduction and aim: Hepatocellular carcinoma (HCC) is the most frequent liver tumor disease with an overall annual incidence of 2-4%. Its treatment must account for HCC features, liver function and comorbities, but often it's diagnosed in primary care units that lacks the facilities, the experties and the transplant assesment capability, to properly manage HCC. Referral to Hub centres assures best clinical outcomes, therefore according to AISF guidelines in dicember 2021 a network among primary and tertiary hepatological centres was set up in Veneto (REPAV).
Methods: We compared HCC referrals to our Hub centre for liver desease and patients trajectories in the first eight months of REPAV activity to the previous eight months.

Results: After REPAV set-up, 29.1% of all referrals were for new diagnosis of HCC (14/48). When compared to the prevoius 8 months, HCC referrals increased of 180% (5 vs. 14 patients) and both first hepathological visit and first locoregional treatment time decreased (8 days vs. 29 days, p=0.039, and 42 vs. 21 days, p=0.048 respectively). A significantly higher transplant activity was observed in post-network era: 10/14 vs. 1/5, +51.4%; among those, 3/10 were put on waiting list and 1/3 transplanted. As a result of the network referral acrivity 9 TACE/TAE on 5 patients were performed and 2 MW (+ 225% and +120%, respectively).
Discussion: The implementation of a digital hepatological network increased and improved HCC referrals, allowing a quicker and more effective accessibility to hub centre facilities, reducing appropriate treatment delivery wait-time. The network overcomes the inequity of distribution of facilities and makes tratment delivery more fair, as in AISF guidelines aims.
Conclusion: A matching network to AISF purposes of a reasonate clinical-assistential network model can significantly improve effectiveness in HCC treatment. The setup of digital referral networks should be encouraged everywhere to optimally manage HCC patients.

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T-03

Predictors of extrahepatic progression in patients with hepatocellular carcinoma receiving transarterial chemoembolization

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Introduction: Even though hepatocellular carcinoma (HCC) is mainly characterized by a locoregional progression, the prognosis of some patients is burdened by the development of metastases.
AIM: We aimed to identify risk factors of extrahepatic progression (EHP) in HCC patients undergoing transarterial chemoembolization (TACE).
Materials and Methods: From the ITA.LI.CA database, 890 patients treated with first-line TACE were retrieved. Incidence and predictors of EHP were compared between patients with tumor burden score (TBS) ≤4.2 and >4.2 (cut-off determined by ROC curve analysis). Validation (n=442) and derivation (n=448) cohorts were used to create a predictive model for EHP after TACE (EHPaT score).
Results: During a median follow-up of 28.6 months (IQR, 14.0-50.0), 76.2% of patients showed progression after treatment. In the TBS >4.2 group, a significantly higher proportion of patients demonstrated extrahepatic spread at first progression (11.2% vs. 4.3%; p<0.001) and overall during follow-up (35.4% vs. 19.3%; p<0.001). The most common sites of metastases were lymph nodes and lung. Patients with TBS ≤4.2 had a significantly longer progression free survival (11.6 vs. 9.0 months; p<0.001) and overall survival (54.1 vs. 31.1 months; p<0.001). Independent predictors of EHP were TBS, radiological response and alpha-fetoprotein (AFP) levels. The Cox Score for the prediction of EHP (incorporating TBS, AFP, radiological response and etiology) yielded an AUROC of 0.743 (95% CI 0.656-0.830) at first progression and an AUROC of 0.701 (95% CI 0.645-0.757) overall during the follow-up in the derivation cohort. Similar results were obtained in the validation cohort.
Conclusions: Although HCC is characterized by predominantly locoregional progression, identifying risk factors for metastases development is relevant for prognostic prediction and treatment allocation. Tumor burden, together with radiological response and AFP, has to be considered in the prediction of EHP after TACE. The EHPaT score revealed to be a useful tool in predicting of metastases development.

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T-04

Long term outcome of patients with hepatocellular carcinoma treated with transarterial radioembolization

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Introduction: Yttrium-90 trans-arterial radioembolization (TARE) is a treatment indicated across many stages of hepatocellular carcinoma (HCC).
Aims: to assess radiological response, safety and overall survival (OS) of TARE in a cohort of consecutive patients treated from 2012 to 2021 in a single centre, identifying also predictors of OS.
Materials and Methods: incuded patients had: at least one measurable HCC, absence of extra-hepatic metastases, Child-Pugh (CPS) score A/B, ECOG performance status 0/1. Only the first TARE was considered in those patients who received more than one procedure. The radiological response by mRECIST criteria was evaluated 3/4 months after TARE. Uni- and multivariable analysis were used to explore the features at time of TARE and at time of the radiological evaluation possibly related with OS.
Results: Among 142 patients (median age 67 years, 85% males, 92% cirrhotics, BCLC A 29%, B 35%, C 36%, CPS A 85%, median AFP 27 ng/mL) the median OS was 16,7 months with a 28% of 3-yrs cumulative survival rate. According to radiological evaluation: 31%, 39%, 9% and 21% of patients had complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), respectively. BCLC stage and AFP levels at time of TARE, delta AFP (difference between the value at TARE and at radiological evaluation), and radiological response were found to be statistically related to OS. AFP >21.4 ng/mL and BCLC C at TARE were significantly related with death [HR 1.48 (95%CI 1.00-2.18, p=0.048) and 1.71 (95%CI 1.05-2.79, p=0.031), respectively] although only radiological nonresponse had higher HR [3.34 (95%CI 2.03-5.79, p<0.0001)] for death at multivariate analysis. Adverse events, of which only one severe, occurred in 27% of patients.
Conclusions: TARE is an effective therapy for HCC patients across the different stages of the disease, and response to treatment remains the most important predictor of OS.

