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Hepatoma Research

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Hepatoma Research Publications in 2022 (Being Updated)

Original Article

Changes in hepatic fibrosis and incidence of HCC following direct-acting antiviral treatment of F3 chronic hepatitis c patients: a prospective observational study

[Full-Text](#) [PDF](#)

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Shiha G, Soliman R, Hassan AA, Mikhail NNH. Changes in hepatic fibrosis and incidence of HCC following direct-acting antiviral treatment of F3 chronic hepatitis c patients: a prospective observational study. *Hepatoma Res* 2022;8:29. <http://dx.doi.org/10.20517/2394-5079.2022.13>

Abstract:

Aim: Studies of clinical outcomes in chronic hepatitis C (CHC) patients with pretreatment advanced liver fibrosis (F3) after sustained virologic response (SVR) are scarce, and most studies are of small cohorts and retrospective in nature. Our aim was to assess the clinical outcomes following direct acting antiviral (DAA) treatment among hepatitis C F3 patients after SVR.

Methods: This study included 1517 chronic hepatitis C patients with F3 fibrosis receiving DAAs in the out-patient clinics at the Egyptian Liver Research Institute and Hospital (ELRIAH). We included patients 18 years or older with HCV who received DAAs, have F3 by transient elastography, and have no history of hepatocellular carcinoma (HCC). Patients were followed up every six months after end of treatment using ultrasonography and AFP.

Results: Significant improvement of fibrosis occurred with decreases in LSM, FIB-4, APRI, and FIB-6. When changes in LSM were categorized depending on delta LSM, 873 patients (57.5%) showed regression, 454 (29.9%) were stable, and 190 patients (12.5%) showed progression of fibrosis. Overall, 33 cases developed HCC during follow-up with incidence rate of 0.915/100 py (95%CI: 0.64-1.27). Incidence was high with progression of liver fibrosis (6.17/100 py) compared to patients with stable fibrosis (1.09/100 py) and regression of liver fibrosis (0.75/100 py). There were no significant differences as regards fibrosis indicators at baseline (LSM, FIB-4, APRI, and FIB-6) between those who developed HCC and those who did not.

Conclusion: CHC Patients with F3 fibrosis showed a high rate of regression of fibrosis and decreased HCC incidence after achieving SVR following DAAs.

Keywords:

HCC, fibrosis changes, F3, DAAs

Review

Impact of direct-acting antivirals on the recurrence of hepatocellular carcinoma in chronic hepatitis C

[Full-Text](#) [PDF](#)

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Tagkou NM, Goossens N, Negro F. Impact of direct-acting antivirals on the recurrence of hepatocellular carcinoma in chronic hepatitis C. *Hepatoma Res* 2022;8:28.

<http://dx.doi.org/10.20517/2394-5079.2022.08>

Abstract:

Chronic hepatitis C virus (HCV) infection is estimated to affect 56.8 million individuals globally and is a major and independent risk factor for the development of hepatocellular carcinoma (HCC). After the introduction of safe and potent direct-acting antivirals (DAAs), capable of curing HCV infection also in patients with advanced liver disease at high risk of HCC, the beneficial effect on *a de novo* HCC development after viral clearance has been established. However, studies addressing the relationship between DAA-induced eradication and risk of HCC recurrence (i.e., reappearance of HCC treated before starting antivirals) have produced contradictory data, suggesting either an increase or a decrease of HCC recurrence rate, while some report no effect of these treatments. Thus, there seems to be an unclear benefit of viral clearance in patients with a history of HCC curative treatment, where the recurrence rate remains worryingly high. This short review aims to summarize current evidence on the impact of DAAs on HCC recurrence rates, the pathogenic mechanisms and characteristics of HCC recurrence after DAA treatment, the predictors of tumor recurrence, and the impact of DAAs on overall survival.

Keywords:

Hepatitis C virus, hepatocellular carcinoma, liver oncogenesis, direct-acting antivirals, tumor recurrence

Review

Understanding immune perspectives and options for the use of checkpoint immunotherapy in HCC post liver transplant

[Full-Text](#) [PDF](#)

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Anugwom CM, Leventhal TM, Debes JD. Understanding immune perspectives and options for the use of checkpoint immunotherapy in HCC post liver transplant. *Hepatoma Res* 2022;8:7.

<http://dx.doi.org/10.20517/2394-5079.2021.123>

Abstract:

Treatment modalities for hepatocellular carcinoma (HCC) vary from surgical techniques and interventional radiologic strategies to systemic therapy. For the latter, the use of immune checkpoint inhibitors (ICIs) has gained popularity due to successful trials showing increased survival. In patients who have undergone liver transplantation, recurrence of HCC poses a significant challenge. There is indeed considerable debate on the efficacy and safety of ICI use in liver transplant recipients due to competing immune interests in maintaining a healthy graft and combating the tumor. Recent reports and case series have highlighted a role for the type of immune therapy, timing of therapy, tissue expression of PD-1 and modulation of immunosuppression, in the understanding of the efficacy and risks of ICIs for HCC in liver transplant. In this article, we appraise the available literature on the usage of ICIs for HCC in liver transplant recipients and provide perspectives on immune concerns as well as potential recommendations to consider during the management of such complex cases.

Keywords:

Hepatocellular carcinoma, liver transplant, checkpoint inhibitors

Original Article

Experience of living donor liver transplantation for hepatocellular carcinoma in the University of Hong Kong Hospital

[Full-Text](#) [PDF](#)

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Mok JHM, Ma KW, Chok KSH. Experience of living donor liver transplantation for hepatocellular carcinoma in the University of Hong Kong Hospital. *Hepatoma Res* 2022;8:6.

<http://dx.doi.org/10.20517/2394-5079.2021.125>

Abstract:

Aim: To describe the current practise of living donor liver transplantation (LDLT) for hepatocellular carcinoma (HCC), including the patient selection criteria, surgical techniques, management of small-for-size syndrome, postoperative complications, and the results of our units, in the Liver Transplant Centre of Queen Mary Hospital, Hong Kong, one of the high-volume centres for LDLT in Asia.

Methods: Our centre practises careful selection for HCC patients using the University of California, San Francisco (UCSF) criteria, supplemented by alpha-fetoprotein level and the model for end-stage liver disease score. Slight flexibility is offered to enthusiastic donors and recipients in LDLT while balancing the risks and benefits. We pioneered in using the extended right lobe graft and the novel hepatic venoplasty technique, which lessen the risk of hyperperfusion and small-for-size syndrome with improved overall recipient survival. Data were collected prospectively and presented as the mean values and ranges, or the number of patients in proportion of total patient population.

Results: Of our patients, 74.9% met the UCSF criteria, and 64.5% met the Milan criteria. A 5-year overall and disease-free survival rate of 78.9% and 76.3% were achieved.

Conclusion: LDLT is an ideal treatment for HCC in Hong Kong with regard to the critical organ shortage and high demand for transplantation. The current surgical techniques and post-transplant surveillance contribute to the positive outcome.

Keywords:

Living donor liver transplantation, hepatocellular carcinoma, high volume centre, LDLT, HCC

Original Article

Association of human leukocyte antigen-DR-DQ-DP haplotypes with the risk of hepatitis B virus-related hepatocellular carcinoma

[Full-Text](#) [PDF](#)

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Chen Y, Lin J, Deng Y, Liu W, Li Z, Zhou X, Cai S, Pu R, Yin J, Tan X, Zhao J, Han X, Cao G. Association of human leukocyte antigen-DR-DQ-DP haplotypes with the risk of hepatitis B virus-related hepatocellular carcinoma. *Hepatoma Res* 2022;8:8.

<http://dx.doi.org/10.20517/2394-5079.2021.133>

Abstract:

Aim: Genetic polymorphisms of human leukocyte antigen (HLA) class II molecules are associated with chronic hepatitis B virus (HBV) infection. We aimed to investigate the impacts of HLA-II haplotypes on viral evolution and the risks of HBV-caused liver diseases.

Methods: *HLA-DR-DQ-DP* haplotypes were estimated in 1210 healthy controls, 296 HBV clearance subjects, 301 asymptomatic hepatitis B surface antigen carriers, 770 chronic hepatitis B patients, 443 HBV-related liver cirrhosis (LC) patients, and 1037 HBV-related hepatocellular carcinoma (HCC) patients. HBV mutations were determined by sequencing. The associations of *HLA-DR-DQ-DP* haplotypes with viral mutations and the risks of liver diseases were assessed by multivariate logistic regression.

Results: Compared to HBV-free subjects, the haplotypes CCAACG, CCGACG, TCAATA, and TCGATA were associated with decreased HCC risk, with an odds ratio (OR) [95% confidence interval (CI)] of 0.62 (0.40-0.95), 0.60 (0.39-0.92), 0.73 (0.54-0.98), and 0.58 (0.42-0.78), respectively. CCAACG, CCGACG, and TCAATA were significantly associated with decreased frequencies of the HCC-risk HBV mutations: preS1 deletion, APOBEC-signature HBV mutations in the core promoter and preS regions, A51C/T, G104C/T, and G146C/T. TCGATA and TTAACG were associated with increased LC risk, with an OR (95%CI) of 1.54 (1.03-2.30) and 2.23 (1.50-3.33), respectively. However, TCGATA and TTAACG were not consistently associated with the cirrhosis-risk HBV mutations.

Conclusion: CCAACG, CCGACG, and TCAATA are inversely associated with HCC risk, possibly because they are involved in creating an immune microenvironment attenuating the generation of HCC-risk HBV mutations. TCGATA and TTAACG might predispose the polarity of immunity towards Th17 isotype related to LC.

Keywords:

Chronic hepatitis B, HBV mutation, hepatocellular carcinoma, human leukocyte antigen class II, haplotype

Review

The pros and cons of biological effects of herbs and herb-derived compounds on liver tumorigenesis

[Full-Text](#) [PDF](#)

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Khalil M, Calasso M, Bonfrate L, Di Ciaula A, De Angelis M, Wang DQH, Portincasa P. The pros and cons of biological effects of herbs and herb-derived compounds on liver tumorigenesis.

Hepatoma Res 2022;8:23. <http://dx.doi.org/10.20517/2394-5079.2022.04>

Abstract:

Consumption of natural products such as herbs, spices, plant-derived compounds, and foods is on the rise globally. The use of these substances is widely recognized as an integral part of culture and tradition, with the philosophy being “no benefit is no harm”. The utility of medicinal plants and extracts is under scrutiny, and the scientific community needs to clarify many conceptual gaps.

Medicinal plants are rich in bioactive phytochemicals that produce chemopreventive effects at different levels, including cellular, animal, and clinical. The ultimate translational value is often missing, and some studies suggest that botanicals may contain toxic compounds that cause acute or chronic toxicity. In this regard, the liver is the center, and herbal products can show protective effects or induce hepatotoxicity, thereby promoting liver cancer. In this review article, we examine a range of herbal products implicated in hepatocarcinogenesis and extend the discussion to herbal products that may be potentially involved in the prevention and treatment of liver carcinoma.

Keywords:

Herbs, hepatocellular carcinoma, liver cancer, natural compounds

Editorial

Liver tumors in children

[Full-Text](#) [PDF](#)

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Aronson DC, Czauderna P. Liver tumors in children. *Hepatoma Res* 2022;8:22.

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Editorial

Minimally invasive surgery for HCC

[Full-Text](#) [PDF](#)

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Cassese G, Han HS. Minimally invasive surgery for HCC. *Hepatoma Res* 2022;8:24.

<http://dx.doi.org/10.20517/2394-5079.2022.15>

Original Article

The duration of the conventional chemoembolization for hepatocellular carcinoma: factors affecting the procedural time

[Full-Text](#) [PDF](#)

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Renzulli M, Gentilini M, Marasco G, Brandi N, Granito A, Lo Monaco S, Ierardi AM, De Cinque A, Tovoli F, Bartalena L, Spinelli D, Piscaglia F, Golfieri R. The duration of the conventional chemoembolization for hepatocellular carcinoma: factors affecting the procedural time. *Hepatoma Res* 2022;8:27. <http://dx.doi.org/10.20517/2394-5079.2022.18>

Abstract:

Aim: The present study evaluated the duration of chemoembolization in patients with hepatocellular carcinoma, analyzing possible factors affecting the procedural time.

Methods: In total, 175 patients who underwent chemoembolization have been prospectively enrolled. The procedural length was considered the time between the insertion and the removal of the angiographic sheath. The features related to the tumor burden and angiographic procedures, which could be related to the procedural time, were recorded.

Results: The chemoembolization time resulted in a mean of 58.1 min. The longer procedural time was associated with a number of nodules treated per patient ≥ 2 ($P < 0.001$), a number of segments

with nodules ≥ 2 ($P < 0.001$), the presence of more than 1 nodule in the same segment ($P < 0.001$), the location of the tumor in the left lobe ($P = 0.001$), the exclusion from the Milan criteria ($P < 0.001$), and a number of segments treated ≥ 2 ($P < 0.001$). Only the number of nodules treated per patient resulted significantly in multivariate analysis (OR 2.927, 95% CI: 2.015-4.251, $P < 0.001$).

Conclusion: The factors related to longer procedural time are the number of nodules treated ≥ 2 , the number of segments with nodules ≥ 2 , the involvement of the left lobe, the tumor burden outside the Milan criteria, and the number of segments treated ≥ 2 . All these characteristics, known in the pre-procedural phase, represent useful tools for a correct planning of the angiographic room's workflow during the pandemic era as well as in the future to reduce downtime and increase productivity.

Keywords:

Chemoembolization, hepatocellular carcinoma, procedural time, angiographic room, management

Review

A focused review on recent advances in diagnosis and management of fibrolamellar hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Aryan M, Forrister N, Panchani N, Vashi B, Chowdhury Z, Mejbil HA, Shoreibah M. A focused review on recent advances in diagnosis and management of fibrolamellar hepatocellular carcinoma. *Hepatoma Res* 2022;8:25. <http://dx.doi.org/10.20517/2394-5079.2022.07>

Abstract:

Fibrolamellar hepatocellular carcinoma (FHCC) is a rare primary malignancy of the liver for which data remain limited. This tumor is more often diagnosed in younger patient populations in the absence of underlying cirrhosis and hepatitis. These lesions can be diagnosed on computed tomography scan or magnetic resonance imaging with common findings including central calcifications, a central stellate scar, and radiating fibrotic bands. Laboratory markers have not proved useful for diagnosis; however, pathologic analysis can be implemented to aid in diagnosis with findings including ample granular eosinophilic cytoplasm, nuclei with open chromatin and prominent macronuclei, hyaline and pale bodies, and dense lamellar fibrosis that divides the cells into cords or trabeculae. FHCC demonstrates aggressive malignant potential with nodal spread. Treatment patterns have remained mainly surgical; however, systemic therapies have been implemented and are under further investigation with clinical trials. Locoregional therapies and radiation therapies have been trialed sparingly. In this focused review, we discuss the most up-to-date perspective on epidemiology, clinical presentation, diagnostic approach, differential diagnosis, treatment regimens, prognosis, and future directions of FHCC.

Keywords:

Fibrolamellar hepatocellular carcinoma, diagnosis, treatment, surgery, systemic, histology, review

Review

The role of minimally invasive surgery in the treatment of HCC

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Cassese G, Han HS, Lee B, Lee HW, Cho JY, Troisi RI. The role of minimally invasive surgery in the treatment of HCC. *Hepatoma Res* 2022;8:26. <http://dx.doi.org/10.20517/2394-5079.2022.14>

Abstract:

Liver surgery is the first-line treatment for hepatocellular carcinoma (HCC). Minimally invasive liver resection (MILS) has become an attractive option thanks to reduced intraoperative blood losses, shortened length of hospital stay, and similar oncological outcomes when compared to open liver resection. Nonetheless, the safety of MILS is still debated in challenging situations, such as in cirrhotic patients, difficult tumor locations, multiple or large tumors, and repeat resection. The aim of this review is to discuss current indications of laparoscopic liver resection for HCC treatment in the light of its outcomes, focusing on technical aspects of minimally invasive anatomic liver resection and state of the art of MILS in challenging situations.

Keywords:

Laparoscopic liver resection, hepatocellular carcinoma, minimally invasive liver surgery, anatomic liver resection

Original Article

Liver cancer understaging in liver transplantation in the current era of radiologic imaging and newer generation locoregional therapies

[Full-Text](#) [PDF](#)

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Lee HM, McClish D, John BV, Winks S, Clayton R, Albhaisi S, Allawy A, Patel S, Fields EC, Matherly S, Strife B, Bhati C, Sharma A, Sterling RK. Liver cancer understaging in liver transplantation in the current era of radiologic imaging and newer generation locoregional therapies. *Hepatoma Res* 2022;8:20. <http://dx.doi.org/10.20517/2394-5079.2021.139>

Abstract:

Background: Discordance in hepatocellular carcinoma (HCC) staging between pre-transplant imaging and explant pathology is associated with an increased risk of recurrence and death. Our aim was to evaluate variables that predicted concordance/discordance in the era of new generation locoregional therapies (LRT) and improved radiologic technology in diagnosis.

Methods: A single-center retrospective study was performed on patients who received a liver transplant for HCC between 2008-2019. Pre- and post-LT variables, including type of LRT, downstaging (DS), transplant time period, and radiologic response to LRT, were analyzed for concordance/discordance. Kaplan-Meier analysis was used to assess post-LT survival.

Results: Of 146 patients transplanted within Milan Criteria (MC), discordance rates (understaged) were 45%. Discordance was associated with ≥ 3 HCC lesions at diagnosis but not newer generation LRT (transarterial radioembolization/ stereotactic body radiation therapy), traditional LRT or combination. No differences in discordance were seen between transplant periods (2008-2013 vs. 2014-2019), but those within MC in the earlier period had higher concordance rates. A trend was observed between DS and discordance.

Conclusion: HCC stage discordance remains common and poorly predictable. Discordance was associated with three or more HCC lesions at the time of diagnosis. Patients within MC

transplanted between 2008-2013 was associated with concordance, while a trend was noted between DS and discordance. No other pre- or post- LT variables predicted discordance/concordance. Discordance was associated with decreased survival.

Keywords:

Hepatocellular carcinoma, understaging, liver transplant, radioembolization, stereotactic body radiation therapy (SBRT)

Original Article

Safety and efficacy of DEM-TACE performed with drug-eluting microspheres smaller than 300 μm in patients with HCC and TIPS

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Copy here to cite this article:

Lucatelli P, Zilahi De Gyurgyokai S, De Rubeis G, Argirò R, Ciaglia S, Rocco B, Ferri F, Parisse S, Forlino M, Cannavale A, Basilico F, Nardis PG, Corona M, Cantisani V, Catalano C. Safety and efficacy of DEM-TACE performed with drug-eluting microspheres smaller than 300 μm in patients with HCC and TIPS. *Hepatoma Res* 2022;8:18.

<http://dx.doi.org/10.20517/2394-5079.2021.143>

Abstract:

Aim: Safety and efficacy evidence of drug-eluting-microspheres trans-arterial chemoembolization (DEM-TACE) in patients with hepatocellular carcinoma (HCC) and trans-jugular intrahepatic portosystemic shunt (TIPS) is lacking. The aim of this retrospective study was to report the safety and efficacy of DEM-TACE procedures performed with microspheres smaller than 300 μm in patients with HCC and TIPS in a high-volume transplant center.

Methods: Embolization was standardized by initiating DEM-TACE with microspheres smaller than 100 μm , and if stasis was not achieved, adjunctive embolization with 100-300 or 200 μm microspheres was administered. With regards to efficacy, the oncological response was evaluated and categorized according to mRECIST criteria at 1, 3-6, 9-12, and 15-18 months. Reporting the safety profile, detailed laboratory analysis was performed before, at 36-48 h, and 30-60 days after the procedure. Adverse events (AEs) were recorded; post-embolic syndrome was defined as the onset of fever/nausea/pain after the procedure. Late onset hepatobiliary complications were evaluated by follow-up imaging with computed tomography or magnetic resonance (CT/MR).

Results: From December 2007 to November 2020, 17 HCC patients (25 HCC nodules) with patent TIPS underwent 20 DEM-TACE. Embolization was performed only with microspheres smaller than 100 μm in 3/20 DEM-TACE (15%); adjunctive embolization with 100-300 or 200 μm microspheres was required in 17/20 DEM-TACE (85%). Reported early AEs were post-embolic syndrome (9/20; 45%) all of grade 1-2, late AEs were asymptomatic acute liver bile duct injury (2/20; 10%), and in one case we observed hepatic abscess (1/20; 5%) resulting in death due to sepsis. With regards to efficacy, the oncological response was evaluated and categorized according to mRECIST criteria. Complete response (CR) at 1, 3-6, 9-12, and 15-18 months was 52%, 50%, 50%, and 50%, respectively. Objective response (CR + partial response) at 1, 3-6, 9-12, and 15-18 months was 95%, 71%, 70%, and 50%, respectively.

Conclusion: DEM-TACE with drug-eluting-microspheres smaller than 300 μ m can be performed in appropriately selected patients with TIPS.

Keywords:

HCC, TIPS, DEM-TACE, CT, MR

Original Article

Epidemiology of cholangiocarcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Turati F, Bertuccio P, Negri E, Vecchia CL. Epidemiology of cholangiocarcinoma. *Hepatoma Res* 2022;8:19. <http://dx.doi.org/10.20517/2394-5079.2021.130>

Abstract:

Aim: We aimed to analyze temporal trends in mortality from intrahepatic (ICC) and extrahepatic (ECC) cholangiocarcinoma in selected countries worldwide.

Methods: Official death certification data for ICC and ECC and populations estimates for 29 countries worldwide (17 from Europe, 8 from the Americas, and 4 from Australasia) and for Hong Kong Special Administrative Region of the People's Republic of China (SAR), from 1995 to 2018, were extracted from the World Health Organization and the Pan American Health Organization databases. Age-standardized mortality rates were computed. A joinpoint regression analysis was performed.

Results: In both sexes, ICC mortality rates increased in most countries considered, including the USA, the UK, and Australia; in some countries, including Italy and France, the increasing trends leveled off over the most recent years. In men, around 2016, the highest rates (1.7-2.3/100,000) were observed in Hong Kong SAR, Portugal, France, Spain, Australia, Austria, the UK, and Canada; Latin American countries and some eastern European countries had the lowest rates (0.2-0.8/100,000). A similar pattern was observed in women, but with lower rates (from 1.7/100,000 in Hong Kong SAR to 0.14/100,000 in Argentina). ECC mortality declined in most European and Australasian countries, but it tended to increase in Americas. In both sexes, rates were below 1/100,000 around 2016, with the only exceptions being Japan (2.6/100,000 men and 1.2/100,000 women) and Hungary (1.5/100,000 men and 1.1/100,000 women).

Conclusion: ICC mortality increased in most areas of the world, likely due to increased prevalence of risk factors and improved cancer recognition and classification. ECC mortality fell in most countries, largely due to the widespread use of cholecystectomy.

Keywords:

Cholangiocarcinoma, mortality, epidemiology, temporal trends, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma

Review

Role of locoregional therapies in the management of patients with hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Kung JWC, Ng KKC. Role of locoregional therapies in the management of patients with hepatocellular carcinoma. *Hepatoma Res* 2022;8:17.

<http://dx.doi.org/10.20517/2394-5079.2021.138>

Abstract:

Hepatocellular carcinoma (HCC) was the sixth most common cancer and the third cause of cancer-related deaths worldwide in 2020. Liver resection and transplantation remain the cornerstone for patients with early-stage disease and represent the only option for potential cure in HCC. However, fewer than 10% of patients are considered suitable for surgery at the time of diagnosis. Locoregional therapies, defined as minimally invasive image-guided liver tumour-directed procedures, are integral to in the management of HCC. This review discusses the role of locoregional therapies in HCC management in the emergence of immune and systemic treatments.

Keywords:

Locoregional therapy, hepatocellular carcinoma, ablation, transarterial embolization, radiation therapy

Review

Hepatocellular carcinoma on the background of nonalcoholic fatty liver disease: epidemiological update

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Desjonqueres E, Gigante E. Hepatocellular carcinoma on the background of nonalcoholic fatty liver disease: epidemiological update. *Hepatoma Res* 2022;7:16.

<http://dx.doi.org/10.20517/2394-5079.2021.136>

Abstract:

The epidemiological features of hepatocellular carcinoma have changed significantly in the last decades. While for a long-time viral hepatitis and alcohol consumption have been the leading risk factors, the current spread of obesity and type 2 diabetes has contributed to the emergence of non-alcoholic fatty liver disease (NAFLD) worldwide, which has become the leading chronic liver disease as well as one of the main etiologies of hepatocellular carcinoma (HCC), especially in western countries. In this review, we resume the latest data about the epidemiology of metabolic liver disease and HCC arising from NAFLD and discuss the main clinical and molecular features leading to the progression of liver disease and the development of HCC in NAFLD. The emerging concept of metabolic associated fatty liver disease and its association with the development of HCC are also introduced.

Keywords:

Hepatocellular carcinoma, non-alcoholic fatty liver disease, metabolic associated fatty liver disease

Editorial

Promise and pitfalls of new viral biomarkers for hepatocellular carcinoma risk prediction in patients with chronic hepatitis B

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Zhou K, Terrault N. Promise and pitfalls of new viral biomarkers for hepatocellular carcinoma risk prediction in patients with chronic hepatitis B. *Hepatoma Res* 2022;8:15.

<http://dx.doi.org/10.20517/2394-5079.2022.06>

Editorial

Hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) in sub-Saharan Africa: no room for complacency

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Matthews PC, Kramvis A. Hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) in sub-Saharan Africa: no room for complacency. *Hepatoma Res* 2022;8:14.

<http://dx.doi.org/10.20517/2394-5079.2022.11>

Perspective

Tenofovir disoproxil fumarate is not associated with a lower risk of hepatocellular carcinoma compared to entecavir in patients with chronic hepatitis B

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Lee HW, Kim SU. Tenofovir disoproxil fumarate is not associated with a lower risk of hepatocellular carcinoma compared to entecavir in patients with chronic hepatitis B. *Hepatoma Res* 2022;8:13.

<http://dx.doi.org/10.20517/2394-5079.2021.114>

Abstract:

A paper published several years ago suggested that tenofovir disoproxil fumarate (TDF) was superior to entecavir (ETV) for reducing the risk of hepatocellular carcinoma (HCC). Since then, many observational studies have been conducted comparing TDF and ETV. Many studies in Asia demonstrated similar HCC risks between ETV and TDF groups. Similarly, recent studies involving Caucasian and European did not observe any differences in HCC risk between these groups. In this article, we briefly review studies that compared the incidence rates of HCC between ETV and TDF and discuss potential reasons for the discrepant results.

Keywords:

Hepatitis B, entecavir, tenofovir, hepatocellular carcinoma

Case Report

Repeat laparoscopic anatomical liver resection in a hepatocellular carcinoma patient: a case report

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Igarashi K, Mishima K, Ozaki T, Wakabayashi G. Repeat laparoscopic anatomical liver resection in a hepatocellular carcinoma patient: a case report. *Hepatoma Res* 2022;8:21.

<http://dx.doi.org/10.20517/2394-5079.2022.02>

Abstract

Anatomical resection (AR) has been reported to achieve better long-term outcomes than non-anatomical resection for the treatment of hepatocellular carcinoma (HCC). The surgical feasibility and oncological significance of laparoscopic AR (LAR), especially “subsegment

resection”, “cone unit resection”, and repeat LAR for HCC, remain unproven. We present a 67-year-old patient with alcoholic liver cirrhosis and HCC who underwent full LAR three times, focusing on the technical aspects of the Glissonean approach. Repeating LAR for recurrent HCC could be a safe and feasible procedure. However, HCC recurred in the neighboring segment twice, even though pathological vascular invasion and marginal remnants were not confirmed. We should investigate the oncological significance and advancements in subsegmentectomy and cone unit resection, in the future.

Keywords:

Repeat laparoscopic anatomical liver resection, HCC, Glissonean approach, subsegmentectomy, cone unit resection

Original Article

Protective benefit of minimally invasive liver surgery for hepatocellular carcinoma prior to transplant

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Khouzam S, Pagano D, Barbara M, Di Marco V, Pietrosi G, Maringhini M, Canzonieri M, Calamia S, Gruttadauria S. Protective benefit of minimally invasive liver surgery for hepatocellular carcinoma prior to transplant. *Hepatoma Res* 2022;8:9. <http://dx.doi.org/10.20517/2394-5079.2021.147>

Abstract

Aim: The purpose of this study is to assess the benefit of laparoscopic liver resection (LLR) for hepatocellular carcinoma (HCC) given recurrence and future need for liver transplantation (LT).

Methods: Data on liver resections were gathered from the Istituto di Ricovero e Cura a Carattere Scientifico-Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione (IRCCS-ISMETT) from 2003-2021. A retrospective analysis of 1408 consecutive adult patients who had a liver resection was performed with categorization based on the underlying disease process. A sub-analysis studied the 291 patients who had an LLR with an intention to transplant approach after LLR.

Results: From 2012 to 2020, ISMETT’s mean annual LLR rate was 45%. Data suggests that a laparoscopic approach to iterative surgical treatment for HCC has demonstrated protective benefits. Compared to open surgery or LT, LLR is protective against the risk of de-listing, post-transplant patient death, tumor recurrence, adhesions, and bleeding in a cirrhotic patient. Kaplan Meier’s analysis showed no difference between post-LT survival curves for those with prior open abdominal surgery or LLR ($P = 0.658$).

Conclusion: Laparoscopic surgery has important protective advantages over laparotomy surgery for the surgical treatment of HCC, particularly since treatment is not always curative. LLR can be considered a bridge therapy for transplantation, ensuring less crowding of waiting lists, a desirable condition in areas of donor storage.

Keywords:

Laparoscopic, liver resection, hepatocellular carcinoma, minimally invasive liver surgery

Review

Overview of methodologies and statistical strategies in observational studies and meta-analyses on the risk of hepatocellular carcinoma in patients with chronic hepatitis B on entecavir or tenofovir therapy

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Copy here to cite this article:

Yip TCF, Wong VWS, Lai MSM, Hui VWK, Tse YK, Wong GLH. Overview of methodologies and statistical strategies in observational studies and meta-analyses on the risk of hepatocellular carcinoma in patients with chronic hepatitis B on entecavir or tenofovir therapy. *Hepatoma Res* 2022;8:12. <http://dx.doi.org/10.20517/2394-5079.2021.144>

Abstract

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are first-line antiviral therapies for patients with chronic hepatitis B (CHB) and reduce the risk of disease progression and liver-related complications, as well as improve survival by effectively suppressing viral replication. Nevertheless, since the first publication in 2019 on a lower risk of hepatocellular carcinoma (HCC) in Korean patients receiving TDF than those receiving ETV, the topic has remained a hot and unsettled debate. Multiple studies and meta-analyses have yielded conflicting results. As HCC takes time to develop, studies are mainly observational to benefit from a larger sample size and longer follow-up that provides a higher statistical power to compare the two treatments. However, TDF was available to CHB patients a few years later than ETV in most countries, thus leading to a difference in follow-up duration. Moreover, despite studying the same topic, the difference in data sources and available parameters, inclusion and exclusion criteria, and use of statistical methods complicated the interpretation and comparison of the findings and contributed to between-study heterogeneity in meta-analyses. This review describes some caveats in interpreting and comparing the results from these observational studies and meta-analyses. Future studies should explore better designed observational studies with high-quality data sources, and aggregation of patient data in meta-analysis to tackle between-study heterogeneity.

Keywords:

Bias, confounding, hepatitis B virus, hepatocellular carcinoma, liver cancer, nucleos(t)ide analogues, propensity score

Review

Tumor microenvironment and immunology of cholangiocarcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Cadamuro M, Fabris L, Zhang X, Strazzabosco M. Tumor microenvironment and immunology of cholangiocarcinoma. *Hepatoma Res* 2022;8:11. <http://dx.doi.org/10.20517/2394-5079.2021.140>

Abstract

Cholangiocarcinoma (CCA), an aggressive tumor originating from both intra- and extra-hepatic biliary cells, represents an unmet need in liver oncology, as treatment remains largely unsatisfactory. A typical feature of CCA is the presence of a complex tumor microenvironment (TME) composed of neoplastic cells, a rich inflammatory infiltrate, and cancer-associated fibroblasts and desmoplastic matrix that makes it extremely chemoresistant to traditional

chemotherapeutic drugs. In this review, we describe the cell populations within the TME, in particular those involved in the innate and adaptive immune response and how they interact with tumor cells and with matrix proteins. The TME is crucial for CCA to mount an immune escape response and is the battlefield where molecularly targeted therapies and immune therapy, particularly in combination, may actually prove their therapeutic value.

Keywords:

Tumor reactive stroma, extracellular matrix, immunotherapy, checkpoint inhibitor, immune escape

Review

Hepatocellular carcinoma surveillance: current practice and future directions

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Ahn JC, Lee YT, Agopian VG, Zhu Y, You S, Tseng HR, Yang JD. Hepatocellular carcinoma surveillance: current practice and future directions. *Hepatoma Res* 2022;8:10. <http://dx.doi.org/10.20517/2394-5079.2021.131>

Abstract

Hepatocellular carcinoma (HCC) is among the leading causes of cancer incidence and mortality worldwide. Surveillance of individuals with cirrhosis or other conditions that confer a high risk of HCC development is essential for early detection and improved overall survival. Biannual ultrasonography with or without alpha-fetoprotein is widely recommended as the standard method for HCC surveillance, but it has limited sensitivity in early disease and may be inadequate in certain individuals. This review article will provide a comprehensive overview of the current landscape of HCC surveillance, including the rationale and indications for HCC surveillance, standard methods for HCC surveillance, and their strengths/limitations. Alternative surveillance methods such as the role of cross-sectional imaging, emerging circulating biomarkers, as well as the problem of under-utilization of HCC surveillance and surveillance-related harms will also be discussed in this review.

Keywords:

Hepatocellular carcinoma, surveillance, cirrhosis, hepatitis B virus, alpha-fetoprotein, liquid biopsy, under-utilization

Review

Histopathology of hepatocellular carcinoma - when and what

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Gisder DM, Tannapfel A, Tischhoff I. Histopathology of hepatocellular carcinoma - when and what. *Hepatoma Res* 2022;8:4. <http://dx.doi.org/10.20517/2394-5079.2021.106>

Abstract

When do you need to take biopsies of the liver, and what information will you get is the topic of this review on hepatocellular carcinoma (HCC). If, clinically, the differential diagnosis of HCC after imaging is suggested, a biopsy has become obligatory as a diagnostic confirmation of HCC in the non-cirrhotic liver prior to definitive therapeutic interventions, as well as in a palliative therapy concept. In the case of hepatic lesions with an uncharacteristic contrast uptake, a biopsy should be performed immediately to confirm the diagnosis of HCC. After diagnosing HCC, a

treatment strategy is evaluated. Further, the biopsy, or in case of surgical treatment, the resected tissue, shows us the different subtypes of HCC, with the steatohepatitic subtype being the most common and the lymphocyte-rich subtype being the least common. Further, the histological grade of HCC is determined according to the grading system of the WHO or the Edmonson and Steiner System. Through biopsies, HCC can be differentiated from intrahepatic cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma or metastases of other malignant tumors, especially metastases of the gastrointestinal tract. In summary, biopsies are fundamental in the diagnosis of HCC.

Keywords:

Hepatocellular carcinoma, biopsies, histology

Review

Molecular mechanisms of liver carcinogenesis related to metabolic syndrome

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Campani C, Nault JC. Molecular mechanisms of liver carcinogenesis related to metabolic syndrome. *Hepatoma Res* 2022;8:3. <http://dx.doi.org/10.20517/2394-5079.2021.126>

Abstract

Global prevalence of non-alcoholic fatty liver disease (NAFLD) and of NAFLD-hepatocellular carcinoma (HCC) is estimated to grow in the next years. The burden of NAFLD and the evidence that NAFLD-HCC arises also in non-cirrhotic patients, explain the urgent need of a better characterization of the molecular mechanisms involved in NAFLD progression. Obesity and diabetes cause a chronic inflammatory state which favors changes in serum cytokines and adipokines, an increase in oxidative stress, DNA damage, and the activation of multiple signaling pathways involved in cell proliferation. Moreover, a role in promoting NAFLD-HCC has been highlighted in the innate and adaptive immune system, dysbiosis, and alterations in bile acids metabolism. Several dietary, genetic, or combined mouse models have been used to study nonalcoholic steatohepatitis (NASH) development and its progression to HCC, but models that fully recapitulate the biological and prognostic features of human NASH are still lacking. In humans, four single nucleotide polymorphisms (*PNPLA3*, *TM6SF2*, *GCKR*, and *MBOAT7*) have been linked to the development of both NASH and HCC in cirrhotic and non-cirrhotic patients, whereas *HSD17B13* polymorphism has a protective effect. In addition, higher rates of somatic *ACVR2A* mutations and a novel mutational signature have been recently discovered in NASH-HCC patients. The knowledge of the molecular pathogenesis of NAFLD-HCC will be helpful to personalized screening programs and allow for primary and secondary chemopreventive treatments for NAFLD patients who are more likely to progress to HCC.

Keywords:

Hepatocellular carcinoma, mouse model, genetic predisposition, cirrhosis, non-alcoholic fatty liver disease, immune system

Review

Advances in Y-90 radioembolization for the treatment of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Woerner AJ, Johnson GE. Advances in Y-90 radioembolization for the treatment of hepatocellular carcinoma. *Hepatoma Res* 2022;8:2. <http://dx.doi.org/10.20517/2394-5079.2021.122>

Abstract

Hepatocellular carcinoma remains a prominent cause of cancer-related mortality globally. Transarterial yttrium-90 radioembolization is a versatile therapy and plays an important role in the treatment of hepatocellular carcinoma. This review summarizes the establishment of radioembolization in the hepatocellular carcinoma treatment paradigm, treatment considerations across cancer stages, and recent advances in evidence.

Keywords:

Hepatocellular carcinoma, radioembolization, yttrium-90, dosimetry, radiation segmentectomy

Perspective

Robotic donor hepatectomy: a niche advancement or the way forward? A perspective from the world's largest center

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Sturdevant M, Zidan A, Broering D. Robotic donor hepatectomy: a niche advancement or the way forward? A perspective from the world's largest center. *Hepatoma Res* 2022;8:1. <http://dx.doi.org/10.20517/2394-5079.2021.111>

Abstract

The application of minimally invasive liver surgery (MILS) in the field of living donor hepatectomy has been exceedingly slow, and its impact is limited to a handful of centers worldwide. Widespread adoption has been primarily hampered by the technical limitations of laparoscopy, namely rigid instrumentation, suboptimal optics, and a seemingly steep learning curve. These deficiencies are magnified in the donor hepatectomy operation wherein the parenchyma and vasculature must be handled atraumatically to produce a pristine allograft fit for implantation. Donor safety concerns and medicolegal ramifications are also cited as impediments to MILS in donor surgery. In 2013, our institution embraced a purely laparoscopic approach to living donor left lateral sectionectomy, and it quickly became our default technique. However, with donor hemi-hepatectomy, we gravitated to the robotic surgical system as our preferred modality. Herein, we describe our experience with minimally invasive donor hepatectomy, which we now universally offer to all living donors. Our extensive familiarity with robotic donor hepatectomy will provide the reader with an instructive perspective on the attributes and merits of the robotic approach. With appropriate collaboration and proctorship, we believe that the robotic platform will actualize a more rapid and widespread adoption than that experienced with the purely laparoscopic technique.

Keywords:

Robotic liver surgery, robotic living donor hepatectomy, minimally invasive donor hepatectomy, live donor liver transplant

Review

Radiological imaging and non-surgical local treatments for cholangiocarcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Della Corte A, Di Gaeta E, Steidler S, De Cobelli F. Radiological imaging and non-surgical local treatments for cholangiocarcinoma. *Hepatoma Res* 2022;8:5. <http://dx.doi.org/10.20517/2394-5079.2021.103>

Abstract

Cholangiocarcinoma (CC) is a malignancy with a very heterogeneous spectrum of morphopathological and prognostic characteristics. Diagnostic imaging is fundamental for early detection, preoperative staging, and resectability assessment, as well as early recognition of prognostic factors. Radical surgical treatment is limited by disease stage and technical feasibility. Interventional radiology has acquired a critical function in addressing disease control and survival improvement through loco-regional therapies, specifically in the setting of intrahepatic CC. In this review, we will describe the current state of art of diagnostic imaging, focusing on intrahepatic CC and proximal extrahepatic CC, and delineate the available loco-regional therapies strategies for unresectable intrahepatic CC.