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T-05

Towards a rational approach to priority in liver transplant oncology

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Introduction: In the last two decades, the number of oncological "exceptions" equated or even exceeded the number of non-oncological indications to liver transplantation (LT) in many countries. However, the prioritization of oncological patients within common waiting lists (WL) is still an unmet need.
Aim: The aim of this study is to define and grade the factors that influence WL priority amongst all oncologic indications to liver transplant.
Material and Methods: A literature search was made to define which factors influence urgency, utility and transplant benefit principles in oncologic indications to LT. Those factors found to be shared by all oncological indications were then defined and qualitatively graded. For each grade, an evaluation of priority according to the three allocation principles was assessed, and priority for each grade (from 1 to 5) was given according to a blended principle.
Results: The following factors were identified: time on treatment before WL, response to therapy, availability of maintenance therapies while on WL, presence of alternative curative treatments, expected progression-free survival on WL, tumor burden with respect to transplant criteria, age and liver function. Each factor was graded according to a blended principle that takes into account urgency, utility and transplant benefit. A scale was then derived, summing a minimum of 15 and a maximum of 36 points, that allows for grading priority within oncologic indications to LT and with non-oncologic indications.
Conclusions: We propose a prioritization scheme of oncologic indications to LT according to the principle of transplant benefit blended with those of urgency and utility. Its feasibility should be discussed within the transplant community and prospectively tested.

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T-06

The expression of Aurora Kinase A and its potential role as a regulator of Programmed Death-Ligand 1 in hepatocellular carcinoma: Implications for immunotherapy and immune checkpoint regulation in hepatocarcinogenesis

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Introduction: Aurora Kinase A (AURKA) plays a key role in G2/M transition and is overexpressed in HCC. AURKA is involved in the activation of Programmed Death-Ligand 1 (PD-L1) in breast cancer, while no information is available in HCC.
Aim: We aim to analyze AURKA expression in hepatocarcinogenesis and explore its involvement in PD-L1 regulation.
Materials and methods: *AURKA* and *PD-L1* mRNA expression was evaluated by RT-qPCR in 54 HCC nodules (N) and paired distal (D) tissues, 17 chronic liver disease (CLD), and 12 healthy (H) liver tissues. *AURKA* and *PD-L1* mRNA was analyzed at 3, 6, 9, 12, and 15 months of age in 11 male wild-type (WT) and transgenic (TG) mice

with chronic HBV, developing HCC at 12 months. AURKA was inhibited with Alisertib or AK-01 or knocked down with siRNA in the HCC-derived JHH6 cell line. PD-L1 protein expression was determined by Western Blot.
Results: *AURKA* expression showed a gradual increase during the liver disease progression in human samples ($p<0.0001$). PD-L1 mRNA expression was similarly higher in HCC (N and D) compared to CLD and H tissues ($p<0.01$). We observed a positive correlation between *AURKA* and *PD-L1* in HCC (N and D) ($p<0.0001$). *AURKA* expression was increased in the nodules of TG mice compared to paired distal tissues (12m: $p=0.0074$; 15m: $p=0.0023$) and WT (both $p<0.0001$) mice. *PD-L1* median expression was stable in WT mice, while it changed according to time in TG mice, and N and D tissues have similar expressions, supporting the results in human tissues. *In vitro,* AK-01 or siR-AURKA treatment reduced PD-L1 protein expression (-38% and -40%; $p<0.001$).
Conclusions: AURKA increased from healthy livers to HCC and positively correlated with PD-L1 both in HCC and non-tumor tissues. AURKA inhibition decreased PD-L1, suggesting new strategies for cancer therapy, possibly in combination with immune checkpoint inhibitors.

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T-07

Liver transplantation for perihilar cholangiocarcinoma after neoadjuvant chemoradiation with brachytherapy versus stereotactic beam radiotherapy: Pretransplant toxicity and posttransplant outcomes