Keywords:

Cholangiocarcinoma, diagnostic imaging, loco-regional therapies, ablation, embolization

Hepatoma Research Publications in 2021

Review

Surgical management of cholangiocarcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Hewitt DB, Brown ZJ, Pawlik TM. Surgical management of cholangiocarcinoma. *Hepatoma Res* 2021;7:75. <http://dx.doi.org/10.20517/2394-5079.2021.83>

Abstract

Cholangiocarcinoma (CCA) is a rare but lethal tumor that arises from the intrahepatic, perihilar, or extrahepatic bile ducts. Complete surgical resection remains the only chance at long-term survival. Unfortunately, most cases of CCA are clinically silent until late in the disease process, and, combined with the lack of effective screening tests, many CCAs present as unresectable tumors. CCA workup typically includes a multiphasic chest, abdominal, and pelvic imaging, liver function tests, and tumor markers (CEA, CA 19-9). Tissue diagnosis is encouraged but not always

necessary. In certain situations, esophagogastroduodenoscopy, colonoscopy, and mammography are recommended. If resectable, intrahepatic CCAs and perihilar CCAs require a hepatectomy ranging from a wedge resection to an extended hepatectomy with reconstruction depending on the location and tumor size. In certain specialized centers, portal vein and hepatic artery reconstruction can be performed with good outcomes and acceptable morbidity. For resectable extrahepatic CCAs, a pancreaticoduodenectomy is recommended. Traditionally, few effective adjuvant options have existed for patients after surgery. However, recent randomized controlled trials support the use of either adjuvant chemotherapy or chemoradiation therapy after surgical resection. In select patients, intra-arterial therapy options such as transarterial chemoembolization, hepatic artery infusion therapy, or yttrium-90 radioembolization, as well as liver transplant, are effective treatment modalities. Improved surgical techniques, regionalization of care to high-volume centers, and appropriate application of preoperative optimization techniques have safely expanded the candidates of potentially resectable patients and improved patient outcomes.

Keywords:

Cholangiocarcinoma, hepatectomy, pancreaticoduodenectomy, bile duct, intrahepatic, extrahepatic, perihilar

Review

Treatment of advanced biliary tract cancers: from chemotherapy to targeted agents

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Casolino R, Braconi C. Treatment of advanced biliary tract cancers: from chemotherapy to targeted agents. *Hepatoma Res* 2021;7:76. <http://dx.doi.org/10.20517/2394-5079.2021.79>

Abstract

Biliary tract cancers (BTCs) are usually diagnosed at an advanced stage and have a dismal prognosis. The treatment of advanced disease is mainly based on systemic chemotherapy, which is demonstrated to improve survival in the first- and second-line setting. Following the results of phase III clinical trials, the combination of cisplatin and gemcitabine is the regimen of choice in the frontline, while 5-fluorouracil plus oxaliplatin is considered the standard after first-line progression in unselected patients. Recent advances in molecular biology have unravelled the molecular heterogeneity of BTCs and identified patient subgroups harbouring unique molecular aberrations such as isocitrate dehydrogenase (IDH) mutations and fibroblast growth factor receptor (FGFR) fusions that can be targeted by specific agents. This knowledge has opened the way to personalised medicine in BTCs. Molecules targeting IDH and FGFR are currently approved for the treatment of advanced, refractory, intrahepatic cholangiocarcinoma. Beyond targeted therapies, novel combinatorial approaches that target the immune microenvironment and the crosstalk between cancer and stroma are being explored based on strong preclinical rationale. This review discusses the current therapeutic opportunities for the management of patients with advanced BTCs and provides an overview of the promising new strategies on the horizon with a particular focus on ongoing clinical trials.

Keywords:

Biliary tract cancers, cholangiocarcinoma, precision medicine, targeted therapies, fibroblast growth factor receptor, isocitrate dehydrogenase, chemotherapy

Review

Hepatocellular carcinoma in transfusion dependent thalassemia patients: a review from a clinical perspective

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Papadopoulos N, Koskinas J. Hepatocellular carcinoma in transfusion dependent thalassemia patients: a review from a clinical perspective. *Hepatoma Res* 2021;7:77. <http://dx.doi.org/10.20517/2394-5079.2021.118>

Abstract

Survival in patients with transfusion-dependent thalassemias (TDT) has increased, and complications such as hepatocellular carcinoma (HCC) are emerging. Risk factors include viral infection, mainly hepatitis C virus (HCV), iron overload, the presence of cirrhosis, and immune dysregulation. Median survival after HCC occurrence has been estimated at 12 months, while data regarding the incidence of HCC in this population are minimal. Implementing effective hepatitis B virus (HBV)/HCV antiviral treatment and universal HBV vaccination programs is expected to decrease the risk for hepatocarcinogenesis substantially. Significant hemosiderosis and hepatic fibrosis are common in patients with TDT despite chelation therapy and have been correlated with HCC development. Thus, iron overload should be monitored with liver iron concentration and ferritin levels, and effective chelation therapy should be applied. In addition, all TDT patients, particularly those with cirrhosis, should be under surveillance every six months with abdominal ultrasound ± alpha-fetoprotein levels, as this combination seems to provide better sensitivity for early HCC detection.

Keywords:

Transfusion-dependent thalassemias, hepatocellular carcinoma, hepatitis B virus, hepatitis C virus, iron overload, liver iron concentration, liver stiffness measurement

Original Article

Clinicoradiographic predictors of progression of an intermediate hepatic lesion (LI-RADS 3) to hepatocellular carcinoma (LI-RADS 5)

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Hannan LM, Ojeda PI, Mieloszyk RJ, Harris WP, Park JO, Bhargava P. Clinicoradiographic predictors of progression of an intermediate hepatic lesion (LI-RADS 3) to hepatocellular carcinoma (LI-RADS 5). *Hepatoma Res* 2021;7:78. <http://dx.doi.org/10.20517/2394-5079.2021.110>

Abstract

Aim: We sought to identify predictors of progression of an indeterminate observation (LI-RADS 3) to hepatocellular carcinoma (LI-RADS 5).

Methods: Imaging reports with LI-RADS (LR) assignments were identified among patients at the University of Washington, 2013-2017. Patients with an LR3 lesion and follow-up scan within 1 year of LR3 lesion date were included ($n = 313$). Features of interest were abstracted from chart

review. Survival analyses employing interval censoring were performed, with variables potentially predictive of LR3 progression identified in univariate analyses. Backwards elimination ($P < 0.05$) was used to obtain the final multivariate model.

Results: 20.4% of LR3 lesions progressed to LR5; 73% remained LR3, 8% LR4. The cohort was predominantly male (61%), Caucasian (54%), older than 55 (63%). 47% had a history of hepatitis C virus (HCV), 33% with alcohol abuse, not mutually exclusive. Alpha-fetoprotein (AFP) at the time of LR3 scan was low if available (39% with AFP < 5 , 29% unknown). CT was the most common exam (56%). Men (HR = 2.0, $P = 0.02$), earlier scan year (HR = 0.47 per year, $P < 0.0001$), and older age (HR = 1.48, $P = 0.03$), appeared as predictors of LR progression in the final model. HCV and alcohol use were more common among men but did not appear to explain the difference in LR progression by sex.

Conclusion: Our analysis is an early exploration of characteristics that may predict the risk of progression of an LR3 observation to hepatocellular carcinoma. Future efforts may allow for risk stratification to identify high-risk indeterminate lesions that may benefit from earlier intervention or more frequent surveillance.

Keywords:

LI-RADS, hepatocellular carcinoma, liver imaging

Original Article

Nonalcoholic fatty liver disease-related hepatocellular carcinoma growth rates and their clinical outcomes

[Full-Text](#) [PDF](#)

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Benhammou JN, Lin J, Aby ES, Markovic D, Raman SS, Lu DS, Tong MJ. Nonalcoholic fatty liver disease-related hepatocellular carcinoma growth rates and their clinical outcomes. *Hepatoma Res* 2021;7:70 . <http://dx.doi.org/10.20517/2394-5079.2021.74>

Abstract

Aim: Nonalcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma (HCC) is projected to become the leading indication for liver transplantation. Previous studies indicate that tumor growth rates (TGR) may predict survival and were helpful in determining HCC surveillance intervals. Therefore, we aimed to determine its usefulness in predicting clinical outcomes and treatments.

Methods: We conducted a retrospective study of hepatitis B, C and NAFLD-HCC cases. TGR was measured using 2-consecutive pre-treatment contrast-enhanced imaging studies ≥ 25 days apart. A multivariate regression model was used to determine predictors of TGR. In addition, the Cox regression model was used to evaluate the relationship between TGR and overall survival.

Results: From 2000-2019, the study cohort comprised 38, 60, and 47 HBV, HCV, and NAFLD patients, respectively, with TGRs. NAFLD-HCC tumor size was inversely correlated to the extent of liver disease as measured by Child-Pugh score (7.2 cm in non-cirrhosis; 3.7 cm, 2.6 cm, and 2.1 cm in Child A, B, and C, respectively; $P < 0.001$). After adjusting for baseline characteristics, the

TGR per month was fastest in HBV (9.4%, 95%CI: 6.3%-12.5%) compared to HCV (4.9%, 95%CI: 2.8%-7%) and NAFLD patients (3.6%, 95%CI: 1.6%-6.7%). Predictors of TGR included elevated AFP, low albumin, and smaller tumor size. Fast TGR in viral etiologies had higher mortality [adj. hazard ratio (HR) = 2.6, 95%CI: 1.2-5.7, $P = 0.02$] than slow TGRs, independent of treatments. Fast TGR in NAFLD had a trend towards higher mortality (HR = 3.6, 95%CI: 0.95-13.3, $P = 0.059$).

Conclusion: NAFLD-HCC patients have more indolent growths than viral-related HCC TGRs. The addition of TGR as a biomarker may assist in stratifying treatment options.

Keywords:

Nonalcoholic fatty liver disease, hepatocellular carcinoma, tumor growth rates, biomarker

Review

The roles of autophagy and thyroid hormone in the pathogenesis and treatment of NAFLD

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Zhou J, Sinha RA, Yen PM. The roles of autophagy and thyroid hormone in the pathogenesis and treatment of NAFLD. *Hepatoma Res* 2021;7:72 . <http://dx.doi.org/10.20517/2394-5079.2021.82>

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disorder worldwide. It comprises simple steatosis and non-alcoholic steatohepatitis (NASH), which can further progress to cirrhosis and hepatocellular carcinoma. The pathogenesis of NAFLD involves genetic, environmental, and endocrine factors, and several molecular mechanisms have been identified. In this review, we discuss the recent findings on the role of autophagy, in particular lipophagy and mitophagy, in hepatic lipid oxidation. We discuss the pre-clinical and clinical evidence suggesting that impairment of autophagy exacerbates NAFLD progression and restoration of autophagy exerts beneficial effects on NAFLD. We discuss how thyroid hormone (TH) simultaneously regulates lipophagy, mitophagy, and mitochondrial biogenesis to increase β -oxidation of fatty acids and reduce steatosis in the liver. Lastly, we discuss the recent clinical progress in using TH or thyromimetics in treating NAFLD/NASH.

Keywords:

Autophagy, mitophagy, thyroid hormone, lipid oxidation, NAFLD

Review

Pathology and molecular pathology of cholangiocarcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Pedica F, Grassini G. Pathology and molecular pathology of cholangiocarcinoma. *Hepatoma Res* 2021;7:71 . <http://dx.doi.org/10.20517/2394-5079.2021.89>

Abstract

Biliary tract cancers are a wide group of heterogeneous neoplasms of the biliary tree, composed of intrahepatic cholangiocarcinoma perihilar bile duct cancer and distal bile duct cancer, according to location. The variability in location reflects the different morphologies and molecular alterations. In particular, intrahepatic peripheral mass forming cholangiocarcinoma is represented by the

“small duct type” cholangiocarcinoma, which is different from the “large duct type” cholangiocarcinoma that, although intrahepatic, behaves similar to extrahepatic bile duct cancers, perihilar and distal ones. Recently, molecular targetable alterations, mainly FGFR2 fusions and IDH1 mutations, have been described, mostly in the intrahepatic “small duct type” subgroup and have opened the way, together with rarer targetable alterations, for personalisation of therapy also in these aggressive neoplasms.

Keywords:

Biliary tract cancer, cholangiocarcinoma, molecular pathology, WHO classification, targetable alterations

Review

A review of current adjuvant and neoadjuvant systemic treatments for cholangiocarcinoma and gallbladder carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Allen MJ, Knox JJ. A review of current adjuvant and neoadjuvant systemic treatments for cholangiocarcinoma and gallbladder carcinoma. *Hepatoma Res* 2021;7:73 .
<http://dx.doi.org/10.20517/2394-5079.2021.98>

Abstract

Biliary tract cancers are a relatively rare heterogenous group of malignancies, including gallbladder cancer, intrahepatic, perihilar, and distal cholangiocarcinoma. Most patients are diagnosed with locally advanced or metastatic disease, and survival outcomes remain poor. This is also the case in the relatively few who undergo curative surgery. Efforts to improve patient survival outcomes have focussed on adjuvant and neoadjuvant chemotherapy and chemoradiotherapy. Adjuvant trials investigating the efficacy of systemic chemotherapy have primarily been negative to date, with challenges including compliance, recruitment rate, percentage of node-positive and R1 resections, and tumor heterogeneity observed. As reported in BILCAP, adjuvant capecitabine is currently considered the standard of care in many countries and guidelines, while chemoradiotherapy improves R1 outcomes as observed in the phase II trial SWOG S0809. Trials are ongoing to elicit the ideal combination of adjuvant treatment. Evidence for neoadjuvant chemotherapy continues to be based on retrospective analysis and a few phase II trials, with observed downstaging to surgery and improved R1 resection rates documented. This review documents the current evidence for systemic chemotherapy in adjuvant and neoadjuvant treatment of biliary tract cancers and highlights the ongoing clinical trials.

Keywords:

Cholangiocarcinoma, gallbladder carcinoma, neoadjuvant chemotherapy, adjuvant chemotherapy

Review

Use of tenofovir disoproxil fumarate is associated with a lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B

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Choi WM, Choi J. Use of tenofovir disoproxil fumarate is associated with a lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B. *Hepatoma Res*

2021;7:74 . <http://dx.doi.org/10.20517/2394-5079.2021.113>

Abstract

In patients with chronic hepatitis B (CHB), entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are equally recommended as first-line treatment by the international guidelines. These two drugs have shown similar short and intermediate clinical outcomes, including virologic, biochemical, and histologic responses. However, there is considerable controversy as to whether ETV and TDF differ in reducing the risk of hepatocellular carcinoma (HCC) in patients with CHB despite many observational studies and meta-analyses being published. In this review, we summarize recent evidence comparing the preventive effects of these two drugs against HCC from the perspective that TDF is associated with a lower risk of HCC compared with ETV in patients with CHB.

Keywords:

Hepatocellular carcinoma, hepatitis b virus, tenofovir disoproxil fumarate, entecavir, prevention

Review

C-kit expression in cancer cells or hematopoietic cells of the tumoral microenvironment: which is the basis for efficacy of TK inhibitors and immunotherapy in HCC?

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Ramadori G. C-kit expression in cancer cells or hematopoietic cells of the tumoral microenvironment: which is the basis for efficacy of TK inhibitors and immunotherapy in HCC?. *Hepatoma Res* 2021;7:69 <http://dx.doi.org/10.20517/2394-5079.2021.80>

Abstract

Twenty years ago, hematologists introduced imatinib, a tyrosine kinase inhibitor (TKI), as a long-term oral systemic therapy for patients suffering from chronic myeloid leukemia (CML) and gastrointestinal stroma tumor (GIST) (400 mg/day) who have normal liver function. The mechanism of action of imatinib was considered to be the specific interruption of the activation of the BCR-ABL kinase in CML patients and the autoactivated c-kit-tyrosine kinase in GIST patients. After the first successful long-term treatment of a c-kit-positive HCC patient with imatinib, 10 further patients with unresectable HCC were treated in Göttingen. After 18 months of therapy (200 mg/day), four patients remained alive. The first approval of a TKI, sorafenib, occurred in 2008 and several other TKIs have been approved since for patients with advanced HCC and CHILD A cirrhosis. As immune cells of the tumoral microenvironment (c-kit positive or PD-1- and PD-L1 positive) can contribute to cancer cell survival, it could be assumed that those cells are the real target not only of TKIs but also of recently approved monoclonal antibodies. In fact, histological studies of the first treated GIST in Finland and the first HCC patient treated in Göttingen showed similar results, acellular necrotic material. As most patients with HCC are older than those recruited for the studies published thus far and systemic therapy duration is quite short, imatinib at a lower dose (200 mg/day) may be an additional alternative in long-term treatment of HCC/cholangiocellular carcinoma in patients unfit for resection or transplantation and who are unresponsive or intolerant of other treatments.

Keywords:

Hepatocellular carcinoma, cholangiocellular carcinoma c-kit expression, tyrosine kinase inhibitors, imatinib, long-term systemic therapy, chronic disease, immune cells immune therapy,

microenvironment, checkpoint inhibitors

Review

Adjuvant treatment of hepatocellular carcinoma after resection

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Brown ZJ, Tsung A. Adjuvant treatment of hepatocellular carcinoma after resection. *Hepatoma Res* 2021;7:68 <http://dx.doi.org/10.20517/2394-5079.2021.85>

Abstract

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, and surgical resection offers an opportunity for cure in patients fortunate enough to have tumors amenable to resection. Unfortunately, recurrence rates are as high as 70% five years after resection, and recurrent disease proves to be a major obstacle to improving prognosis. Many adjuvant treatments have been utilized after resection in hopes of improving survival and have failed. This review outlines previous adjuvant strategies for patients with resected HCC and discusses potential steps forward to finding a successful adjuvant therapy.

Keywords:

Hepatocellular carcinoma, adjuvant therapy, immunotherapy

Perspective

Neoadjuvant and adjuvant systemic treatment for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Mathias-Machado MC, da Fonseca LG. Neoadjuvant and adjuvant systemic treatment for hepatocellular carcinoma. *Hepatoma Res* 2021;7:67 <http://dx.doi.org/10.20517/2394-5079.2021.84>

Abstract

Hepatocellular carcinoma (HCC) is a highly lethal malignancy, and few patients are candidates for curative-intended therapies. The mainstay of curative treatment in HCC is surgical resection, ablation, and transplantation. However, rates of recurrence are high, and there is no established approach to reduce the risk of recurrence and mortality. We discuss the available data and current landscape of (neo)adjuvant therapies aimed at decreasing recurrence risk and improving overall survival, including liver-directed therapies, tyrosine kinase inhibitors, and immunotherapy. Neoadjuvant strategies aimed at downstaging advanced HCC to enable local treatment and minimize the risk of recurrence using novel agents are also a topic of interest in current research. The improvements achieved in the advanced stages with immune-checkpoint inhibitors are priming ongoing trials that address potential future directions for both adjuvant and neoadjuvant strategies that may change the treatment paradigm of HCC in the near future.

Keywords:

Liver neoplasm, hepatocellular carcinoma, neoadjuvant treatment, adjuvant treatment, immunotherapy

Review

Anatomic vs. non-anatomic liver resection for hepatocellular carcinoma: standard of care or

unfilled promises?

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Copy here to cite this article:

Nevarez NM, Yopp AC. Anatomic vs. non-anatomic liver resection for hepatocellular carcinoma: standard of care or unfilled promises?. *Hepatoma Res* 2021;7:66
<http://dx.doi.org/10.20517/2394-5079.2021.66>

Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death not only in the United States but in the world. One of the curative treatment options for early-stage HCC is surgical resection, which can be divided into two approaches: anatomic and nonanatomic. The theoretical advantage of anatomic liver resection is excising the entire primary tumor along with adjacent liver parenchyma containing micrometastases that reside in the surrounding portal tributaries. However, the superiority of anatomic vs. nonanatomic liver resection in patients with HCC is controversial. While this is a feasible strategy for patients with preserved liver function, it may not be ideal for patients with cirrhosis, who rely on parenchymal-sparing or nonanatomic approaches to maximize their future liver remnant and prevent post-operative liver failure. This review identifies and critically analyzes the evidence for anatomic vs. nonanatomic liver resection for HCC.