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Introduction: Liver transplantation (LT) is the only curative treatment for patients with unresectable perihilar cholangiocarcinoma (pCC). Before listing, patients undergo neoadjuvant chemoradiation (CT-RT) according to the Mayo Clinic protocol (radiosensitizing chemotherapy + brachytherapy). In 2020, at our center we substituted brachytherapy with stereotactic beam radiotherapy (SBRT).
Aim: To compare pretransplant toxicity and post-transplant outcomes of LT for pCC after brachytherapy versus SBRT.
Materials & Methods: We performed a retrospective analysis of patients who underwent LT for pCC at our center between 2011 and 2023. Pre-LT adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE).
Results: Eight patients underwent LT: 4 after brachytherapy and 4 after SBRT (4, 50% women, median age 52 in brachytherapy and 62.5 in SBRT). CT-RT-related adverse events $\geq$ grade 3 occurred in all after brachytherapy and in one patient after SBRT ($p=0.028$). Median post-LT length of stay was 16.5 days (range, 9 - 25) for brachytherapy and 12 (range, 10-12) for SBRT. Post-LT 90-day complications occurred in 2 (50%) patients after brachytherapy (Clavien Dindo grade II and IVa) and one after SBRT (grade IIIa). In the brachytherapy group, one patient had microfoci of pCC on the bile duct margin; all LT in the SBRT group were R0. One brachytherapy patient and one SBRT patient had positive lymph nodes at histology. Overall survival at 1-, 3- and 5- years for the entire cohort was 100%, 80% and 40. No differences in survival were observed between the two groups. After a median follow-up of 146 months for brachytherapy and 12 months for SBRT, recurrences were 3 for brachytherapy and one for SBRT. Two deaths occurred in the brachytherapy group, none in the SBRT group.
Conclusion: Preliminary data suggest that neoadjuvant SBRT is comparable to brachytherapy regarding post-LT outcomes, but with lower pre-LT toxicity.

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T-08

Early post-treatment changes in body composition parameters are associated with overall survival and need of transplantation in cirrhotic patients with HCC undergoing locoregional treatments

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Introduction: Radiofrequency thermo-ablation (RFTA) and transarterial chemoembolization (TACE) represent effective therapeutic strategies for cirrhotic patients with hepatocellular carcinoma (HCC). It has been proposed that body composition parameters, particularly skeletal muscle index (SMI), may predict outcomes in patients with HCC. However, only few studies investigated the role of visceral (VATI) and subcutaneous adipose tissue index (SATI) on patients' outcomes, and no data are available on the effect of their post-treatment changes in patients with HCC.
Aims: to investigate the impact of early post-treatment changes in body composition parameters on the overall-survival (OS) of cirrhotic patients with HCC and on the probability of being transplanted.
Methods: All cirrhotic patients with HCC treated for the first time with TACE or RFTA from 2012 to 2021 were retrospectively enrolled. Early changes of body composition (SMI, SATI and VATI) were extrapolated from abdominal CT scan performed before and one month after treatment and expressed as DELTA, following the formula: (one-month value- pre-procedure value)/ elapsed time. OS and probability of being transplanted were investigated with Fine-Gray multivariate competing risk analysis considering, respectively, LT and HCC progression outside the LT criteria (up-to-seven) as competitive risk events.
Results: 189 patients were enrolled, 132 undergoing TACE and 57 RFTA. In the multivariate analysis, across the entire population, the early decrease of VATI (DELTA-VATI negative) one month after treatment was associated to a increased risk of death (SHR=1.636; 95.0% CI=1.230-1.979; P=0.018), adjusting for age, MELDNa, Up-to-seven status and DELTA-SMI. In a sub-analysis, conducted considering only patients potentially eligible for LT, the early decrease in SMI (DELTA-SMI negative), but not in VATI was significantly associated to the need for LT (SHR=5.155; 95.0% CI=4.212-6.098; P<0.0001).
Conclusions: early body composition parameters post-treatment changes are useful in identifying cirrhotic patients with HCC at increased risk of death or need of LT.

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T-09

A machine learning enabled score based on large varices predicts 5- and 10-year hepatocellular carcinoma (HCC) development in a 12-year prospective cohort of patients with compensated advanced chronic liver disease

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Introduction: Most scores for HCC prediction assess 3- or 5-year HCC risk. We developed a 5- and 10-year HCC risk score from a prospective cohort of patients with compensated advanced chronic liver disease (cACLD) of any etiology followed up for 12 years.
Materials and Methods: 545 patients with cACLD,HCC-free, were prospectively enrolled using a convenience sampling from 2011 to 2022. Cox proportional models were used to assess the association between esophageal varices (EV), adjusted for all the relevant covariates, and HCC incidence. Random Survival Forest (RSF), a machine learning (ML) prediction model, was used as a sensitivity analysis to test prediction power of the same covariates, considering all the possible interactions and non-linear relationships with HCC incidence as the outcome.
Results: Median f-up was 5.9 years. 78 incident HCCs (14.3%) occurred. In the fully adjusted Cox models, large EV had 4-fold risk of developing HCC than no/small varices. Viral etiology, LSM, male sex, were also meaningfully associated with HCC risk. At RSF analysis, large EV had the best prediction power for HCC, followed by LSM,viral etiology, BMI, albumin. RSF prediction power was in line with the magnitude of association with Cox model, but ML further identified BMI & albumin as related and excluded sex. The score built with the RSF-selected variables (EV score) had excellent discrimination and calibration in assessing both 5- (AUROC 0.823) and 10-year (AUROC 0.792) HCC risk irrespective of etiology, with a significantly better overall performance at both time points than aMAP score, built on the same data (figure).
Conclusion: The machine learning approach, used to build this score, allowed us to identify large varices as the most important predictor for HCC risk (stressing the critical pathogenetic role of longstanding and severe portal hypertension in HCC development).