Keywords:

Hepatocellular carcinoma, anatomic liver resection, parenchymal-sparing liver resection, liver surgery

Review

Epigenetics in hepatoblastoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Clavería-Cabello A, Arechederra M, Berasain C, Fernández-Barrena MG, Ávila MA. Epigenetics in hepatoblastoma. *Hepatoma Res* 2021;7:65 <http://dx.doi.org/10.20517/2394-5079.2021.77>

Abstract

Hepatoblastoma (HB) is the most frequent pediatric primary liver tumor. When the tumoral lesions can be resected, prognosis is generally favorable. However, there is a significant number of cases in which resection is not possible at diagnosis, and patients usually receive neo-adjuvant cisplatin-based chemotherapy prior to surgery. Unfortunately, some HBs develop resistance to initial chemotherapy or after recurrence, progressing to metastatic disease. Moreover, long-term side effects of chemotherapy remain a serious concern. Understanding the molecular bases of HB development and progression is thus essential for the identification of more efficacious therapies. HBs have a very low mutational burden, and the most frequent mutations occur in the *CTNNB1* gene (> 80% of cases) and to a lesser extent in *NFE2L2* (~10% of cases). These observations suggest that other pathogenic processes besides genetic mutations may play a role in HB tumorigenesis. Epigenetic mechanisms encompass a variety of molecular processes with a tremendous potential to regulate gene expression. They include the covalent modifications of DNA and histones, the activity of enzymatic chromatin remodelers, and the expression of non-coding RNAs. Dysregulation of epigenetic processes has clearly become a hallmark of cancer. Regarding HB, recent studies have explored its epigenetic landscape, the expression of specific

epigenetic effectors, and the tumorigenic consequences of epigenetic alterations. The reversible nature of most epigenetic modifications and the possibility to target non-coding RNAs may pave the way for new therapeutic avenues in HB. Here, we summarize and discuss the most relevant findings in this less explored aspect of HB.

Keywords:

Hepatoblastoma, molecular mechanisms, epigenetics, therapy

Review

Management of future liver remnant: strategies to promote hepatic hypertrophy

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Beppu T, Yamamura K, Okabe H, Miyata T, Kitano Y, Imai K, Hayashi H, Akahoshi S.

Management of future liver remnant: strategies to promote hepatic hypertrophy. *Hepatoma*

Res 2021;7:64 <http://dx.doi.org/10.20517/2394-5079.2021.49>

Abstract

The resectability of hepatocellular carcinoma (HCC) has been assessed based on the liver functional test, the liver volume of the future liver remnant (FLR), and, more recently, the functional liver volume of FLR. Liver volume is estimated via multi-detector computed tomography and three-dimensional image visualization technologies, and functional liver volume is investigated via ^{99m}Tc-galactosyl human serum albumin scintigraphy, ^{99m}Tc-mebrofenin hepatobiliary scintigraphy, and gadoxetic acid-enhanced magnetic resonance imaging. Several special techniques have been developed to promote FLR hypertrophy, thus allowing for safe hepatectomy. As an interventional technique, portal vein embolization (PVE) is essential, and, along with transarterial chemoembolization or hepatic vein embolization, this is beneficial in promoting a much larger FLR. Dual embolization is recommended for patients with very small FLR or with PVE failure. Radioembolization by Yttrium-90 microspheres (i.e., radiation lobectomy) can help in achieving FLR hypertrophy and has an anticancer effect on HCC. Transarterial chemoembolization on PVE has a similar anticancer effect. Surgical procedures, such as two-stage hepatectomy as well as associated liver partition and portal vein ligation for staged hepatectomy, are somewhat invasive. Therefore, they should be applied as a salvage procedure for patients with HCC who had inadequate response to the interventional approach. However, the best approach should be selected mainly based on the functional volume of FLR and the patients' condition; in addition, the resources of each facility should be considered.

Keywords:

Hepatectomy, future liver remnant, functional liver volume, portal vein embolization, transarterial chemoembolization, hepatic vein embolization, radiation lobectomy, two-stage hepatectomy, portal vein ligation for staged hepatectomy

Review

Hepatocellular carcinoma beyond Barcelona clinic liver cancer resection criteria: resecting the aggressive tumor

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Tsilimigras DI, Pawlik TM. Hepatocellular carcinoma beyond Barcelona clinic liver cancer

resection criteria: resecting the aggressive tumor. *Hepatoma Res* 2021;7:63
<http://dx.doi.org/10.20517/2394-5079.2021.51>

Abstract

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, surgical resection is recommended only for BCLC-0 and BCLC-A hepatocellular carcinoma (HCC). Nevertheless, several investigators have recently advocated for widening the resection criteria for HCC to select patients with BCLC-B and less frequently BCLC-C tumors. The available studies have reported a 5-year survival rate ranging from 25% to 63% following resection of select patients with multinodular HCC. The role of liver resection for macrovascular invasive HCC still remains unclear. The present review aimed to summarize the available evidence regarding the outcomes of patients who underwent resection for BCLC-B/C HCC as well as highlight the proposed criteria for resection beyond the current BCLC guidelines.

Keywords:

Resection, HCC, BCLC, surgery, criteria

Original Article

Racial difference of mutational signature in hepatocellular carcinoma

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Zhang BF, Guan XY. Racial difference of mutational signature in hepatocellular carcinoma. *Hepatoma Res* 2021;7:62. <http://dx.doi.org/10.20517/2394-5079.2021.81>

Abstract

Aim: Previous studies have demonstrated the racial disparities of new incidence and mortality rate of hepatocellular carcinoma (HCC) patients, but the racial differences in the tumor characteristics causing these disparities remain unclear.

Methods: We collected genomic mutation profile of 589 HCC patients, including Asian-Korea ($n = 231$), Asian-TCGA ($n = 156$), White-TCGA ($n = 176$), and Black-TCGA ($n = 16$). We applied a non-negative factorized matrix algorithm to decipher the mutational signatures of HCC patients, compared racial differences of mutational signature, performed molecular subtyping analysis of HCC patients based on their composition of mutational signatures, and evaluated their influence on clinical outcome.

Results: Asian patients showed a significantly higher level of SBS96F-aristolochic acid exposure signature related to the widespread usage of Chinese herbs in East Asia, and they also showed higher SBS96B-MMR at T > C mutations but lower SBS96D-MMR at C > T mutations than White patients, suggesting the heterogeneous mechanisms related to defective DNA mismatch repair across races. Asian-Korea patients showed a significantly higher SBS96C-tobacco chewing and aflatoxin exposure than the other three populations, indicating the higher levels of aflatoxin contamination in food and environment in this area. The SBS96G-Unclear signature was also observed to be significantly higher in Asian-Korea patients, and their dominated subgroup patients showed better prognosis for both disease-free and overall survival probability.

Conclusion: Our study found racial differences of mutational signatures to be associated with differences in diverse genetic backgrounds and environmental factors, which might help guide the personalized treatment of HCC patients.

Keywords:

Mutational signatures, aflatox in exposure, tobacco chewing, aristolochic acid exposure

Original Article

BOOST: a phase 3 trial of sorafenib vs. best supportive care in first line treatment of hepatocellular carcinoma in patients with deteriorated liver function

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Daniele G, Schettino C, Arenare L, Bilancia D, Farinati F, Federico P, Tamperi S, Crivellari G, Barni S, Tortora R, Izzo F, Frassoldati A, Cavanna L, Mucciari C, Bolondi L, Dinota A, Pelizzaro F, Piccirillo MC, Gargiulo P, Di Maio M, Gallo C, Perrone F, Daniele B. BOOST: a phase 3 trial of sorafenib vs. best supportive care in first line treatment of hepatocellular carcinoma in patients with deteriorated liver function. *Hepatoma Res* 2021;7:61.

<http://dx.doi.org/10.20517/2394-5079.2021.58>

Abstract

Aim: Only patients with good liver function {[Child-Pugh (CP)] A class} were eligible for trials testing sorafenib as first-line treatment of hepatocellular carcinoma (HCC); nevertheless, the drug was authorized without restrictions based on liver function. Therefore, we planned to test sorafenib efficacy and safety in patients with HCC and deteriorated liver function (CP-B).

Methods: This was an open-label, multicenter, randomized phase 3 trial. Patients with HCC, no previous systemic therapy, and CP-B score 7-9 were assigned 1:1 to best supportive care alone (control arm) or with standard dose sorafenib (experimental arm). Overall survival (OS) was the primary endpoint. To detect a 0.70 HR of death, with 80% power, and two-tailed α error 0.05, 234 events were required. The study closed prematurely because of slow accrual. Descriptive analyses are reported.

Results: From 2012 to 2017, 13 Italian centers randomized 35 patients. In total, 28 deaths were recorded, 12 without and 16 with sorafenib; median OS was 4.9 (95%CI: 1.2-5.6) and 3.5 months (95%CI: 1.3-5.3), respectively. At least one severe adverse event was reported in 2/15 (13.3%) without and 9/17 (52.9%) patients with sorafenib.

Conclusions: This trial failed its planned enrolment goal, showing the difficulty in performing clinical trials with drugs already registered with a label broader than what available evidence supports.

Keywords:

Hepatocellular carcinoma, Child-Pugh B class, sorafenib

Original Article

3D Organoid modelling of hepatoblast-like and mesenchymal-like hepatocellular carcinoma cell lines

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Oz O, Iscan E, Batur T, Ozturk M. 3D Organoid modelling of hepatoblast-like and mesenchymal-like hepatocellular carcinoma cell lines. *Hepatoma Res* 2021;7:60.

<http://dx.doi.org/10.20517/2394-5079.2021.43>

Abstract

Aim: We wished to establish 3D organoid-like hepatocellular carcinoma (HCC) models from HCC

cell lines.

Methods: Hep3B, Huh7, HepG2, SNU398, SNU449, and SNU475 cell lines were inoculated into Matrigel and grown up to 9 days in hepatocyte specific or standard RPMI media. Spheroid formation was followed by light microscopy. Matrigel scaffolds were immobilized and embedded in paraffin, and sections were subjected to H&E and immunohistochemical staining for different hepatobiliary biomarkers. Stained material was examined under light microscopy and micro photo were taken.

Results: Organoid-like structures were obtained successfully from all selected cell lines except mesenchymal-like SNU475 cells. Hep3B, Huh7, and HepG2 cell lines from hepatoblast-like sub-group formed compact 3D colonies and showed hepatocyte-like morphology and staining with different hepatocyte lineage markers as well as hepatobiliary progenitor markers. SNU398 and SNU449 cell lines from mesenchymal-like group formed irregular and loose 3D colonies that expressed vimentin homogeneously, but also several epithelial and hepatocyte lineage markers. The pattern of biomarker expression was unique for each cell line tested. Such features, not observed in tested monolayer cultures were confirmed with single-cell derived Hep3B cells.

Conclusion: We described experimental conditions to obtain organoid-like structures from five different HCC cell lines representing hepatoblast-like and mesenchymal-like subgroups. These models are useful as an alternative to monolayer cultures to study phenotypic features of HCC cells. Our detailed analysis of biomarker expression in five different organoid-like structures provide convincing evidence for highly specific phenotypic features of these cell lines although they share some common or subtype-restricted features also.

Keywords:

HCC cell-lines, differentiation, proliferation, paraffin blocking

Review

Neoplastic risk for liver and colon in primary sclerosing cholangitis

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Copy here to cite this article:

Lundberg Båve A, Bergquist A. Neoplastic risk for liver and colon in primary sclerosing cholangitis. *Hepatoma Res* 2021;7:58. <http://dx.doi.org/10.20517/2394-5079.2021.27>

Abstract

Primary sclerosing cholangitis (PSC) is a rare disease that may well be notified as a premalignant condition due to the increased cancer risk. The risk is highest for hepatobiliary cancer and increased by 28-398 times compared to the general population. When comorbidity with inflammatory bowel disease exists, the risk for colorectal cancer is increased 5-12 times and may even be higher after liver transplantation. The cancer risk estimates have decreased with time but vary according to study design. More recent population-based studies have approximated lower cancer risk than previous studies. Higher awareness and earlier detection of PSC together with increased surveillance over time may have influenced risk estimates. Surveillance for PSC patients is recommended for early tumor detection in both the liver and colon to enable curative treatment. The evidence for the efficacy of surveillance for early detection of hepatobiliary cancer is weak and an accepted common strategy worldwide is lacking. The high risk of hepatobiliary cancers has been confirmed repeatedly and future studies in PSC should focus on individualizing follow-up

strategies and treatment.

Keywords:

Epidemiology, inflammatory bowel disease, hepatobiliary cancer, cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma, pancreatic cancer, colorectal cancer

Review

A practical approach to pediatric liver transplantation in hepatoblastoma and hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Calinescu AM, Héry G, Goyet JV, Branchereau S. A practical approach to pediatric liver transplantation in hepatoblastoma and hepatocellular carcinoma. *Hepatoma Res* 2021;7:59. <http://dx.doi.org/10.20517/2394-5079.2021.26>

Abstract

Progressively, as chemotherapy has become more effective, more children with liver malignancies are amenable to liver transplantation, and indications have expanded from a limited range of cases (mostly hepatoblastoma) to a range of other unresectable malignant liver tumors; as a result, more children with hepatocellular carcinoma are also now proposed to transplantation, even and often outside the Milan criteria, for a cure. Recent series have highlighted that patient and graft survivals after transplantation for hepatoblastoma and hepatocellular carcinoma have improved in the last decade. Although consensus has not yet been reached about transplantation as a possible cure for other tumor types than hepatoblastoma and hepatocellular carcinoma, liver transplantation, generally speaking, has become an important pillar in the management of pediatric liver malignancies. Remaining limitations and inquiries relate to patient selection (in term of selection criteria considering the risk of recurrence), the role and usefulness of chemotherapy after transplantation, or the best immunosuppression strategy to both protect renal function and improve outcome. Although some prospective studies are on the way regarding these aspects, more studies are needed to explore this rapidly changing aspect of care.

Keywords:

Pediatric liver transplantation, hepatoblastoma, hepatocellular carcinoma

Commentary

From nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease: more than a single-letter change in an acronym

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Targher G. From nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease: more than a single-letter change in an acronym. *Hepatoma Res* 2021;7:47. <http://dx.doi.org/10.20517/2394-5079.2021.59>

Abstract

Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized public health problem worldwide. To emphasize the close pathophysiological links between NAFLD and overweight/obesity, insulin resistance, and related metabolic comorbidities, a consensus statement

of international experts in 2020 has recommended to replace the old acronym NAFLD with “metabolic dysfunction-associated fatty liver disease” (MAFLD). A set of “positive” criteria to diagnose MAFLD, regardless of daily alcohol consumption, has also been proposed. A “positive” definition of MAFLD and its special focus on the metabolic causative drivers of this liver disease is expected to reduce patient confusion on disease etiology, which can, in turn, improve the identification and awareness of this common and burdensome liver disease among both primary care physicians and specialists. However, the proposal to change the terminology from NAFLD to MAFLD is still under intense discussion, as also recently highlighted by a panel of international experts (led by Dr. Polyzos and Mantzoros), which is the main topic of discussion of this commentary. Further studies are required to better understand whether, and how, the proposed changes to the diagnostic criteria for MAFLD may impact on the risk of adverse hepatic and extra-hepatic clinical outcomes.

Keywords:

Nonalcoholic fatty liver disease, metabolic dysfunction-associated fatty liver disease

Review

Gut microbiota and their metabolites in the progression of non-alcoholic fatty liver disease

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Zhou J, Tripathi M, Sinha RA, Singh BK, Yen PM. Gut microbiota and their metabolites in the progression of non-alcoholic fatty liver disease. *Hepatoma Res* 2021;7:11. <http://dx.doi.org/10.20517/2394-5079.2020.134>

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disorder worldwide. It comprises a spectrum of conditions that range from steatosis to non-alcoholic steatohepatitis, with progression to cirrhosis and hepatocellular carcinoma. Currently, there is no FDA-approved pharmacological treatment for NAFLD. The pathogenesis of NAFLD involves genetic and environmental/host factors, including those that cause changes in intestinal microbiota and their metabolites. In this review, we discuss recent findings on the relationship(s) of microbiota signature with severity of NAFLD and the role(s) microbial metabolites in NAFLD progression. We discuss how metabolites may affect NAFLD progression and their potential to serve as biomarkers for NAFLD diagnosis or therapeutic targets for disease management.

Keywords:

Non-alcoholic fatty liver disease, gut microbiome, gut microbiota metabolites

Guideline

Guideline for stratified screening and surveillance in patients with high risk of primary liver cancer (2020)

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Ding H, Tu H, Qu C, Cao G, Zhuang H, Zhao P, Xu X, Yang Y, Lu S, Committee for Prevention and Control of Hepatobiliary and Pancreatic Diseases of Chinese Preventive Medicine Association , Committee of Hepatology of Chinese Research Hospital Association , Hepatology Society of Chinese Medical Association , Prevention of Infection Related Cancer (PIRCA)

Group, Specialist Committee of Cancer Prevention and Control of Chinese Preventive Medicine Association. Guideline for stratified screening and surveillance in patients with high risk of primary liver cancer (2020). *Hepatoma Res* 2021;7:17. <http://dx.doi.org/10.20517/2394-5079.2021.13>

Abstract

The age-adjusted incidence of primary liver cancer (PLC) has been declining in China. However, PLC cases in China account for 55% globally. The disease burden is still high and the five-year survival rate has not improved significantly in the past two decades. This guideline outlines PLC screening in populations with high risk, both in the hospital and community settings. Liver cirrhosis and chronic hepatitis B are the main causes of PLC in China. For better PLC surveillance and screening in clinical practices, it is recommended that these populations be stratified into four risk levels, namely, low-, intermediate-, high-, and extremely high-risk. A lifelong surveillance is suggested for those with risks of PLC. The intervals and tools for surveillance and screening are recommended based on risk levels. Abdominal ultrasonography combined with serum alpha-fetoprotein tests (routine surveillance) is recommended every 6 months for high risk PLC. Routine surveillance every 3 months and enhanced CT/MRI examinations every 6-12 months is recommended for those with extremely high risk of PLC. The surveillance interval can be extended to one year or longer for those with low or intermediate risk because the annual incidence of low risk PLC is relatively low. The cost-effectiveness of these recommendations remains to be evaluated.

Keywords:

Primary liver cancer, cirrhosis, chronic hepatitis B, screening, surveillance

Review

Hepatitis B-related hepatocellular carcinoma: surveillance strategy directed by immune-epidemiology

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Anugwom CM, Allaire M, Akbar SMF, Sultan A, Bollipo S, Mattos AZ, Debes JD. Hepatitis B-related hepatocellular carcinoma: surveillance strategy directed by immune-epidemiology. *Hepatoma Res* 2021;7:23. <http://dx.doi.org/10.20517/2394-5079.2021.06>

Abstract

Hepatitis B infection (HBV) is one of the most common causes of hepatocellular carcinoma (HCC) worldwide. The age of occurrence, prognosis and incidence vary dramatically depending on the region of the world. This geographic variation is largely dependent on the contrasting incidence of HBV, age of transmission of the virus, the timing of integration into the human genome, and different HBV genotypes, as well as environmental factors. It results in a wide difference in viral interaction with the immune system, genomic modulation and the consequent development of HCC in an individual. In this review, we describe many factors implicated in HCC development, provide insight regarding at-risk populations and explain societal recommendations for HCC surveillance in persons living with HBV in different continents of the world.

Keywords:

HCC, HBV, continent, risk

Review

HCC in metabolic syndrome: current concepts and future directions

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Zampaglione L, Ferrari J, Pedica F, Goossens N. HCC in metabolic syndrome: current concepts and future directions. *Hepatoma Res* 2021;7:55. <http://dx.doi.org/10.20517/2394-5079.2021.22>

Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths globally. In recent years, the metabolic syndrome epidemic is changing the etiological landscape of HCC, with metabolic liver disease comprising an exponentially increasing proportion of HCC cases. In this review, we discuss HCC in the context of metabolic syndrome, including its epidemiology, its unique clinical and pathological characteristics, and its multifactorial pathogenesis. We also discuss HCC prevention and management as relates to these patients.

Keywords:

Hepatocellular carcinoma, metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic associated fatty liver disease, PNPLA3, HSD17B13, sorafenib, steatosis

Perspective

Surgical perspective on treatment of pediatric undifferentiated sarcoma of the liver

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Calinescu AM, Wildhaber BE, Guérin F. Surgical perspective on treatment of pediatric undifferentiated sarcoma of the liver. *Hepatoma Res* 2021;7:54. <http://dx.doi.org/10.20517/2394-5079.2021.25>

Abstract

Surgical resection and chemotherapy are the mainstay of the treatment for undifferentiated embryonal sarcoma of the liver. Whether neoadjuvant chemotherapy should be systematically performed is a matter of debate; perioperative morbidity and mortality should be carefully weighed against chemotherapy-associated complications. In order to manage undifferentiated embryonal sarcoma of the liver and to allow for accurate outcome analysis, there is a clear need for standardization of disease extent as well as for a risk stratification system, including the PRETEXT grouping system, patient age, and tumor size.