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T-10

Systematic review and meta-analysis of safety and efficacy of atezolizumab/ bevacizumab in Child-Pugh class B patients with hepatocellular carcinoma

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Introduction: The safety and efficacy of atezolizumab/bevacizumab in patients with hepatocellular carcinoma (HCC) and impaired liver function is not completely defined.
Aims: To address safety and efficacy of atezolizumab/bevacizumab in Child-Pugh class B patients reviewing the published data and analysing them by meta-analysis.
Materials and Methods: Safety and efficacy of atezolizumab/becavizumab in patients with HCC and Child-Pugh B cirrhosis were compared to the respective figures in Child-Pugh A patients. Overall, 8 retrospective, non-randomized, cohort studies were identified, including a total of 1,071 class A and 225 class B patients.
Results: Adverse events grade $\geq$3 were observed in 11.8% and 26.8% of class A and B patients, respectively (P=0.0001; Odds Ratio 0.43, confidence interval 0.21–0.90; P=0.02). Median overall survival was 16.8±2.0 and 6.8±3.2 months in class A and B patients, respectively (mean difference 9.06 months, 7.01–11.1, P<0.0001). Progression Free Survival at both 6- (4.90±2.08 vs 4.75±2.08 months; P=0.0004) and 12-month (8.83±2.32 vs 7.26±2.33 months; P=0.002) was lower in class B patients. A trend towards higher Objective Response Rate (ORR) (25.6% vs 18.1%, P=0.070) and a significantly greater probability of obtaining an ORR was observed in class A patients (Odds Ratio 1.79, 1.12–2.86, P=0.02). Disease Control Rate (DCR) was observed in 78.4% of class A and in 66.9% of class B patients (P=0.102), although class A had significantly higher probability of DCR than class B patients (Odds Ratio 1.73, 1.17–2.56; P=0.006).
Conclusions: Oncological efficacy of atezolizumab/bevacizumab is moderate in Child-Pugh class B patients, and the shorter survival figures associated with a greater likelihood of experiencing treatment-related adverse events observed in these patients compared to patients with less impaired liver function suggest caution and individualization of treatment. Comparative studies with best supportive care may provide further evidence supporting treatment in these patients.

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Friday Posters: Monothematic Conference of the Italian Association for the Study of the Liver – A.I.S.F. (Padua, September 28th-29th 2023)

F-01

Outcomes of Sorafenib and Metronomic Capecitabine in Child-Pugh B patients with advanced hepatocellular carcinoma in the era of immunotherapy: A real-life comparison with best supportive care

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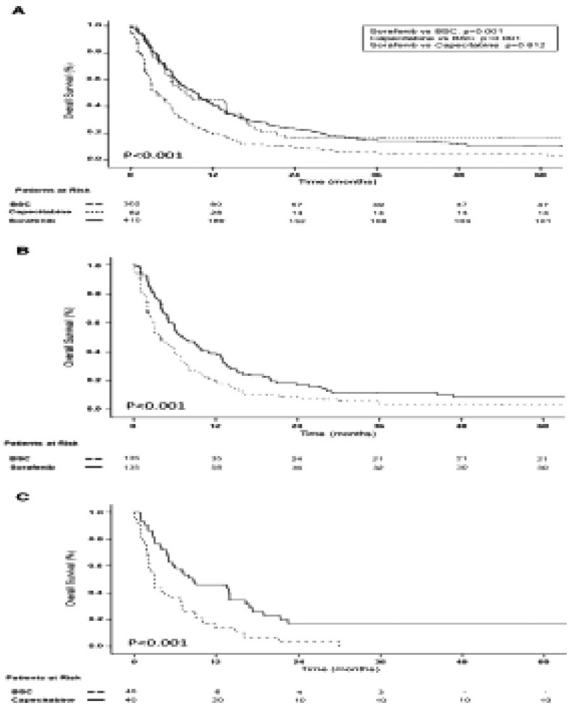
Background and Aims: The efficacy of systemic therapy for unresectable advanced hepatocellular carcinoma (aHCC) has not been proven in patients with Child-Pugh (C-P) B cirrhosis. Nevertheless, in real-world these patients are treated with tyrosine-kinase inhibitors (TKIs) since their toxicity is similar to that observed in C-P A patients and, off-label, with Metronomic Capecitabine (MC) in patients not amenable to TKIs. This study aimed to compare Sorafenib and MC's outcomes versus best supportive care (BSC) in C-P B-HCC patients.
Method: Between 2008 and 2020, among 774 consecutive C-P B patients with aHCC not amenable/responding to locoregional treatments extracted from the ITA.LI.CA database, 410 underwent Sorafenib, 62 MC, and 302 BSC. The propensity score matching method was used to correct the baseline unbalanced prognostic

factors, with a 1:1 allocation of Sorafenib vs BSC, MC vs BSC, and Sorafenib vs MC patients, and Kaplan-Meier method and Log-rank test were used to define overall survival (OS) and differences.
Results: in the unmatched population median OS (95% CI) was 9.9 (8.3-11.4) months in Sorafenib, 8.0 (0.4-15.7) months in MC, and 3.9 (3.1-4.8) months in BSC-treated patients (p<0.001 for Sorafenib vs BSC and for MC vs BSC; p=0.812 for Sorafenib vs MC).