Keywords:

Undifferentiated embryonal sarcoma of the liver, staging system, positive margins, neoadjuvant chemotherapy

Review

Immune checkpoint inhibitors in liver transplant recipients - a review of current literature

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Yin C, Baba T, He AR, Smith C. Immune checkpoint inhibitors in liver transplant recipients - a review of current literature. *Hepatoma Res* 2021;7:52. <http://dx.doi.org/10.20517/2394-5079.2021.11>

Abstract

Immuno-oncology, particularly with the development of immune checkpoint inhibitors (ICIs), has become a front-line category of cancer-directed therapy, including in the treatment of hepatocellular carcinoma (HCC). While liver transplant (LT) offers a potential cure for HCC, the use of ICIs is a topic of safety concern both pre- and post-transplant due to the risk of donor graft rejection. Nonetheless, some scenarios for which the therapeutic effects of ICI may be highly beneficial include the downstaging of unresectable HCC pre-transplant, or the treatment of recurrent HCC and secondary malignancies post-transplant. In this review, we explored the evidence surrounding the use of ICI in the peri-transplant setting, including safety and efficacy. In a comprehensive review of 28 cases of ICI use post-transplant, we found graft rejection in 9 of 28 cases (32%). Some factors that may increase the risk of rejection include younger age, less time between LT and ICI therapy, and PD-1/PD-L1 expression in the donor graft (particularly when using anti-PD-1/anti-PD-L1 ICIs). Despite these concerns, we relay a case of successful HCC downstaging with nivolumab and subsequent LT. We also describe several cases of response to ICIs post-LT (7 of 28 cases) among a group that is often heavily pre-treated. We conclude that ICIs are valuable options in the peri-transplant setting that have demonstrated promising efficacy based on case reports. Controlled clinical trials are needed to further investigate the conditions that may allow safe delivery of these therapies.

Keywords:

Immunotherapy, immune checkpoint inhibitors, CTLA-4 inhibitors, PD-1 inhibitors, hepatocellular carcinoma, liver transplant, allograft rejection

Review

Preoperative planning in paediatric liver tumour surgery - a literature review

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Kościszko D, Niemirycz-Makurat A, Anzelewicz S, Gołębiewski A, Czauderna P. Preoperative planning in paediatric liver tumour surgery - a literature review. *Hepatoma Res* 2021;7:51.

<http://dx.doi.org/10.20517/2394-5079.2021.17>

Abstract

Radiological assessment is evolving rapidly, including in paediatric liver tumour surgery. There are advancements in the fields of conventional radiology, 3D imaging and preoperative planning. This article presents the current research in paediatric liver imaging for liver tumour surgery and shows the results of a systematic search in computer-aided liver surgery in children. Sixteen original papers were found. We summarise the progress made and offer the directions in which further research could go. Computer-assisted surgery is a promising field for research and clinical application.

Keywords:

Paediatric liver tumours, computer-assisted surgery, preoperative planning, paediatric hepatectomy, segmentation

Review

Risk factors and management of post-liver transplant recurrence of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Rammohan A, Rela M. Risk factors and management of post-liver transplant recurrence of hepatocellular carcinoma. *Hepatoma Res* 2021;7:49.

<http://dx.doi.org/10.20517/2394-5079.2020.160>

Abstract

Hepatocellular carcinoma (HCC) is one of the most common indications for liver transplantation (LT). With expanding criteria and increasing number of transplants, post-transplant recurrence of HCC remains an important cause for concern and portends a poor survival in these patients. Traditionally, HCC recurrence post-LT has been notoriously difficult to manage and their outcomes dismal. A better understanding of the tumour biology and its interplay with the immune system, combined with newer oncological interventions has allowed for improved survivals in these patients. A useful classification of HCC recurrence is where it is divided into oligo-recurrence and disseminated recurrence. This system helps strategize their multi-disciplinary management algorithm and prognosticate outcomes. We provide an overview of the factors which may predict recurrence and summarise the current evidence on the management of post-LT HCC recurrence.

Keywords:

Hepatocellular carcinoma, post-liver transplantation, recurrence, management

Review

Bridging molecular basis, prognosis, and treatment of pediatric liver tumors

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Armengol C, Cairo S, Kappler R. Bridging molecular basis, prognosis, and treatment of pediatric liver tumors. *Hepatoma Res* 2021;7:50. <http://dx.doi.org/10.20517/2394-5079.2021.19>

Abstract

A deeper understanding of the genetic and molecular basis of hepatoblastoma (HB) has fueled the hope to help in identifying genes and signaling pathways that are amenable to therapeutic intervention. However, it has become clear that HB is a genetically very simple cancer and that rather alterations of the transcriptome or epigenome will facilitate a more stratified and rationalized approach to current therapeutics. In this review, we discuss recent findings on genomic, transcriptomic, and epigenomic data and their potential to serve as biomarkers and predictors of patient's outcome. We also describe the state of the art in HB experimental biology, the *in vitro* and *in vivo* HB models that are currently available, and their use to improve our understanding of this disease and identify new treatment options.

Keywords:

Hepatoblastoma, childhood liver cancer, genomics, transcriptomics, epigenomics, cell models, xenograft, therapeutic target

Letter to Editor

Non-invasive detection of liver cirrhosis - the “Essen algorithm”

[Full-Text](#) [PDF](#)

Copy here to cite this article: Buechter M, Gerken G. Non-invasive detection of liver cirrhosis - the “Essen algorithm”. *Hepatoma Res* 2021;7:57. <http://dx.doi.org/10.20517/2394-5079.2021.99>

Original Article

Prognostic factors associated with survival in patients with hepatocellular carcinoma undergoing transarterial chemoembolisation: an Australian multicenter cohort study

[Full-Text](#) [PDF](#)

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Mishra G, Dev A, Paul E, Kemp W, Majeed A, Lubel J, Bell S, Gow P, Nicoll A, Sood S, Thompson A, Ryan M, Roberts SK. Prognostic factors associated with survival in patients with hepatocellular carcinoma undergoing transarterial chemoembolisation: an Australian multicenter cohort study. *Hepatoma Res* 2021;7:56. <http://dx.doi.org/10.20517/2394-5079.2021.37>

Abstract

Aim: Transarterial chemoembolisation (TACE) is recommended therapy for intermediate-stage hepatocellular carcinoma (HCC). However, the wide variations in outcomes reflect significant heterogeneity of this patient group. We evaluated the prognostic factors associated with survival in a real-world setting to identify those at high risk of a poor outcome.

Methods: Patients with HCC who underwent initial TACE at six tertiary hospitals between 2009 to 2014 were included via an extensive search of hospital databases and electronic medical records. Overall survival (OS) was measured from the date of initial treatment to the date of death or last follow-up. Univariate and multivariate Cox regression analyses were used to assess the effects of baseline variables on post-TACE survival.

Results: The majority of the 431 eligible patients were Caucasian (80%), male (87%), with a mean age of 66 years and had alcohol-related cirrhosis (43%). Most were Child-Pugh A (69%) with BCLC stage A (59%) or B (35%) disease, with a median OS of 28 months. On multivariate analysis, pre-treatment ascites ($P = 0.001$) and larger HCC ($P < 0.001$) were associated with worse overall survival, while higher serum albumin ($P < 0.001$) and HBV ($P = 0.005$) were associated with improved survival.

Conclusion: Patients with advanced liver disease, including the presence of ascites and lower serum albumin, as well as those with greater tumour burden, have poorer outcomes following TACE treatment. Such findings provide a better understanding of the variation in survival after TACE and are helpful in facilitating selection and timely stage migration of patients undergoing this therapy.

Keywords:

Liver Cancer, tumour stage, unresectable hepatocellular carcinoma, transarterial chemoembolisation, treatment allocation, patient selection, treatment outcomes, prognostic factors, aetiology of liver disease, chronic hepatitis B infection, cirrhosis severity

Perspective

Effect of mesenchymal stem cell in liver regeneration and clinical applications

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Copy here to cite this article:

Lee SM, Lee SD, Wang SZ, Sarkar D, Lee HM, Khan A, Bhati C, Sharma A, Kumaran V, Bruno D, Cotterell A, Levy MF. Effect of mesenchymal stem cell in liver regeneration and clinical applications. *Hepatoma Res* 2021;7:53. <http://dx.doi.org/10.20517/2394-5079.2021.07>

Abstract

Liver disease accounts for approximately 2 million deaths per year worldwide with cirrhosis, viral hepatitis, and malignancy being the most common causes. Consequently, the regenerative capacity of the liver is a topic of extreme interest in the search for curative therapies to end-stage liver disease. Mesenchymal stem cells (MSCs) have emerged as a promising new therapy for hepatic regeneration. MSCs have multiple properties that make them an appropriate treatment option for liver disease including easy accessibility, targeted migration, immunomodulatory potential and antifibrotic/antioxidant effects. Additionally, MSCs have potential clinical applications in acellular therapy and tissue engineering. Liver regeneration with concurrent attenuation of liver injury makes MSCs a compelling therapeutic target in the setting of severe liver disease. This review outlines the mechanisms of MSC-driven liver regeneration and suggests potential clinical applications.

Keywords:

Mesenchymal stem cell, liver regeneration, end-stage liver disease

Editorial

Evaluation of liver function before and during therapy

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Copy here to cite this article:

Buechter M, Gerken G. Evaluation of liver function before and during therapy. *Hepatoma Res* 2021;7:48. <http://dx.doi.org/10.20517/2394-5079.2021.76>

Review

Autoimmune liver diseases, hepatocellular carcinoma, and recurrence of autoimmunity post-liver transplantation

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Wang S, Dong V, Montano-Loza AJ, Mason AL. Autoimmune liver diseases, hepatocellular carcinoma, and recurrence of autoimmunity post-liver transplantation. *Hepatoma Res* 2021;7:42. <http://dx.doi.org/10.20517/2394-5079.2020.163>

Abstract

Liver transplantation for the autoimmune liver diseases (AILD), which includes autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), is indicated in the setting of decompensated cirrhosis, liver failure, and hepatocellular carcinoma (HCC). The risk of HCC is thought to be low in AILD, though data on the risk factors and predictors of HCC are limited in this population. Recurrence of AILD can occur in over half of the patients, complicating the post-transplant course. The pathogenesis of recurrent AILD involves a complex interaction of genetic and environmental influences, as well as a variety of clinical risk factors. Graft and patient survival are negatively impacted by recurrent AILD and the optimal approach to the treatment of AILD recurrence is the subject of ongoing research. This review will address the current literature on the risk of HCC in AILD, as well as the development and management of recurrent AILD post-liver transplantation.

Keywords:

Recurrence, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hepatocellular carcinoma

Perspective

The future of pediatric hepatocellular carcinoma: a combination of surgical, locoregional, and targeted therapy

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Weeda VB, Murawski M. The future of pediatric hepatocellular carcinoma: a combination of surgical, locoregional, and targeted therapy. *Hepatoma Res* 2021;7:43. <http://dx.doi.org/10.20517/2394-5079.2021.10>

Abstract

Despite hepatocellular carcinoma’s position as the second most common pediatric liver tumor, it is a rare tumor in children warranting international collaboration to improve outcomes. Few cases diagnosed in earlier stages, when confined to the liver and responding to systemic treatment or with resectable metastases, may be cured by complete resection and/or orthotopic transplantation. Complete resection is the only chance for cure; therefore, all attempts should be made to make these options available. Despite modest progress in locoregional treatments, these serve in most cases as palliative treatment or as a bridge to definitive treatment at best. Currently used systemic treatments have response rates below 50%. Five-year survival in advanced stages is below 30%. The international Paediatric Hepatic International Tumour Trial trial is evaluating novel systemic treatments in pediatric hepatocellular carcinoma. Patients suffering from these tumors likely benefit from targeted treatment based on molecular aberrations corresponding with tumor subtype.

Keywords:

Hepatocellular carcinoma, pediatric, liver tumor, liver transplantation, surgery, locoregional treatment, targeted treatment

Review

Involvement of DNA methylation in tissue regeneration upon liver injury

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Cabral LKD, Tiribelli C, Sukowati CHC. Involvement of DNA methylation in tissue regeneration upon liver injury. *Hepatoma Res* 2021;7:41. <http://dx.doi.org/10.20517/2394-5079.2020.127>

Abstract

Following injury such as partial hepatectomy, the liver activates its response to proliferate and repopulate the lost liver mass. This process is associated with the re-expression of pro-regenerative genes that are controlled epigenetically. While epigenetic control of gene expression can be observed in many forms (DNA methylation, histone modification, chromatin remodeling, etc.), this review will focus on the role of regulators of DNA methylation in the concept of cell proliferation and progression and its relevance to tissue regeneration. Obligate proteins UHRF1 and DNMT1 are key players in the maintenance of methylation in the process of DNA replication. Both proteins have a well-established role in cell proliferation, progression and methylation maintenance, and are indicators of the stress response. Understanding how these regulatory mechanisms function is crucial in determining clinical applications on restoring lost tissue in the liver as a result of infection, toxins, or other liver pathologies.

Keywords:

Original Article

The prognostic evaluation of marginal positive resection in hepatoblastoma: Japanese experience

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Copy here to cite this article:

Hiyama E, Hishiki T, Watanabe K, Ida K, Yano M, Kurihara S, Kojima M, Saeki I, Inoue T, Tanaka Y. The prognostic evaluation of marginal positive resection in hepatoblastoma: Japanese experience. *Hepatoma Res* 2021;7:44. <http://dx.doi.org/10.20517/2394-5079.2021.21>

Abstract

Aim: In the Japanese study group for Pediatric Liver Tumor (JPLT) studies, the survival of patients with hepatoblastoma (HB) was improved by cisplatin/pirarubicin-based chemotherapy with combined surgical resection. We aimed to clarify whether marginal positive resection is correlated with the prognosis of HB patients from the JPLT-2 study (1999-2012).

Methods: Of the 361 JPLT-2 patients, we excluded 4 who died before surgery, 14 inoperable following preoperative chemotherapy, and 6 macroscopically positive resections and analyzed local recurrence and survival rates in 337 patients who underwent primary resection including liver transplantation.

Results: The five-year event-free survival (EFS) and overall survival (OS) rates were 76.0% and 87.7% in patients ($n = 312$) with complete resection of their primary tumors and 59.1% and 83.0% in those ($n = 25$) with microscopically margin-positive resection (microMPR), respectively. Among patients without distant metastasis, the five-year EFS and OS rates were 81.4% and 90.8% in those ($n = 263$) with complete resection vs. 62.5% and 90.9% in those ($n = 22$) with microMPR, respectively. The EFS, but not OS, was significantly lower ($P < 0.05$) in patients with microMPR vs. complete resection. The local recurrence rate was significantly different (chi-square = 12.11, $P < 0.01$) between the two groups.

Conclusion: In patients administered cisplatin/pirarubicin-based chemotherapy, the presence of microMPR influenced local recurrence but not outcome. Advance of liver surgery including LT correlated with improving of resection rates. The presence of microMPR influenced the local recurrence but not the outcome in the JPLT-2 study. The outcome of patients with microMPR might depend on the postoperative treatment and/or tumor biology rather than occurrence of recurrence.

Keywords:

Hepatoblastoma, surgical margin, outcome, surgery, chemotherapy, microscopic positive

Original Article

Defining the role of laparoscopic liver resection in elderly HCC patients - a propensity score matched analysis

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Copy here to cite this article:

Wong PWY, Ma KW, Cheung TT, She WH, Dai WC, Chan ACY, Chok KSH, Lo CM. Defining the role of laparoscopic liver resection in elderly HCC patients - a propensity score matched analysis. *Hepatoma Res* 2021;7:45. <http://dx.doi.org/10.20517/2394-5079.2021.28>

Abstract

Aim: To elucidate the role and efficacy of laparoscopic liver resection for elderly patients with hepatocellular carcinoma (HCC).

Methods: A retrospective comparative analysis was performed between laparoscopic and open liver resection operated from year 2008 to 2018. Consecutive HCC patients aged 65 or above at the time of operation were recruited. Patients with recurrent HCC and/or alternative pathology were excluded. Short-term and long-term outcomes between the laparoscopic and the open group were compared. Propensity score matching of patients in a ratio of 1:2 was conducted before comparison.

Results: A total of 911 patients underwent hepatectomy for primary HCC from 2008 to 2018. Among them, 320 elderly patients aged over 65 years old were eligible for analysis. Heterogeneities between laparoscopic and open groups were identified namely pre-operative albumin level, aspartate transaminase, and magnitude of hepatectomy (major vs. minor). After propensity score matching of 1:2, 46 patients in the laparoscopic group and 92 patients in the open group were included for comparison. The laparoscopic group had less blood loss (326 mL vs. 735 mL; $P < 0.001$), shorter operative time (223 min vs. 324 min; $P < 0.001$), and shorter hospital stay (6.3 days vs. 10.5 days; $P < 0.001$). No significant differences in postoperative morbidity and hospital mortality were noted between the groups. For oncological outcome, the laparoscopic group had a superior disease-free survival (59.7% vs. 44.5%; $P = 0.041$), and a trend towards better overall survival compared with the open group. (78.4% vs. 64.8%; $P = 0.110$).

Conclusion: Laparoscopic liver resection is a safe approach for elderly patients with HCC with benefits from faster recovery and better oncological outcomes.

Keywords:

Hepatectomy, open hepatectomy, laparoscopic liver resection, open liver resection, elderly, hepatocellular carcinoma, propensity score matching analysis

Review

Role of CD4⁺ T-cells in the pathology of non-alcoholic fatty liver disease and related diseases

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Seike T, Mizukoshi E, Kaneko S. Role of CD4⁺ T-cells in the pathology of non-alcoholic fatty liver disease and related diseases. *Hepatoma Res* 2021;7:46. <http://dx.doi.org/10.20517/2394-5079.2021.46>

Abstract

Non-alcoholic fatty liver disease (NAFLD), which is considered a liver phenotype of metabolic diseases, is becoming a major cause of chronic liver disease. Multiple factors influence and interact with each other in a complex manner to form this pathological condition. As evidenced by low-grade chronic inflammation in obesity, which is a basic pathological feature of NAFLD, immune cell infiltration can occur in various organs, and immune cell infiltration into the liver plays an important role in the development of steatohepatitis. In recent years, an increasing number of reports indicate the involvement of innate immunity and adaptive immunity in the pathogenesis of NAFLD. CD4⁺ T-cells, which serve as an essential and complex element of the immune system and major regulators of host health and disease, are differentiated into functional T helper 1 (Th1), Th2, Th9, Th17, Th22, T follicular helper, and regulatory T-cells upon antigen

stimulation in a special cytokine environment. In NAFLD patients, various pathological conditions such as obesity, diabetes, dyslipidemia, and adipose tissue inflammation coexist. Hence, T-cells can be affected by each of these pathological conditions. This review covers and discusses the reports on NAFLD and its associated pathologies as well as their effects on CD4⁺ T-cells.

Keywords:

NAFLD, non-alcoholic fatty liver disease, NASH, MAFLD, T-cell, lymphocyte, adaptive immunity

Opinion

Prevention of hepatitis B virus recurrence

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Fung J. Prevention of hepatitis B virus recurrence. *Hepatoma Res* 2021;7:33. <http://dx.doi.org/10.20517/2394-5079.2020.153>

Abstract

Despite universal vaccination and antiviral therapies being available for decades, chronic hepatitis B (CHB) remains the leading primary liver disease for liver transplantation in many parts of the Asia-Pacific region. The main indications include decompensated cirrhosis, severe acute flares, and hepatocellular carcinoma. Liver transplantation is not a sterilizing cure for CHB infection, therefore long-term antiviral prophylaxis is required. As the virus is never completely eradicated after transplant, the main goal of antiviral prophylaxis is to prevent reactivation, rather than recurrence or reinfection. Current available antiviral prophylaxis using nucleos(t)ide analogs (NUCs) ± hepatitis B immunoglobulin (HBIG) are highly effective in preventing HBV reactivation after liver transplantation. Only NUCs with high potency and high barriers to resistance should be used, as there is still a risk of developing resistance and subsequent virological rebound and reactivation for older NUCs. Over the past decade, there has been a trend towards using less HBIG, with HBIG-free regimens showing excellent long-term outcomes and survival. Although cessation of prophylaxis may be feasible in a highly selected group, this should only be attempted within clinical trial settings, and life-long prophylaxis is still recommended. Future novel agents may restore the immune control of HBV, whereby antiviral therapy can be safely discontinued.