In Sorafenib vs BSC-matched patients (135 couples) median OS was 7.3 (4.8-9.7) vs 3.9 (2.6-5.2) months (p<0.001). Independent predictors of survival were ECOG-Performance Status >1 [HR: 1.61 (1.22-2.13)], tumour size [HR: 1.04 (1.01-1.07)] macrovascular invasion [HR: 1.48 (1.12-1.96)], AFP >400 ng/mL [HR: 1.52 (1.14-2.04)], treatment-naïve [HR: 1.54 (1.15-2.07)] and Sorafenib [HR: 0.51 (0.38-0.68)].

In MC vs BSC matched patients (40 couples) median OS was 9.0 (0.2-17.8) vs 3.0 (2.2-3.8) months (p<0.001). In Sorafenib vs MC-matched patients (55 couples) the median OS did not differ (p=0.283).
Conclusion: C-P B patients with aHCC undergoing BSC have poor survival. Both Sorafenib and MC treatment improve their prognosis.



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F-02

Liposomal doxorubicin targeted with the Fab' of atezolizumab as a novel strategy against HCC

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Introduction: Although the continuous evolution in hepatocellular carcinoma (HCC) therapy, and the promising results obtained by new regimens based on the combination of different pharmacological approaches, HCC treatment remains challenging and overall survival is still poor.
Aim: This study aims at investigating the effect of a novel liposomal doxorubicin (DXR) formulation targeted with the Fab' of the immune checkpoint inhibitor atezolizumab in preclinical settings, i.e., 2D and 3D cellular models, and a syngeneic model of HCC.
Materials and Methods: We evaluated the activity of atezolizumab-targeted liposomal DXR (Stealth ImmunoLiposomes, SIL) and untargeted liposomal DXR (Stealth Liposomes, SL) in vitro on the human HepG2 and murine Hepa1-6 HCC cell lines, and on 3D HepG2 spheroids, either co-cultured or not with THP-1-derived macrophages. INF-g was used to induce PD-L1 overexpression in HepG2 spheroids. The HCC mouse model was obtained by injecting Hepa1-6 cells in C57BL/6J immunocompetent mice. SIL and SL were administered e.v. once a week for 4 weeks (n=4 per group), and tumor growth was assessed by an electronic caliper. A group of untreated mice was used as control.
Results: In 2D cultures, the IC50 values of SIL were significantly lower than those of SL (p<0.05), demonstrating to the efficacy of atezolizumab targeting. In spheroids, both SL and SIL decreased clonogenicity and invasiveness of HepG2 cells (p<0.0001) and reduced pro-tumoral CD-163-expressing macrophages (p<0.0001), but only SIL decreased the PD-L1 overexpression induced by INF-g(p<0.001), suggesting an immunomodulatory activity. In vivo, tumor growth was significantly reduced by both SL and SIL (p<0.05 vs. untreated controls). Moreover, the survival increase was more evident in SIL treated mice.
Conclusions: The combination of the already approved liposomal DXR targeted with Fab' of atezolizumab showed promising results in preclinical models of HCC, by exerting a cytotoxicity toward tumor cells and modulating the immune tumor microenvironment.

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F-03

An innovative patient-specific cholangiocarcinoma-on-chip as a platform for personalized therapy

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Background and Aims: Cholangiocarcinoma (CCA) is a deadly cancer with limited treatment options. The development of new therapies is urgently needed and Organ-On-Chip has emerged as a promising tool for studying diseases in a more reliable 3D environment. In this study, we evaluated the reliability of CCA-on-chip as a patient-specific platform by integrating the immune cells and assessing their migration based on patient characteristics.
Materials and Methods: Primary CCA cells were isolated from surgically resected patients at Humanitas Research Hospital. The CCA microenvironment was recapitulated in the device by co-culturing CCA cells and cancer-associated fibroblasts (CAFs) in the central channel, flanked by endothelial cells in one lateral channel.
Results: T-cells exhibited a high ability to migrate within the tumor niche, spreading throughout the central channel. Two culture conditions were compared to investigate the influence of crosstalk between CCA cells and CAFs on T-cell migration. In the monoculture, T-cells showed greater trafficking compared to the co-culture. Furthermore, T-cells formed aggregates surrounding tumor spheroids in the monoculture, while they appeared dispersed in the co-culture. Interestingly, the co-culture exhibited higher lev-

els of immunosuppressive molecules, suggesting that CAFs could contribute to an immunosuppressive microenvironment. Furthermore, in immunohistochemistry, CCA patient-derived cells were divided into two groups according to CD3+ cells: high-infiltrating (HOT) patients showed increased T-cell migration compared to low-infiltrating (COLD) patients. T-cells exhibited higher migration in the monoculture in HOT and COLD patients compared to their respective co-culture, further corroborating the role of CAFs in influencing immune cell recruitment and immunosuppression. Indeed, the expression of chemoattractant or immunosuppressive molecules, such as CXCL9, CXCL10, IL6 and IL10, varied between HOT and COLD patients and between culture conditions, suggesting their roles in immune cell recruitment and immunosuppression.
Conclusions: Our CCA-on-chip platform recapitulates the heterogeneity of the tumor microenvironment, demonstrating differences in T-cell trafficking and the expression of immunomodulatory molecules between high-infiltrating and low-infiltrating patients.

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F-04

Hepatocellular Carcinoma in HIV-Infected Patients: Clinical Presentation and Outcomes

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Introduction: Hepatocellular carcinoma (HCC) has become a non-AIDS complication with high impact on morbidity and mortality of people living with HIV (PLWH). We sought to compare outcomes in PLWH versus non-HIV-infected patients with cirrhosis treated for HCC in three hospitals in Lombardy.
Methods: A retrospective analysis of prospectively followed patients diagnosed with HCC from 01/06/2006 to 15/04/2022 was performed. The clinical characteristics, access to treatment and survival of HIV-patients with HCC were described. Propensity score (PS) to address potential confounders due to unbalanced distribution of baseline characteristics was used to estimate the effect of HIV status on overall survival (OS) of PLWH.
Results: We identified 65 HIV patients with cirrhosis and first HCC diagnosis (median age 54 [44-73] years, 92% males, 63% HCV-pos, 73% Child-Pugh A, median CD4+ count 405 [44-1701] cells/mm3, 12.5% with previous AIDS diagnosis, median nadir CD4+ count 164.5 [11-750] cells/mm3) and 464 non-HIV patients (median age 68 [33-89] years, 75% male, 77% Child-Pugh A). In PLWH, HCC was single nodule in 55%, median size was 2.5 cm (1.0-6.3), 57% "Milan-in". BCLC stages were 55% 0/A, 13% B, 21% C and 11% D. 31 (50%) patients received first-line curative treatment. In non-HIV patients, HCC were single nodule in 57%, median size was 2.6 cm (0.5-18), 66% "Milan in". BCLC stages were 68% 0/A, 17% B, 14% C and 1% D; 284 (61%) patients received a first line curative treatment. Median follow up was 47 (0.2-175) months for PLWH and 30 (0.5-199) for non-HIV patients. For PLWH the 5-year overall survival rate was 58% compared to 56% for non-HIV (log rank p =0.61).
Conclusion: HCC patients with HIV were more frequently male, younger, with multiple etiologies, poorer liver function and worse HCC stage at presentation. Nevertheless, PLWH have similar prognosis and access to HCC treatments as non-HIV patients.

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F-05

Clinical impact of relative dose intensity of cabozantinib during the first 8 weeks and of subsequent dose reductions in patients with unresectable hepatocellular carcinoma

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Background: Cabozantinib is a second-third line agent for sorafenib-experienced HCC patients. Therefore, it can be prescribed as part of a lenvatinib-sorafenib-cabozantinib or atezo/bev-sorafenib-cabozantinib sequence. Tolerability and safety are key concerns, especially for patients reaching a third-line treatment. However, dose reductions to manage adverse events (AEs) may induce fears of reduced efficacy.
Methods: Analysis of the MULTICABO cohort (96 patients from 15 Italian centers). We evaluated the relative dose-intensity of

cabozantinib during the first 8 weeks (8W-DI; expressed a ratio between the cumulative dose actually received and the maximum theoretical dose). The 8W-DI was correlated with disease control at the first imaging, progression-free survival (PFS), and overall survival (OS). To assess the effects of dose reductions after the first 8 weeks on the OS, multivariable time-dependent Cox regressions were carried out.
Results: Disease control rate was 63%. The median PFS and OS were and 5.2 and 11.3 months, respectively. The majority of patients (n=45) received the full 60mg daily dose during the first 8 weeks (median 8W-DI 100%, IQR 70-100%). A 90% 8W-DI (equating to a mean 54 mg/daily dose) was chosen for further analysis. A high 8W-DI did not correlate with worse radiological response (OR 1.72, 95% CI 0.72-4.15), PFS (HR 1.39, 95% CI 0.87-2.22), or OS (HR 1.06, 95% CI 0.61-1.83). Sixty-one (63.5%) and 19 (19.8%) patients permanently reduced cabozantinib to 40 and 20 mg/day to manage AEs. In the time-dependent analyses, reduction to 40 mg and 20 mg were associated with increased OS (HR 0.47, 95% CI 0.29-0.76; HR 0.41 95% CI 0.21-0.80, respectively].
Conclusions: Our results underline the importance of tailored dosing of cabozantinib. Dose adjustements to manage AEs should not automatically induce fears of reduced efficacy, as higher 8W-DI were not related to better outcomes while dose reductions to manage AEs were associated with increased OS.

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F-06

Targeting the AAA+ ATPase RuvBL1 reduces mTOR-driven NASH-HCC development in mice