Keywords:

Hepatitis B, hepatocellular carcinoma, recurrence, prophylaxis, antiviral

Review

Extrahepatic cancer risk after liver transplantation for hepatocellular carcinoma: incidence, risk and prevention

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Vajdic CM, van Leeuwen MT, McCaughan GW. Extrahepatic cancer risk after liver transplantation for hepatocellular carcinoma: incidence, risk and prevention. *Hepatoma Res* 2021;7:34. <http://dx.doi.org/10.20517/2394-5079.2020.159>

Abstract

This article synthesises the current evidence on the risk of de novo extrahepatic cancer in people

living with a liver transplant after hepatocellular carcinoma, the risk factors for cancer, and the recommended approaches to cancer prevention and surveillance. People living with a transplanted liver have an elevated risk of cancer and cancer death, and the indication for transplantation does not markedly alter the cancer risk. The excess risk of cancer is double that of the age- and sex-matched general population. Virus-related cancers, especially non-Hodgkin lymphoma, Kaposi sarcoma, Merkel cell carcinoma, oral, and anogenital cancers occur at increased risk, as do cancers causally associated with high prior sun exposure, smoking and excessive alcohol consumption, including skin, oesophageal, larynx, lung, kidney, and bladder cancer. The risk of incident breast and prostate cancer is not increased. Cancer-related deaths largely mirror that for cancer incidence, and extend to include the more common malignancies such as breast, colorectal, prostate cancer and non-melanoma skin cancer. As medical immunosuppression is the principal risk factor for cancer, the regimen should be reviewed on a regular basis to achieve immunosuppression minimisation. An individual, risk-based approach to cancer screening according to test characteristics and personal and family cancer history, medical history, lifestyle factors, and life expectancy is recommended. Multicomponent interventions may achieve the best results in supporting the adoption and maintenance of cancer risk-reducing behaviours. Regular, empowering patient counselling and education is a cornerstone for the care of people living with a liver transplant.

Keywords

Cancer, risk, prevention, screening, surveillance, cohort

Review

GNMT: a multifaceted suppressor of hepatocarcinogenesis

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Simile MM, Feo CF, Calvisi DF, Pascale RM, Feo F. GNMT: a multifaceted suppressor of hepatocarcinogenesis. *Hepatoma Res* 2021;7:35. <http://dx.doi.org/10.20517/2394-5079.2020.162>

Abstract

Glycine N-methyltransferase (GNMT) exerts a pivotal role in the methionine cycle and, consequently, contributes to the control of methylation reactions, and purine and pyrimidine synthesis. Numerous observations indicate that GNMT is a tumor suppressor gene, but the molecular mechanisms of its suppressive action have only been partially unraveled to date. Present knowledge indicates that GNMT acts through both epigenetic and genetic mechanisms. Among them are the decrease of AKT signaling through the inhibition of the RAPTOR/mTOR complex and the interaction of GNMT with the PTEN inhibitor, PREX2. Furthermore, GNMT is a polycyclic aromatic hydrocarbon-binding protein and a mediator of the induction, by polycyclic hydrocarbons of the cytochrome *P450-1A1* gene, whose polymorphism is involved in favoring different types of cancers. Finally, GNMT suppresses the expression of the transcription factor NRF2, whose overexpression is associated with HCC development. These findings suggest a multifaceted suppressor mechanism of the GNMT gene.

Keywords

GNMT, hepatocarcinogenesis, methionine cycle

Commentary

Systemic therapies for hepatocellular carcinoma: an evolving landscape

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Pelizzaro F, Ramadori G, Farinati F. Systemic therapies for hepatocellular carcinoma: an evolving landscape. *Hepatoma Res* 2021;7:36. <http://dx.doi.org/10.20517/2394-5079.2021.24>

Abstract

In the last few years, there has been a significant widening of the landscape of systemic therapy for unresectable hepatocellular carcinoma (HCC) patients. After the landmark drug sorafenib, several other molecules have been approved for treatment in first-line (lenvatinib) and second-line (regorafenib, cabozantinib, and ramucirumab) regimens. Very recently, another important step forward has been made with the demonstration that the combination of an anti-programmed death ligand 1 and an anti-vascular endothelial growth factor (atezolizumab + bevacizumab) provides better survival results compared to sorafenib, thus becoming the new paradigm in first-line treatment of HCC. In consideration of this rapidly evolving situation, with the availability of many potential active drugs, the American Society of Clinical Oncology recently published a guideline in order to advise on the selection of systemic treatment options. However, also considering the uncertainties and the unmet needs in the current treatment of patients with advanced liver cancer is mandatory.

Keywords

Hepatocellular carcinoma, systemic therapies, tyrosine kinase inhibitors, immune checkpoint inhibitors, atezolizumab, bevacizumab, American Society of Clinical Oncology (ASCO)

Original Article

Gut microbiome profiles associated with steatosis severity in metabolic associated fatty liver disease

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Dong TS, Luu K, Lagishetty V, Sedighian F, Woo SL, Dreskin BW, Katzka W, Chang C, Zhou Y, Arias-Jayo N, Yang J, Ahdoon AI, Ye J, Li Z, Pisegna JR, Jacobs JP. Gut microbiome profiles associated with steatosis severity in metabolic associated fatty liver disease. *Hepatoma Res* 2021;7:37. <http://dx.doi.org/10.20517/2394-5079.2021.55>

Abstract

Aim: The microbiome has been shown to be pivotal in the development of metabolic associated fatty liver disease (MAFLD). Few have examined the relationship of the microbiome specifically with steatosis grade. Therefore, our aim was to characterize the association of the microbiome with MAFLD steatosis severity while adjusting for metabolic comorbidities including diabetes.

Methods: We enrolled patients with MAFLD at the West Los Angeles Veterans Affairs Hospital. All patients underwent ultrasound elastography, fasting serum collection, and fecal sampling for 16S sequencing. We examined the associations of microbial diversity and composition with advanced steatosis, defined as a CAP score of ≥ 300 dB/m, with or without the presence of metabolic comorbidities.

Results: Seventy-five patients were enrolled. African American were less likely to have advanced steatosis than either Hispanics or Whites ($P = 0.001$). Patients with more advanced steatosis had higher fasting serum triglyceride (192.6 ± 157.1 mg/dL vs. 122.5 ± 57.4 mg/dL), HbA1c ($6.7\% \pm$

1.4% vs. 6.1% ± 0.8%), transaminases, and were more likely to have metabolic syndrome (52.4% vs. 24.2%, $P = 0.02$). Advanced steatosis and diabetes were associated with altered microbial composition. *Bacteroides* was negatively associated with advanced steatosis while *Megasphaera* was positively associated with steatosis. *Akkermansia* was negatively associated with diabetes, while *Anaerostipes* and *Parabacteroides* were positively associated with diabetes.

Conclusion: Diabetes and metabolic syndrome are associated with hepatic steatosis severity in MAFLD patients and both advanced steatosis and comorbid diabetes are independently associated with microbiome changes. These results provide insight into the role of the gut microbiome in MAFLD associated with metabolic syndrome.

Keywords

Metabolic syndrome, nonalcoholic fatty liver disease, microbiome, obesity, ultrasound elastography, advanced steatosis, diabetes

Review

Steatohepatic hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Torbenson MS, Yeh MM. Steatohepatic hepatocellular carcinoma. *Hepatoma Res* 2021;7:38. <http://dx.doi.org/10.20517/2394-5079.2021.08>

Abstract

Subtypes of hepatocellular carcinoma are important for 2 primary reasons: they help improve diagnostic accuracy, as different subtypes have their own diagnostic pitfalls; they are an important building block to the personalization of patient care, as subtypes are enriched for shared genetic changes and biological associations. The most common subtype of hepatocellular carcinoma is steatohepatic hepatocellular carcinoma (SH-HCC), a subtype that is strongly linked to tumorigenesis in the setting of the metabolic syndrome and metabolic-associated liver disease (MAFLD) and/or alcoholic hepatitis. SH-HCC shows macrovesicular steatosis, balloon cells, Mallory hyaline, intratumoral inflammation, and intratumoral fibrosis. This review examines the historical development of this subtype and explores in detail the histological features that are used to define SH-HCC. The strongest molecular correlates to-date include a low frequency of *CTNGB1* mutations and possible activation of the IL6/JAK/STAT pathway. In addition, critical unresolved questions are discussed in detail to refine the histological definition of SH-HCC, including the minimal histological thresholds needed to make the diagnosis, as well as whether or not SH-HCC currently is a mixed category of tumors, containing some tumors where the distinctive morphology is driven by tumor-specific genetic changes, and other tumors where the findings are an epiphenomenon, a reflection of metabolic or alcohol-associated fatty liver disease, and not necessarily of genetic/epigenetic changes.

Keywords

Hepatocellular carcinoma, steatohepatic, steatohepatitis, steatosis

Review

Epidemiology and aetiology of hepatocellular carcinoma in Sub-Saharan Africa

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Mak D, Kramvis A. Epidemiology and aetiology of hepatocellular carcinoma in Sub-Saharan Africa. *Hepatoma Res* 2021;7:39. <http://dx.doi.org/10.20517/2394-5079.2021.15>

Abstract

With the highest annual fatality ratio (mortality-to-incidence ratio), reported for a human cancer, hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related deaths worldwide and its distribution is not uniform. In Sub-Saharan Africa (SSA), HCC is the second leading cause of cancer-related deaths for men and the fourth for women in 2020, with average age-standardised mortality rates of 8.2 and 4.2 per 100,000 persons/year, respectively. In this region, HCC presents in younger age groups and has a median survival rate of ~3-4 months. The major risk factors for HCC include viral [hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV)] and environmental [dietary aflatoxin and iron overload] factors, with more than 50% being attributable to HBV, which is endemic in SSA. HCC control efforts in SSA are faced with a number of unique challenges, including resource restrictions, a paucity of good data, few cancer registries, inaccessibility of treatment for HBV and HCV, co-infection with human immunodeficiency virus (HIV), exposure to co-carcinogen aflatoxin B₁, unique (sub)genotypes of HBV and changing natural history and aetiology of HCC as a result of antiretroviral therapy rollout for HIV and changing lifestyles. The unique features of HCC in SSA, together with the challenges faced in its prevention and appropriate public health intervention, diagnosis and treatment, all suggest that HCC in SSA is deserving of an in depth understanding by further focused research. Considerable motivation of policymakers, work and resources are required to reduce the burden of this cancer on the subcontinent.

Keywords

Liver cancer, hepatitis, Africa, carcinogens, risk factors

Review

Contribution of C3G and other GEFs to liver cancer development and progression

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Porrás A, Sequera C, Bragado P, Gutierrez-Uzquiza A, Guerrero C. Contribution of C3G and other GEFs to liver cancer development and progression. *Hepatoma Res* 2021;7:40. <http://dx.doi.org/10.20517/2394-5079.2021.16>

Abstract

Primary liver cancers constitute the fourth leading cause of cancer mortality worldwide, due to their high morbidity, late diagnosis and lack of effective treatments. Hepatocellular carcinoma (HCC) represents 80% and cholangiocarcinoma (CCA) 15% of liver cancers. Several genetic and epigenetic gene alterations (e.g., *TERT*, *TP53* or *CTNNB1*) are HCC drivers, although many additional gene alterations contribute to HCC initiation and/or progression. Rho and Ras GTPases have been widely implicated in tumorigenesis and their activators (GEFs) have recently emerged as putative key players in liver cancer. The Ras GEF, C3G (*RAPGEF1*), a GEF mainly for Rap proteins, has recently been uncovered as a relevant gene in HCC. Its upregulation promotes tumor growth, although a decrease in C3G levels favors migration/invasion and lung metastasis. Rap1A/1B/2A/2B are overexpressed in HCC tumors, but their effects are controversial and not equivalent to those of C3G. The C3G partner, CRKL, is also overexpressed in HCC, promoting proliferation, migration and invasion. Various Rho GEFs are also deregulated in liver cancer.

Tiam1 and *Tiam2* expression is upregulated in HCC, promoting proliferation, migration and metastasis. In addition, ARHGEF-10L/9/19/39 are overexpressed in HCC tumors, facilitating migration, invasion, metastasis and proliferation. Another Rho GEF, Vav2, is also involved in metastasis. Little is known about the participation of these GEFs and GTPases in CCA. However, analysis of cancer databases uncovered deregulations or genetic alterations in several of these genes, in both CCA and HCC. Hence, GEFs function appear essential for liver homeostasis, although future studies are needed to define their precise function in liver cancer.

Keywords

Liver cancer, C3G, RAPGEF1, Rap, Ras GEFs, Rho GEFs, CRK, hepatocarcinoma, cholangiocarcinoma

Editorial

The narrow ridge from liver damage to hepatocarcinogenesis

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Best J, Gerken G. The narrow ridge from liver damage to hepatocarcinogenesis. *Hepatoma Res* 2021;7:32. <http://dx.doi.org/10.20517/2394-5079.2021.52>

Original Article

The impact of rituximab prophylaxis on hepatocellular carcinoma recurrence after living donor liver transplantation

[Full-Text](#) [PDF](#)

Copy here to cite this article: Kamo N, Yagi S. The impact of rituximab prophylaxis on hepatocellular carcinoma recurrence after living donor liver transplantation. *Hepatoma Res* 2021;7:28. <http://dx.doi.org/10.20517/2394-5079.2020.147>

Abstract

Aim: Rituximab is administered for ABO blood type incompatibility or donor-specific anti-HLA (human leukocyte antigen) antibody-positive liver transplantation (LT). However, the impact of rituximab administration on hepatocellular carcinoma (HCC) recurrence over a long term period remains unclear. The present study aimed to retrospectively investigate the impact of rituximab-based prophylaxis on HCC recurrence after living donor LT (LDLT).

Methods: A total of 117 patients who had undergone LDLT for HCC at Kyoto University between February 2006 and October 2018 were retrospectively enrolled for this study. Overall survival (OS) and the recurrence rate (RR) for HCC after LDLT were examined in patients who received rituximab (rituximab group: n = 31) vs. those who did not (control group: n = 86). Additional analyses were conducted as per the Milan criteria, the University of California San Francisco extended criteria (single tumor ≤ 6.5 cm, or ≤ 3 nodules with the largest tumor ≤ 4.5 cm, and total tumor diameter ≤ 8 cm), and the Kyoto criteria (KC) [maximum size ≤ 5 cm, number ≤ 10 , des-gamma-carboxy prothrombin (DCP) ≤ 400]. Moreover, we analyzed risk factors associated with HCC recurrence with a focus on pretransplant factors.

Results: The one-, three-, and five-year (1/3/5-y) OS and RR for all patients were 89%/81%/79%

and 5%/9%/11%, respectively. The 1/3/5-y OS and 1/3/5-y RR in the rituximab group vs. the control group were 87%/77%/69% and 4%/4%/8% vs. 89%/82%/82% and 5%/11%/12%, respectively (P = 0.11 and P = 0.55, respectively). In the subgroup analysis stratified by the selection criteria, the RR was comparable between groups. The number of patients with non-recurrence-related death tended to be higher in the rituximab group than the control group. Multivariate analysis identified maximum tumor size (P = 0.003) and preoperative treatment (P = 0.024) as independent risk factors for HCC recurrence.

Conclusion: Rituximab administration does not seem to affect HCC recurrence after LDLT.

Keywords: Rituximab, ABO incompatible, hepatocellular carcinoma, recurrence, liver transplantation

Technical Note

Laparoscopic isolated caudate lobectomy for HCC

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Kim TS, Kwon CHD. Laparoscopic isolated caudate lobectomy for HCC. *Hepatoma Res* 2021;7:31. <http://dx.doi.org/10.20517/2394-5079.2021.09>

Abstract

Hepatocellular carcinoma (HCC) located in caudate lobectomy is not common, but caudate lobectomy is associated with technical difficulty and high degree of operative risk due to deep location of the caudate lobe and surrounding major vasculature. Recently, with advances in technology and accumulation of techniques, minimal invasive surgery has been widely performed in the field of liver surgery. However, laparoscopic isolated caudate lobectomy is still technically challenging which requires in-depth knowledge of the anatomy of the caudate and extensive experience in laparoscopic liver surgery. This review focuses on the surgical techniques and outcomes of laparoscopic isolated caudate lobectomy. Although it is difficult to make conclusion regarding oncologic outcome because only a few studies with limited case numbers have reported oncologic outcome of laparoscopic isolated caudate lobectomy for HCC, laparoscopic approach could be performed safely with several benefits and become a favorable method for isolated caudate lobectomy, especially for surgeons with relatively large experience in laparoscopic liver surgery.

Keywords: Hepatocellular carcinoma, caudate lobectomy, laparoscopic liver resection, minimal invasive surgery

Opinion

Mechanisms of protective effects of astaxanthin in nonalcoholic fatty liver disease

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Gao LJ, Zhu YQ, Xu L. Mechanisms of protective effects of astaxanthin in nonalcoholic fatty liver disease. *Hepatoma Res* 2021;7:30. <http://dx.doi.org/10.20517/2394-5079.2020.150>

Abstract

Nonalcoholic fatty liver disease is a major contributor to chronic liver disease worldwide, and 10%-20% of nonalcoholic fatty liver progresses to nonalcoholic steatohepatitis (NASH).

Astaxanthin is a kind of natural carotenoid, mainly derived from microorganisms and marine organisms. Due to its special chemical structure, astaxanthin has strong antioxidant activity and has become one of the hotspots of marine natural product research. Considering the unique chemical properties of astaxanthin and the complex pathogenic mechanism of NASH, astaxanthin is regarded as a significant drug for the prevention and treatment of NASH. Thus, this review comprehensively describes the mechanisms and the utility of astaxanthin in the prevention and treatment of NASH from seven aspects: antioxidative stress, inhibition of inflammation and promotion of M2 macrophage polarization, improvement in mitochondrial oxidative respiration, regulation of lipid metabolism, amelioration of insulin resistance, suppression of fibrosis, and liver tumor formation. Collectively, the goal of this work is to provide a beneficial reference for the application value and development prospect of astaxanthin in NASH.

Keywords: Nonalcoholic fatty liver disease, astaxanthin, fibrosis, insulin resistance, mitochondrial dysfunction, oxidative stress

Review

Coffee and hepatocellular carcinoma: epidemiologic evidence and biologic mechanisms

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Pelizzaro F, Cardin R, Sartori A, Imondi A, Penzo B, Farinati F. Coffee and hepatocellular carcinoma: epidemiologic evidence and biologic mechanisms. *Hepatoma Res* 2021;7:29. <http://dx.doi.org/10.20517/2394-5079.2020.148>

Abstract

Coffee is one of the most widely consumed beverages worldwide. It is a complex chemical mixture composed of thousands of physiologically active compounds, including caffeine, chlorogenic acid, and diterpenes (cafestol and kahweol). Recently, coffee has emerged as a beverage with various health benefits, in particular in liver disease. Several epidemiological and observational studies demonstrated an inverse association between coffee consumption and primary liver cancer risk. The biological mechanisms underlying the hepatoprotective effect of coffee are still not completely understood. This article reviews the current available literature about the association between coffee consumption and hepatocellular carcinoma risk and the proposed mechanisms by which coffee exerts its chemopreventive properties.

Keywords: Coffee, primary liver cancer, hepatocellular carcinoma, oxidative stress

Perspective

Prospects for a better diagnosis and prognosis of NAFLD: a pathologist's view

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Lackner C. Prospects for a better diagnosis and prognosis of NAFLD: a pathologist's view. *Hepatoma Res* 2021;7:27. <http://dx.doi.org/10.20517/2394-5079.2020.137>

Abstract

Despite the development of surrogate non-invasive methods, histological evaluation remains an important tool for reliable classification, grading and staging, as well as prognosis in non-alcoholic fatty liver disease (NAFLD). However, histological evaluation has been criticised because it requires a liver biopsy, its propensity for sampling, and inter-observer variation. This

article highlights the future developments in the morphological interpretation of liver biopsy in NAFLD, so as to aid in improving its diagnostic and prognostic utility.

Keywords: Non-alcoholic fatty liver disease, histology, prognosis, grading and staging

Review

The evolution of minimally invasive surgery in liver transplantation for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Sioutas GS, Tsoulfas G. The evolution of minimally invasive surgery in liver transplantation for hepatocellular carcinoma. *Hepatoma Res* 2021;7:26. <http://dx.doi.org/10.20517/2394-5079.2020.111>

Abstract

Hepatocellular carcinoma (HCC) is a malignant neoplasm associated with significant mortality worldwide. The most commonly applied curative options include liver resection and liver transplantation (LT). Advances in technology have led to the broader implementation of minimally invasive approaches for liver surgery, including laparoscopic, hybrid, hand-assisted, and robotic techniques. Laparoscopic liver resection for HCC or living donor hepatectomy in LT for HCC are considered to be feasible and safe. Furthermore, the combination of laparoscopy and LT is a recent impressive and promising achievement that requires further investigation. This review aims to describe the role of minimally invasive surgery techniques utilized in LT for HCC.