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Background and Aims: RuvBL1 is a highly conserved AAA+ ATPases. It is deregulated in various human cancers and its expression correlates with a worse prognosis in HCC patients. We previously found that liver haploinsufficiency of RuvBL1 impairs the PI3K/Akt/mTOR pathway. We thus hypothesized that genetic targeting of RuvBL1 could reduce mTOR driven hepatocarcinogenesis.
Method: $Pten^{hep-/-}$ and $Ruvbl1^{hep+/-}$ mice were crossed to generate $Pten^{hep-/-}Ruvbl1^{hep+/-}$ mice. NASH was assessed by histology at 12 weeks of age. Metabolic and inflammatory markers were evaluated by qPCR and IHC. mTOR pathway was analysed by WB of liver lysates. PPARalpha activity was evaluated by luciferase reporter assay. RuvBL1 interactome was evaluated by MS proteomics of RuvBL1-IP. HCC development was assessed by macroscopic tumour count and by histology. AML-12 PTEN KO cells were generated by CRISPR-Cas9 genome editing.
Results: $Pten^{hep-/-}Ruvbl1^{hep+/-}$ developed significantly less steatosis, fibrosis, and inflammation compared to $Pten^{hep-/-}$ mice. The mTOR-driven lipogenic targets were similarly expressed in the two mice models. However, Ppara and its target CPT1 was increased in $Pten^{hep-/-}Ruvbl1^{hep+/-}$. Inhibition of RuvBL1 activity by CB-6644 increased PPARalpha transcriptional activity in AML-12 hepatocytic cell line. Analysis of RuvBL1-IP in AML-12 and Hepa1-6 cells revealed that RuvBL1 interacts with members of the lysosomal AMPK complex. Furthermore, p-AMPK and p-RAPTOR were increased in $Pten^{hep-/-}Ruvbl1^{hep+/-}$ compared to $Pten^{hep-/-}$mice. The spontaneous and insulin-induced accumulation of lipid droplets in PTEN KO AML-12 cells was completely abrogated by RuvBL1 inhibition with CB-6644. Finally, $Pten^{hep-/-}Ruvbl1^{hep+/-}$mice aged to 15 months showed better survival than $Pten^{hep-/-}$ which developed significantly more HCC and of higher grade. qPCR analysis showed a significant upregulation of key lipolytic genes, such as Cpt1a, Acadl, Acadvl and Ppara, in $Pten^{hep-/-}Ruvbl1^{hep+/-}$ at 15 months of age.
Conclusion: RuvBL1 targeting reduces mTOR hyperactivation hampering NASH-HCC progression in $Pten^{hep-/-}$ mice, likely promoting the switch from mTOR-driven lipogenesis to AMPK-induced fatty acid catabolism.

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F-07

Altered fatty acid metabolism rewires cholangiocarcinoma stemness features

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Introduction: Metabolic reprogramming of cancer stem cells (CSC) has been intensively investigated in recent years. Nevertheless, the role of lipids in the control of tumor-stemness in intrahepatic cholangiocarcinoma (iCCA) remains to be elucidated.
Aim: Our study aimed to explore the contribution of fatty acids (FA) in the regulation of stem-like features in iCCA.
Materials and Methods: iCCA cells grown as 3D spheres (SPH) were used to enrich for stem-like cells. Parental cells grown as monolayer (MON) were used as control. Triglyceride (TG) composition and de novo synthesis products were quantified by LC-MS/QTOF and used for desaturation index calculation. NOD/SCID mice were injected with iCCA-SPH cells and treated with the fatty acid synthase (FASN) inhibitor orlistat. Five-year overall survival was analyzed in 68 patients with iCCA, sub-grouped based on FASN expression.
Results: In vitro exposure of iCCA-MON cells to oleic or palmitoleic monounsaturated FA (MUFA) enhanced stem-like features at both functional (resistance to antineoplastic drugs, spherogenicity) and molecular level (expression of stemness associated genes). Metabolically, iCCA-SPH retained superior unsaturated TG-content in accordance with upregulation of several genes involved in FA metabolism compared to MON. In patients with iCCA, tissue expression levels of FASN, a key gene involved in FA synthesis, correlated with overall survival. In vitro FASN inhibition by orlistat or its depletion by siRNA decreased sphere-forming ability and expression of stem-like markers. In a murine xenograft model

obtained by injection of iCCA-SPH, orlistat significantly inhibited tumor growth and resulted in both downregulation of proliferative markers and upregulation of tumor suppressor genes.
Conclusion: These data provide evidence that an altered FA metabolism contributes to the maintenance of stem-like phenotype in iCCA. Moreover, FASN might be of relevance for CSC-promoting function in iCCA.

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F-08

MerTK-expressing macrophages promote the malignant features of cholangiocarcinoma cells

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Materials and Methods: 3D-tumor sphere (SPH) cultures enriched in CSCs were generated from intrahepatic CCA (iCCA) cell lines and CCA patient-derived organoids (PDOs) were employed. Circulating monocytes were differentiated into M2c MØs and recombinant Gas-6, a MerTK ligand, was used to activate MerTK. MERTK expression in human CCA tissues was analyzed at mRNA level in public database (n=78) and confirmed by immunohistochemistry (IMH) (n=74). Single-cell RNA sequencing of $CD45^+$ sorted cells was performed in paired non-tumoral and tumoral specimens from intrahepatic CCA patients (n=6).
Results: Conditioned media (CM) of iCCA SPH induced higher MerTK expression in macrophages. Conversely, soluble mediators released by Gas-6-stimulated M2c MØs, which express MerTK at high levels, increased sphere number and volume, expression of stem-like genes and drug-resistance in iCCA cells. Moreover, the exposure to CM of M2c MØs induced an increase in the cell viability of organoids CCA PDOs, which was further increased when macrophages were stimulated with Gas-6. These effects were reduced following treatment of macrophages with UNC2025, a small molecule inhibitor of MerTK. Transcriptomic analysis of laser-captured, micro-dissected epithelium and stroma from 23 iCCA patients showed that MerTK mRNA expression is significantly higher in intratumoral stroma. These data were further confirmed in a public iCCA dataset showing that high MerTK levels are associated with immunologically hot iCCA. Single-cell RNA sequencing of $CD45^+$ cells from non-tumoral and tumoral areas in iCCA patients showed that MerTK is predominantly expressed at the level of myeloid cells. Further reclustering showed MerTK expression in ID3 MØs, corresponding to Kupffer cells in tumor tissue. Notably, expression of MerTK correlated with greater tumor size, tumor grade, microvascular invasion, and risk of recurrence in iCCA patients.
Conclusion: These data indicate that a cross-talk between MerTK-expressing cells in the stroma and iCCA cells results in increased malignant features.

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F-09

How field practice complies with BCLC 2022 recommendations for hepatocellular carcinoma management

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Introduction: In 2022 the BCLC staging and treatment algorithm for hepatocellular carcinoma (HCC) management has been updated, granting for higher flexibility and customized management with a multidisciplinary decision process in the choice of the therapeutic strategy for HCC patients as compared to the 2018 version.
Aim: To evaluate the adherence to BCLC 2022 in daily clinical practice as compared to the BCLC 2018 and its impact on patients' survival.
Methods: 464 patients with de novo HCC in different stages, 317 BCLC 0-A, 77 BCLC B, 65 BCLC C and 5 BCLC D were discussed in a multidisciplinary team (MTD) meeting and were treated accordingly to the decision of the team. All patients were then followed until death or end of follow-up.
Results: Overall, adherence to BCLC 2022 recommendations were similar to BCLC 2018 (72.2% vs 70.3%, p=0.56), corresponding to an adherence per stage of 79% in BCLC 0/A, 63% BCLC B, 49% BCLC C and 60% BCLC D. Overall survival was higher in patients treated according to the BCLC 2022 algorithm ad compared to other treatment strategies (72.1% vs 43.7% at 5 years, p-value<0.001) in BCLC 0/A patients. In BCLC B an upward stage migration was associated to a higher overall survival (96% vs 66% at 2 years p=0.007), meanwhile no significant differences were observed in BCLC C (43.8% vs 33.3% p=0.28).
Conclusions: In our hands, the upgraded BCLC staging and treatment system did not modify the adherence to the algorithm, while we observed that the adherence to BCLC 2022 was associated with a better survival in early stages of HCC. In the intermediate stage the access to more radical treatments could improve survival compared to the BCLC 2022 proposals, while no differences were observed in the advanced stage.

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F-10

Prophylaxis of HBV-recurrence after liver transplantation in patients with HCC: Risk of HCC recurrence from a large, multicentre retrospective study from Italy

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Introduction: Discontinuation of hepatitis B (HBV) immune globulin (HBIG) after liver transplantation (LT) for HBV-related cirrhosis with and without hepatocellular carcinoma (HCC) represents a challenging option. The adherence to this option in real-life practice is unknown.
Aim: In a contemporary cohort of patients transplanted for HBV, with and without HCC, we aimed to; 1) assess the rate of HBV recurrence (HBV-R); 2) evaluate risk factors for HBV-R; 3) evaluate the association between HBV-R and HCC recurrence (HCC-R) and patient survival.
Materials and Methods: This is a multicentric, retrospective study designed by the "Permanent Transplant Commission" of the Italian Association for the Study of the Liver. All recipients who underwent LT for HBV cirrhosis were included. Exclusion criteria were: LT prior to January 1, 2010; age <18 years old; combined transplantation; HIV coinfection; duration of follow-up after LT <12 months. HBV-R was defined by positivity of HBV-DNA and/or HBsAg. Uni and multivariate linear regression analysis were used to identify predictors of HBV/HCC-R.
Results: 1115 patients were included. Indications for LT were HCC (51%), decompensated cirrhosis (41.2%), acute on chronic liver failure (ACLF) (3.4%), and acute liver failure (ALF) (4.2%). Life-long HBIG + nuclos(t)ide analogues (NA) was the most common used prophylaxis (94.4%). Overall rate of HBV-R was 2.2% (median time after LT: 7 months). Patients under life-long HBIG + NA had lower rates of HBV-R than those in whom HBIG were withdrawn and those who received NA alone (1.4% vs. 10.7% vs. 13.6%; respectively, $p<0.001$). HBV-R was associated with a lower survival after LT ($p=0.008$). In patients transplanted for HCC (n=535), the rate of HBV-R was 2.8% and of HCC-R was 10.3% (median time from LT: 17 months). Rate of HBV-R was higher in patients with vs. without HCC-R (14.6% vs. 1.2%; $p<0.001$). Multivariate analysis showed that HBV-R was the only parameter independently associated with HCC-R (HR: 20; CI95% 5-86; $p<0.001$). HCC-R was associated with a significantly reduced survival after LT (5-year survival 36% vs. 94%; $p<0.001$).
Conclusion: Life-long HBIG + NA is the most commonly used scheme for HBV-R prophylaxis after LT in Italy, leading to a low risk of HBV-recurrence. In LT recipients, HBV recurrence is associated with an increased risk of death. In patients transplanted for HCC, HBV-R is independently associated with HCC recurrence. Therefore, discontinuation of HBIG in these patients should be considered only in the setting of clinical trials

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