Keywords: Minimally invasive surgery, liver transplantation, laparoscopic hepatectomy, laparoscopic donor hepatectomy

Case Report

Laparoscopic ICG-guided RALPPS procedure for HCC on cirrhosis with 3D reconstruction implementation: a case report

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Pegoraro F, Montalti R, Rompianesi G, Giglio MC, Troisi RI. Laparoscopic ICG-guided RALPPS procedure for HCC on cirrhosis with 3D reconstruction implementation: a case report. *Hepatoma Res* 2021;7:24. <http://dx.doi.org/10.20517/2394-5079.2020.142>

Abstract

We present a fully laparoscopic partial RALPPS (radiofrequency-assisted liver partition with portal vein ligation for staged hepatectomy) on a cirrhotic 71-year-old man with a bifocal hepatocellular carcinoma. The patient's liver was preoperatively studied through a CT-guided 3D-reconstruction. During stage-1, the right portal vein was ligated and injected with alcohol distally; the vascular limit between the right and left anterior sectors was defined through the systemic infusion of indocyanine green for a negative staining. Hence, laparoscopic ablations, guided by luminescence and checked with intraoperative ultrasounds, were performed. After 55 days, the future liver remnant increased from 28.6% to 46.3%, allowing a laparoscopic RALPPS stage-2. Fully laparoscopic RALPPS technique shows several advantages compared to the original procedure, especially in patients with cirrhosis. The avoidance of liver transection during stage-1 reduced blood loss and intraabdominal adhesions, and it eliminated the risk of biliary fistulae and

allowed an easier liver transection during stage-2.

Keywords: Liver resection, 3D reconstruction, fluorescence, HCC, ICG, laparoscopy, LiMON test, RALPPS

Systematic Review

Systematic review of existing guidelines for NAFLD assessment

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Monelli F, Venturelli F, Bonilauri L, Manicardi E, Manicardi V, Rossi PG, Massari M, Ligabue G, Riva N, Schianchi S, Bonelli E, Pattacini P, Bassi MC, Besutti G. Systematic review of existing guidelines for NAFLD assessment. *Hepatoma Res* 2021;7:25. <http://dx.doi.org/10.20517/2394-5079.2021.03>

Abstract

Aim: In this systematic review, guidelines on non-alcoholic fatty liver disease (NAFLD) were evaluated, aiming at a guideline synthesis focusing on diagnosis and staging.

Methods: A systematic literature search was conducted on any relevant database or institutional website to find guidelines on NAFLD assessment intended for clinical use on humans, in English, published from January 2010 to August 2020. Included guidelines were appraised using the AGREE II Instrument; those with higher scores and intended for use in adult patients were included in a comparative analysis.

Results: Fourteen guidelines were included in the systematic review, eight of which reached an AGREE II score sufficiently high to be recommended for clinical use, of which one developed for pediatric patients only. British and North American guidelines received the highest scores. Most guidelines recommend a screening or case-finding approach in patients with metabolic risk factors who are at increased risk of steatohepatitis or fibrosis. Ultrasound is mostly recommended to confirm steatosis, while the presence of metabolic syndrome, liver function tests, fibrosis scores, and elastographic techniques may help in selecting high-risk patients to be referred to the hepatologist, who may consider liver biopsy, although referral criteria for liver biopsy are not clearly defined. Most guidelines identify the development of noninvasive tests to replace liver biopsy as a research priority.

Conclusion: Several high-quality guidelines exist for NAFLD assessment, with no complete agreement on whether to screen high-risk patients and on the tests and biomarkers suggested to stratify patients and select those to be referred to liver biopsy.

Keywords: Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, liver fibrosis, liver biopsy, noninvasive diagnosis, hepatocellular carcinoma, type 2 diabetes mellitus

Perspective

Patient and port positioning in laparoscopic liver resections

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Thiruchelvam N, Lee SY, Chiow AKH. Patient and port positioning in laparoscopic liver resections. *Hepatoma Res* 2021;7:22. <http://dx.doi.org/10.20517/2394-5079.2020.144>

Abstract

Currently, laparoscopic liver resections are routinely performed at an increasing number of centres

and has extended to include major liver resections as well as more challenging segments of the liver. We believe that patient positioning and port placement is a critical yet under described component of successful laparoscopic liver resection to achieve optimal visualisation and allow for an ergonomic and safe dissection. In this article, we describe the advantages of various types of patient positioning as well as provide illustrations for an array of trocar configurations previously described in literature. Whilst there is no universally accepted standardization of port placement for various resection types, this descriptive article can serve as a guide for the various possibilities of port configurations that can be individually adapted by surgeons based on their preference as well as the patient's physique and anatomy.

Keywords: Laparoscopic liver resection, port positioning, patient positioning

Opinion

Optimize nucleot(s)ide analogues' to prevent hepatocellular carcinoma in patients with chronic hepatitis B: a lesson from real-world evidence

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Lim J, Choi J. Optimize nucleot(s)ide analogues' to prevent hepatocellular carcinoma in patients with chronic hepatitis B: a lesson from real-world evidence. *Hepatoma Res* 2021;7:21.

<http://dx.doi.org/10.20517/2394-5079.2020.138>

Abstract

The goal of antiviral treatment for chronic hepatitis B (CHB) is to reduce the risk of liver-related complications, including liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). It is not possible to eliminate hepatitis B virus from the host with currently available antiviral treatments; hence, a realistic goal is to decrease the risk of HCC as much as possible with an appropriate and timely antiviral treatment. For the past decades, real-world evidence has enlarged the field of CHB research. Presently, there is mounting evidence that randomized clinical trials are not technically and ethically possible to conduct. In this review, we focus on secondary prevention by antiviral treatment in patients with CHB, mainly based on real-world evidence.

Keywords: Hepatitis B virus, hepatocellular carcinoma, antiviral agent

Review

Earliest hepatitis B virus-hepatocyte genome integration: sites, mechanism, and significance in carcinogenesis

[Full-Text](#) [PDF](#)

Copy here to cite this article:

ChauhanR, Michalak TI. Earliest hepatitis B virus-hepatocyte genome integration: sites, mechanism, and significance in carcinogenesis. *Hepatoma Res* 2021;7:20.

<http://dx.doi.org/10.20517/2394-5079.2020.136>

Abstract

Hepatocellular carcinoma (HCC) is the fifth most widespread cancer responsible for one fourth of cancer-related deaths globally. Persistent infection with hepatitis B virus (HBV) remains the main cause of HCC summing up to 50% of its causative etiology. Our recent studies, supported by findings from others, uncovered that HBV and its close relative woodchuck hepatitis virus (WHV) integrate into hepatocyte genome almost immediately, hence in minutes after infection.

Retrotransposons and genes with translocation potential were found to be frequent sites of HBV insertions, suggesting a mechanism of HBV DNA spread across liver genome from the earliest stages after virus invasion. Many other genes were identified as the sites of early hepadnavirus merges in human hepatocyte-like lines infected de novo with HBV and in natural woodchuck WHV infection model. It was uncovered that head-to-tail joins (HTJs) prevail among the earliest virus-host fusions, implying their formation via the non-homologous-end-joining (NHEJ) pathway. Overlapping homologous junctions resulting from the micro-homology-mediated-overlapping-joining (MHMOJ) were rarely detected. Formation of the initial HTJs coincided with strong induction of reactive oxygen species (ROS) and transient appearance of inducible nitric oxide (iNOS). This was accompanied by cell DNA damage and activation of the poly(ADP-ribose) polymerase 1 (PARP1)-mediated host DNA repair machinery, which may explain predominant HTJ format of the first virus-host fusions. Identification of initial integration sites and resulting alterations in hepatocyte phenotype may pave a way to discovery of reliable markers of HBV-triggered HCC, including HCC resulting from occult HBV infection. Our research strongly argues that HBV is an ultimate human carcinogen capable of initiation of a pro-oncogenic process immediately after first contact with a susceptible host.

Keywords: Hepatitis B virus, woodchuck hepatitis virus, virus-host genomic integration, virus initial integration sites, retrotransposons, virus-induced oxidative DNA damage, kinetics of DNA repair response, oncogenesis of hepatocellular carcinoma

Case Report

From PVE to HVE to fully laparoscopic rescue ALPPS: a case report of multidisciplinary management of giant HCC

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Malerba V, Benedetti Cacciaguerra A, Zimmitti G, Manzoni A, Sallemi C, Monfardini L, Graffeo M, Bnà C, Natalini G, Zaniboni A, Montresor MC, Codignola C, Garatti M, Abu Hilal M. From PVE to HVE to fully laparoscopic rescue ALPPS: a case report of multidisciplinary management of giant HCC. *Hepatoma Res* 2021;7:19.

<http://dx.doi.org/10.20517/2394-5079.2020.131>

Abstract

Different strategies have been used to induce preoperative liver hypertrophy and reduce the risk of postoperative liver failure. Those have included both radiological-interventional and surgical strategies, such as portal and hepatic vein embolization, 2-stage hepatectomy and associated liver partition with portal vein ligation for staged hepatectomy (ALPPS). Herein, we describe the case of a patient with a large right liver hepatocellular carcinoma not amenable to liver transplantation, with HBV-related chronic hepatitis and a small future liver remnant (FLR), who underwent a multistep approach to ensure a safe major laparoscopic resection with an adequate FLR.

Keywords: Portal vein embolization, hepatic vein embolization, rescue ALPPS, laparoscopic surgery, hepatectomy, hepatocellular carcinoma

Review

Immunotherapy and immunotherapy biomarkers for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Armstrong S, Prins P, He AR. Immunotherapy and immunotherapy biomarkers for hepatocellular carcinoma. *Hepatoma Res* 2021;7:18. <http://dx.doi.org/10.20517/2394-5079.2020.118>

Abstract

Hepatocellular carcinoma (HCC) is increasing in prevalence and has the potential to be a highly lethal malignancy. Patients with early-stage HCC have potentially curative therapeutic options, but treatments for more advanced HCC were limited until recently. Historically, tyrosine kinase inhibitors have been used in both the first- and second-line treatment of patients with advanced HCC; however, given HCC's highly immune-responsive origins, immunotherapy is proving to be a promising systemic therapy in the frontline as well as later lines of treatment. Notably, recent studies of the novel antibody therapy combination atezolizumab (anti-PD-L1) and bevacizumab demonstrated unprecedented, practice-changing efficacy in the advanced HCC setting and led to its Food and Drug Administration approval. Although such landmark studies offer new treatment options for patients with HCC, the role of potential biomarkers to monitor immunotherapy response is largely unknown and undergoing exploration.

Keywords: Hepatocellular carcinoma, immunotherapy, checkpoint inhibitor, biomarkers

Review

Epigenetic mechanisms in hepatitis B virus-associated hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Andrisani O. Epigenetic mechanisms in hepatitis B virus-associated hepatocellular carcinoma. *Hepatoma Res* 2021;7:12. <http://dx.doi.org/10.20517/2394-5079.2020.83>

Abstract

Chronic infection of the liver by the hepatitis B virus (HBV) is associated with increased risk for developing hepatocellular carcinoma (HCC). A multitude of studies have investigated the mechanism of liver cancer pathogenesis due to chronic HBV infection. Chronic inflammation, expression of specific viral proteins such as HBx, the integration site of the viral genome into the host genome, and the viral genotype, are key players contributing to HCC pathogenesis. In addition, the genetic background of the host and exposure to environmental carcinogens are also predisposing parameters in hepatocarcinogenesis. Despite the plethora of studies, the molecular mechanism of HCC pathogenesis remains incompletely understood. In this review, the focus is on epigenetic mechanisms involved in the pathogenesis of HBV-associated HCC. Epigenetic mechanisms are dynamic molecular processes that regulate gene expression without altering the host DNA, acting by modifying the host chromatin structure via covalent post-translational histone modifications, changing the DNA methylation status, expression of non-coding RNAs such as microRNAs and long noncoding RNAs, and altering the spatial, 3-D organization of the chromatin of the virus-infected cell. Herein, studies are described that provide evidence in support of deregulation of epigenetic mechanisms in the HBV-infected/-replicating hepatocyte and their contribution to hepatocyte transformation. In contrast to genetic mutations which are permanent, epigenetic alterations are dynamic and reversible. Accordingly, the identification of essential molecular epigenetic targets involved in HBV-mediated HCC pathogenesis offers the opportunity for the design and development of novel epigenetic therapeutic approaches.

Keywords: Hepatitis B virus, hepatocellular carcinoma, epigenetics, DNA methylation,

Review

Revisiting the role of the hepatic vein in laparoscopic liver resection

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Ban D, Nara S, Takamoto T, Mizui T, Yoshino J, Esaki M, Shimada K. Revisiting the role of the hepatic vein in laparoscopic liver resection. *Hepatoma Res* 2021;7:13.

<http://dx.doi.org/10.20517/2394-5079.2020.104>

Abstract

Laparoscopic liver resection (LLR) has expanded to include major liver resection and systematic resection as the techniques have advanced. Regardless of the oncological significance of anatomical resection, dissection of the intersegmental plane is useful in liver resection because it makes liver dissection easier and does not leave an ischemic area. In laparoscopic surgery, the hepatic vein can be exposed with less bleeding than in open surgery because bleeding can be controlled by pneumoperitoneum pressure. Therefore, the hepatic vein is a useful indicator to guide the dissected surface and to determine the depth. However, the basic technique of exposing the hepatic vein during LLR is required. The hepatic vein root can be approached using either a cranial or dorsal approach, with the dorsal approach providing the favorable view characteristic of laparoscopy. Selecting the dissection layer with the Laennec’s capsule of the hepatic vein roots in mind is also a useful technique to ensure more reliable dissection of the hepatic vein. We summarize previous reports on techniques for facilitating LLR using the hepatic vein as a guide and outline the role of each hepatic vein type. Although there are many reports of procedures using the hepatic vein as a guide, the terminology of the approach awaits standardization in the future.

Keywords: Laparoscopic liver resection, laparoscopic hepatectomy, hepatic vein, anatomical landmark

Original Article

Steatosis/steatohepatitis: how sustainable is the non-invasive instrumental differential diagnosis in clinical practice?

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Salvati A, Faita F, Cavallone D, Ricco G, Colombatto P, Coco B, Romagnoli V, Oliveri F, Bonino F, Brunetto MR. Steatosis/steatohepatitis: how sustainable is the non-invasive instrumental differential diagnosis in clinical practice?. *Hepatoma Res* 2021;7:14.

<http://dx.doi.org/10.20517/2394-5079.2020.115>

Abstract

Aim: Simple, rapid, and non-invasive methods for the early diagnosis of non-alcoholic steatohepatitis (NASH) in patients with fatty liver are an unmet need in clinical practice. Transient elastography (TE), commonly used for measuring liver stiffness (LS), which is significantly influenced by both liver fibrosis and inflammation is a promising tool.

Methods: We studied retrospectively the impact of TE in a cohort of 98 consecutive asymptomatic patients with fatty liver who underwent a liver biopsy [21 non-alcoholic fatty liver (NAFL) and 77

NASH] and TE on the same day at the Hepatology Unit of University Hospital of Pisa. Patients positive for HBsAg, anti-HCV, HIV, autoantibodies, drug-induced liver disease, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, type 2 diabetes, or neoplasia were excluded.

Results: NAFL patients were younger (42.5 years vs. 47.7 years, $P = 0.02$) and with lower BMI (25.5 kg/m² vs. 28.8 kg/m², $P < 0.001$) than NASH patients. TE was higher in NASH than NAFL patients (8.1 kPa vs. 5.4 kPa, $P = 0.01$). Age, BMI, TE, and total/LDL cholesterol were statistically significantly different between NAFL and NASH patients, but with multivariate analysis only BMI ($P = 0.009$) and TE ($P = 0.031$) were independent predictors of NAFL/NASH with AUROCs of 0.771 and 0.754, respectively. A score combining TE and BMI (TE*BMI) showed the best AUROC (0.817, by De Long test, $P = 0.01$) to differentiate NAFL/NASH ($P = 0.005$).

Conclusion: Ultrasound based LS measure qualifies as a candidate tool for the early screening of NASH in fatty liver patients provided that its measure is properly standardized and tested in large prospective studies enrolling patients with different clinical and histological features.

Keywords: Non-alcoholic fatty liver disease, NAFL, NASH, liver-stiffness, transient-elasticography

Review

Clinical implications of hepatic progenitor cell activation in non-alcoholic fatty liver disease

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Younes R, Burgoyne R, Tiniakos D, Govaere O. Clinical implications of hepatic progenitor cell activation in non-alcoholic fatty liver disease. *Hepatoma Res* 2021;7:15.

<http://dx.doi.org/10.20517/2394-5079.2020.119>

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most prominent causes of liver-related morbidity in the Western world. NAFLD is a chronic disease characterised by accumulation of triglycerides in hepatocytes. Upon damage, hepatocytes drive regeneration to sustain homeostasis of the liver. However, 30-40 years of ongoing replication induced by chronic lipid damage and oxidative stress increase senescence of the hepatocytes. At this stage, activation of a reserve compartment is seen, known as the hepatic progenitor cells (HPCs). HPCs are bipotent cells which can differentiate into hepatocytes or cholangiocytes depending on the underlying aetiology in order to facilitate liver regeneration. Activation of HPCs is observed as ductular reaction (DR), comprising an expansion of transit amplifying cells of the terminal branches of the biliary tree. DR is usually observed in advanced NAFLD but is also associated with histological severity and distinct molecular profiles. In this context, information about HPCs and their activation in the form of DR may add a both diagnostic and prognostic values when assessing NAFLD patients. In this review, we analyse HPCs characteristics and development, and the clinical impact of their activation in subjects with NAFLD.

Keywords: Human progenitor cells, ductular reaction, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

Review

Liver regeneration: metabolic and epigenetic regulation

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Verma S, Purohit JS, Arora A, Sinha S, Chaturvedi MM. Liver regeneration: metabolic and epigenetic regulation. *Hepatoma Res* 2021;7:16. <http://dx.doi.org/10.20517/2394-5079.2020.122>

Abstract

The liver is bestowed with an extraordinary regenerative capability, which is accomplished by a well-coordinated cellular and molecular response at different phases of regeneration. Metabolism, as the primary function of liver, displays various alterations as a consequence of hepatic insufficiency from an injury. These metabolic perturbations are physiologically relevant for promoting hepatocellular proliferation and regeneration. On the other hand, proliferation of otherwise quiescent hepatocytes and accompanied regeneration are regulated by transient, but precisely regulated transcriptional reprogramming. This phase- cell- and time-specific gene expression is controlled by epigenetic mechanisms. Hence, both metabolic and epigenetic changes regulate liver regeneration events. But the cross-talk between metabolic and epigenetic changes for a successful liver regeneration needs to be explored. Since most of the enzymatic players of epigenetic mechanisms rely upon metabolites for their substrates and co-factors, we expect a highly coordinated inter-dependence between metabolism and epigenetics during liver regeneration too. In the present review, we discuss various metabolic and epigenetic regulatory mechanisms for liver regeneration, and put forward the possible metabolic-epigenetic-liver regeneration link for a better understanding of the process and identification of novel targets for liver-related diseases in clinical settings.

Keywords: Liver regeneration, Metabolic regulation, Epigenetic regulation

Original Article

Implications of diameter and volume-based measurement in assessment criteria for liver transplantation for hepatocellular carcinoma

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Copy here to cite this article:

Graham AI, Adair A, Harrison EM, Gordon-Smith J, Ireland H, Patel D, Wigmore SJ. Implications of diameter and volume-based measurement in assessment criteria for liver transplantation for hepatocellular carcinoma. *Hepatoma Res* 2021;7:1. <http://dx.doi.org/10.20517/2394-5079.2020.87>

Abstract

Aim: Eligibility for liver transplantation for hepatocellular carcinoma (HCC) is currently based on single-dimension, diameter measurements on cross-sectional imaging, as specified by various selection criteria. This does not account for significant differences in shape, and therefore tumour volume, between patients. This study investigated whether one-dimensional selection criteria disadvantages patients by not considering volume.

Methods: Patient data were collected retrospectively from a prospectively maintained database. Tumours were measured on both computer tomography (CT) and magnetic resonance imaging (MRI). Tumour volume was measured using two methods; semi-automated planimetry and the ellipsoid volume formula. Statistical analysis was performed using SPSS.

Results: A total of 313 patients with HCC were assessed for liver transplantation. For this study, patients who underwent transplantation ($n = 89$) and those who did not based on tumour size ($n = 33$) were included. In total, 213 tumours were measured, showing excellent correlation between

CT and MRI ($R^2 = 0.83$). The majority of tumour nodules (94%) were ellipsoid not spherical. Volumetric measurements of the 84 tumours that did not meet diameter-based Milan criteria confirmed that 76% would have been within a theoretical volume allowance based on Milan criteria diameters.

Conclusion: This study shows that a significant number of patients deemed outside conventional diameter-based Milan criteria have smaller tumour volumes than those considered within criteria. It appears that those with ellipsoid rather than spherical tumours may be disadvantaged by current size-based criteria. Further research using a contemporary patient cohort who have had the benefit of advancements in non-surgical treatments for HCC is required.

Keywords: Hepatocellular carcinoma, liver transplantation, Milan criteria, HCC measurement

Review

Novel high-throughput applications for NAFLD diagnostics and biomarker discovery

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Giraudi PJ, Stephenson AM, Tiribelli C, Rosso N. Novel high-throughput applications for NAFLD diagnostics and biomarker discovery. *Hepatoma Res* 2021;7:2. <http://dx.doi.org/10.20517/2394-5079.2020.92>

Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition worldwide due to the global proliferation of obesity, which has become an insidious healthcare epidemic. While nonalcoholic fatty liver is recognized as a multi-system disease, benign and pernicious in its unfolding, nonalcoholic steatohepatitis is the more severe form progressing from cirrhosis to hepatocellular carcinoma. Unfortunately, liver biopsy - beset by many limitations - is the only accurate diagnostic tool setting the benchmark for a plethora of non-invasive biomarkers which have so far proved limited in their reliability and take-up. As a result, we need better diagnostic and prognostic tools to aid in the identification and stratification of patients at risk of disease progression in order to enhance treatment and monitoring strategies. In this review, we explore the performance as well as pros and cons of three novel technologies that could have the potential to become the next generation in NAFLD diagnostic testing. To harness these technologies, however, we suggest that more work needs to be done to refine and validate the technology features under review, while suggesting ways in which personalized medicine could be mobilized to discover the next generation in non-invasive diagnostics.

Keywords: Biomarkers, steatohepatitis, liver fibrosis, surface-enhanced Raman spectroscopy, glycomics, proteomics, high-throughput technologies

Review

The immune microenvironment and progression of immunotherapy and combination therapeutic strategies for hepatocellular carcinoma

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Copy here to cite this article:

Feng ZY, Xu FG, Liu Y, Xu HJ, Wu FB, Chen XB, Xia HP. The immune microenvironment and progression of immunotherapy and combination therapeutic strategies for hepatocellular carcinoma. *Hepatoma Res* 2021;7:3. <http://dx.doi.org/10.20517/2394-5079.2020.107>

Abstract

Hepatocellular carcinoma (HCC) accounts for 75%-85% of all primary liver cancers and is the leading cause of cancer-related deaths. China accounts for almost half of the global incidence and deaths of HCC. The poor response of chemotherapeutics and targeted drugs may be due to the drug resistance, heterogeneity of HCC, severe chronic liver damage and cirrhosis. Restoration of the liver microenvironment changes caused by chronic injury is crucial. Immunotherapy recently seems to show promise for the treatment of HCC induced by inflammatory injury. However, the unique liver immune system and resident immune tolerance state also pose a challenge for HCC immunotherapy. Different combinations of strategies have been developed for enhancement of HCC treatment. Here, we will discuss the immune microenvironment and progression of immunotherapy and combination therapeutic strategies for HCC..

Keywords: Immune microenvironment, immunotherapy, immune checkpoint inhibitors, Chimeric antigen receptor T, hepatocellular carcinoma

Original Article

The impact of sarcopenia on the outcome of patients with cirrhosis with and without hepatocellular carcinoma who undergo liver transplantation

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Copy here to cite this article:

D’Arcangelo F, Zanetto A, Aliberti C, Shalaby S, Pellone M, Sciarrone SS, Becchetti C, Ferrarese A, Gambato M, Russo FP, Germani G, Senzolo M, Vitale A, Cillo U, Burra P. The impact of sarcopenia on the outcome of patients with cirrhosis with and without hepatocellular carcinoma who undergo liver transplantation. *Hepatoma Res* 2021;7:4. <http://dx.doi.org/10.20517/2394-5079.2020.109>

Abstract

Background: The impact of sarcopenia on the outcome of patients with cirrhosis who undergo liver transplantation (LT) has been analysed in heterogeneous cohorts with mixed results. We sought to determine the prevalence and the impact of pre-LT sarcopenia on morbidity and mortality after LT in a cohort of patients with cirrhosis with and without hepatocellular carcinoma (HCC).

Methods: Patients with cirrhosis who underwent LT between 2010 and 2016 at Padua University Hospital were retrospectively evaluated. Using image software analysis, cross-sectional area of skeletal muscle at 3rd lumbar vertebra was measured and skeletal muscle index (SMI) was calculated. Sarcopenia was defined by SMI < 50 cm²/m² in males and < 39 cm²/m² in females, respectively. Primary outcome was post-LT survival. Secondary outcomes included hospitalization length and post-LT complications.

Results: 197 patients were included, of whom, 122 (62%) had sarcopenia. Demographics and severity of cirrhosis were comparable in patients with vs. without sarcopenia. Overall survival was similar between the groups. When survival analysis was adjusted for severity of liver disease, sarcopenia was associated with a significantly reduced survival in decompensated (80% vs. 91%, 1-year post-LT; *P* = 0.04) but not in compensated (93% vs. 90%, 1-year post-LT; *P* = 0.7) patients. In patients with HCC, sarcopenia was associated with a trend towards lower survival but only in those with HCC beyond Milan criteria. Among secondary outcomes, bacterial infections were more frequent in patients with vs. without sarcopenia (50% vs. 35%; *P* = 0.02), whereas

hospitalization length and other complications were comparable between the groups.

Conclusion: Sarcopenia is a common finding in patients awaiting LT and, in those with decompensated cirrhosis, it is associated with reduced survival after transplantation.

Keywords: Sarcopenia, cirrhosis, hepatocellular carcinoma, liver transplantation, survival

Original Article

Feasibility of totally laparoscopic hemi-hepatectomies for liver tumor, with consideration of correspondence for difficult cases

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Otsuka Y, Ito Y, Matsumoto Y, Kimura K, Kajiwara Y, Okubo K, Tsuchiya M, Okada R, Ishii J, Maeda T, Funahashi K, Kaneko H. Feasibility of totally laparoscopic hemi-hepatectomies for liver tumor, with consideration of correspondence for difficult cases. *Hepatoma Res* 2021;7:5. <http://dx.doi.org/10.20517/2394-5079.2020.112>

Abstract

Aim: Laparoscopic liver resection (LLR) has been recognized as a minimally invasive surgery offering disease curability for liver tumors. Moreover, recent publications suggest that the systematic liver resections including hemi-hepatectomies have been performed safely in high volume centers. We describe our indication, standardized technique, and surgical outcome for totally laparoscopic hemi-hepatectomy (TLHH). Moreover, we hypothesize that TLHHs can be performed feasibly, as well as discuss the technical correspondence of technically difficult cases which have marginal indication for TLHHs.

Methods: From September 2008 to July 2020, in total, 488 cases of liver resections including 222 cases of LLR were performed in our institution. We invented the favorable indication of TLHHs of locally resectable tumors without involvement of tumor to hepatic hilus, confluence of hepatic veins, inferior vena cava, or extrahepatic organs, in patients with sufficient hepatic functional reserve for hemi-hepatectomies. Among 21 TLHHs for liver tumors performed during study period, there were cases which derogate favorable indications; however, they might have been able to undergo TLHHs. We divided these cases into “difficult indication group (DIG)” (10 of 21 cases) and “favorable indication group (FIG)”; compared them on perioperative background, surgical outcome; and discussed the technical correspondence of TLHHs on DIG.

Results: There were no significant differences in patient’s background and operative outcome. Operative duration, blood loss, and postoperative morbidity tended to be larger in DIG, mainly due to tumor factor, than in FIG. However, TLHHs were performed without any severe perioperative complications beyond Clavien-Dindo grade IIIb or mortality.

Conclusion: We believe that hemi-hepatectomies can safely be stylized by totally laparoscopic fashion and correspondence for difficulty can be made through technical standardization.

Keywords: Laparoscopic liver resection, major hepatectomy, laparoscopic hepatectomy, hemi-hepatectomy, liver tumor

Review

Immunological characterization of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Wang SZ, Lee SD, Sarkar D, Lee HM, Khan A, Bhati C, Sharma A, Kumaran V, Bruno D, Cotterell A, Levy MF. Immunological characterization of hepatocellular carcinoma. *Hepatoma Res* 2021;7:6. <http://dx.doi.org/10.20517/2394-5079.2020.113>

Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy and the fourth leading cause of cancer-related deaths globally. HCC is often diagnosed in late stage, difficult to treat, and has poor prognosis with a median survival of 6-20 months. Innate and adaptive immunity play a pivotal role in determining tumor control versus progression. Genomic instability and abnormal signaling in the setting of chronic liver inflammation lead to tumorigenesis. Tumor progression occurs due to a sustained inflammatory response that promotes fibrogenesis and angiogenesis. This review discusses the key innate and adaptive cellular players that mediate the anti-tumor response. This review explores the complex interactions that occur within the tumor microenvironment and their clinical implications. HCC is a fastidious malignancy that is able to evade and downregulate the host immune response. Mechanisms of how this occurs are discussed, along with how they may be exploited in the development of novel therapeutics. From our research, it appears that striking a balance between immunotolerance and a robust immune response may yield the best prognosis. This review assesses major and recent developments in HCC immunotherapy, including adoptive cell therapy, cancer vaccines, and targeted therapy such as checkpoint inhibitors. Overall, the importance of the immune response in determining outcomes for HCC cannot be understated. Improved animal models and better characterization of the tumor microenvironment are needed. We determine that a better understanding of the HCC immune profile would facilitate advancements in diagnosis, monitoring, and ultimately treatment.

Keywords: Hepatocellular carcinoma, immunology, tumor microenvironment, immune evasion, immunotherapy

Review

Statistical strategies for HCC risk prediction models in patients with chronic hepatitis B

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Copy here to cite this article:

Yip TCF, Hui VWK, Tse YK, Wong GLH. Statistical strategies for HCC risk prediction models in patients with chronic hepatitis B. *Hepatoma Res* 2021;7:7. <http://dx.doi.org/10.20517/2394-5079.2020.114>

Abstract

Risk prediction modelling for hepatocellular carcinoma (HCC) has been the focus of research in the last decade. The prediction models would help HCC risk stratification, so that patients at high risk of HCC would be able to receive more appropriate management and HCC surveillance. These models were mostly developed in treatment-naïve chronic hepatitis B patients in the early days. In recent years, more prediction models were derived and validated in patients who have received antiviral treatment, which account for the majority of patients who are at increased risk of HCC. Various statistical tests are adopted in developing and validating a risk prediction model - commonly Cox proportional hazards regression, time-dependent receiver operating characteristic (ROC) curve and area under the ROC curve. Even in well-validated models, there may be some pitfalls, e.g., generalizability and clinical applicability. The future direction of prediction model

development should be directed towards a more personalised approach. Continuous optimisation of the predictive accuracy of the models would be achieved by involving more serial and dynamic parameters.

Keywords: Cirrhosis, hepatitis B virus, hepatocellular carcinoma, liver stiffness measurement, prediction models

Review

Beta-catenin activation and immunotherapy resistance in hepatocellular carcinoma: mechanisms and biomarkers

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Copy here to cite this article:

Kwee SA, Tiirikainen M. Beta-catenin activation and immunotherapy resistance in hepatocellular carcinoma: mechanisms and biomarkers. *Hepatoma Res* 2021;7:8. <http://dx.doi.org/10.20517/2394-5079.2020.124>

Abstract

Mutations involving CTNNB1, the gene encoding beta-catenin, and other molecular alterations that affect the Wnt/beta-catenin signaling pathway are exceptionally common in hepatocellular carcinoma. Several of these alterations have also been associated with scarcity of immune cells in the tumor microenvironment and poor clinical response to immune checkpoint inhibitor therapy. In light of these associations, tumor biomarkers of beta-catenin status could have the potential to serve as clinical predictors of immunotherapy outcome. This editorial review article summarizes recent pre-clinical and clinical research pertaining to associations between beta-catenin activation and diminished anti-tumor immunity. Potential non-invasive biomarkers that may provide a window into this oncogenic mechanism of immune evasion are also presented and discussed.

Keywords: Hepatocellular carcinoma, immunotherapy, immune checkpoint, biomarkers, positron emission tomography, beta-catenin

Review

Prevention of hepatitis B virus-related hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Lin CL, Kao JH. Prevention of hepatitis B virus-related hepatocellular carcinoma. *Hepatoma Res* 2021;7:9. <http://dx.doi.org/10.20517/2394-5079.2020.125>

Abstract

Hepatocellular carcinoma (HCC), especially hepatitis B virus (HBV)-related, remains a major cause of cancer-related mortality worldwide. Unless there is early detection with curative treatment, the 5-year survival rate of advanced HCC is less than 15%. The preventive strategies for HBV-related HCC are thus urgently needed to reduce the global burden of this disastrous cancer. Primary prevention involves the avoidance of viral infection through hepatitis B vaccination and interruption of viral transmission from patients with chronic HBV infection. Universal neonatal hepatitis B vaccination program has successfully reduced the prevalence of HBV carriage rate as well as HCC incidence in vaccinated cohorts. However, HBV elimination is still difficult to achieve. Regarding secondary prevention, long-term treatment with nucleos(t)ide analogues has been proven to reduce the risk of HBV-related HCC. Individual risk stratification

and a periodic HCC surveillance in these patients could facilitate early HCC diagnosis. Finally, tertiary prevention can also be achieved by life-long treatment with NAs to reduce the risk of HCC recurrence after curative treatment of primary HCC. Challenges ahead include the fact that HBV is not yet curable by current antiviral agents. Combination therapy with direct anti-HBV agents and host-targeting immunomodulatory agents is under active development. In addition, HCC risk cannot be eliminated even in patients with HBsAg seroclearance or functional cure. Therefore, HCC surveillance is strongly recommended for every patient with chronic HBV infection.

Keywords: Anti-HBV therapy, hepatitis B vaccination, hepatitis B virus, hepatocellular carcinoma

Original Article

Robotic liver resection for hepatocellular carcinoma: a focus on anatomic resection

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Kato Y, Sugioka A, Uyama I. Robotic liver resection for hepatocellular carcinoma: a focus on anatomic resection. *Hepatoma Res* 2021;7:10. <http://dx.doi.org/10.20517/2394-5079.2020.129>

Abstract

Aim: Robotic liver resection (RLR) is a new platform for minimally invasive hepatobiliary surgery. Minimally invasive surgery can confer benefits to patients with hepatocellular carcinoma (HCC), which is mostly associated with underlying chronic liver disease. Despite the inherent functional merits of robotics for surgical techniques, the clinical advantages of hepatectomy are not well defined. Therefore, we reviewed the short-term and long-term surgical results of 57 HCC cases in 46 patients who underwent RLR at our institution.

Methods: We evaluated the feasibility and safety of robotic anatomic liver resection for HCC by comparing the results of the anatomic resection (AR) group ($n = 23$) and non-anatomic resection (NAR) group ($n = 34$).

Results: Overall ($n = 57$), the liver-specific console time was 487 min, blood loss was 194 g, and there was one open conversion (2%). Postoperative data showed acceptable hepatic functional recovery, with a major complication rate of 11% and no 90-day mortality. Compared to NAR, AR was associated with longer operative and console times, more blood loss, and worse postoperative liver function, thus reflecting the greater extent and complexity of hepatectomies for more advanced-stage tumors than NAR. Nonetheless, major complication rate, mortality rate, length of hospital stay, and R0 resection rate were comparable between groups. Long-term results were comparable to those of previously reported hepatectomies for HCC and were similar between groups.

Conclusion: RLR including AR may be a safe and feasible form of hepatectomy for select patients with HCC.

Keywords: Anatomic liver resection, Glissonian pedicle approach, hepatocellular carcinoma, laparoscopic liver resection, Laennec's capsule, robotic liver resection

Hepatoma Research Publications in 2020

Review

Diabetes and NAFLD: a high-risk cohort with definite therapeutic potential

[Full-Text](#) [PDF](#)

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Brodosi L, Musio A, Barbanti FA, Mita D, Marchesini G, Petroni ML. Diabetes and NAFLD: a high-risk cohort with definite therapeutic potential. *Hepatoma Res* 2020;6:82. <http://dx.doi.org/10.20517/2394-5079.2020.88>

Abstract

Despite the fact that non-alcoholic fatty liver disease (NAFLD) and its severe clinical forms [non-alcoholic steatohepatitis (NASH) and NASH-cirrhosis] are highly prevalent in the general population, there are no licensed drugs for NAFLD, and lifestyle intervention remains the only treatment accepted by international guidelines. This is despite massive investments in research by pharmaceutical companies. In the presence of type 2 diabetes, novel anti-diabetic drugs offer an opportunity to reduce the burden of NAFLD, by adequate control of glucose and lipid metabolism, also reducing the risk of NASH progression, advanced fibrosis, and finally hepatocellular carcinoma. We extensively reviewed the literature, based either on registration studies, ad hoc randomized studies or real-world data, to define the effectiveness of anti-diabetic drugs in the treatment of NAFLD and prevention of hepatocellular carcinoma (HCC). Metformin provides the best evidence for decreased risk of HCC, pioglitazone was associated with decreased progression to fibrosis, glucagon-like peptide-1 receptor agonists offer a possible opportunity to reduce NAFLD progression coupled with a definite protection for cardiovascular outcomes, and sodium-glucose cotransporter-2 inhibitors are likely to reduce lipid burden, simultaneously reducing the risk of progressive renal and heart failure. For the latter two drug classes, the effects on NAFLD might largely explained by decreased body weight, in keeping with the beneficial effects of intensive lifestyle intervention.

Keywords: Hepatocellular carcinoma, repeat liver resection, laparoscopic repeat liver resection

Review

Sex disparity in hepatocellular carcinoma owing to NAFLD and non-NAFLD etiology: epidemiological findings and pathobiological mechanisms

[Full-Text](#) [PDF](#)

Copy here to cite this article: Lonardo A, Ballestri S, Chow PKH, Suzuki A. Sex disparity in hepatocellular carcinoma owing to NAFLD and non-NAFLD etiology: epidemiological findings and pathobiological mechanisms. *Hepatoma Res* 2020;6:83. <http://dx.doi.org/10.20517/2394-5079.2020.89>

Abstract

Nonalcoholic fatty liver disease (NAFLD) exhibits sexual dimorphism, with men being more exposed than women to the risk of simple steatosis, nonalcoholic steatohepatitis fibrosis, and hepatocellular carcinoma (HCC), while the protection conferred to women seemingly disappears with aging and reproductive senescence (i.e., menopause). HCC, the most common primary liver cancer, which carries an ominous prognosis, may result from various genetic and non-genetic risk factors. NAFLD is now projected to become the most common cause of HCC. HCC also exhibits a definite sexual dimorphism in as much as it has a worldwide high male-to-female ratio. In this review article, we focus on sex differences in the epidemiological features of HCC. Moreover, we discuss sex differences in the clinical outcome and molecular pathobiology of NAFLD-HCC. By highlighting the research gaps to be filled, the aim of this review is to prompt future research of sex differences in HCC and facilitate developing personalized cancer prevention strategies,

detection, and treatments to achieve better patient outcomes in NAFLD-HCC, considering sex differences in HCC pathobiology.

Keywords: Liver cancer, pathobiology, personalized medicine, sex differences

Review

Nonalcoholic fatty liver disease in lean subjects: is it all metabolic-associated fatty liver disease?

[Full-Text](#) [PDF](#)

Copy here to cite this article: Machado MV. Nonalcoholic fatty liver disease in lean subjects: is it all metabolic-associated fatty liver disease?. *Hepatoma Res* 2020;6:84. <http://dx.doi.org/10.20517/2394-5079.2020.90>

Abstract

The epidemiology of nonalcoholic fatty liver disease goes hand-in-hand with the obesity pandemic. The pathogenesis of fatty liver has shifted from an hepatocentric view to an adipocentric view, in which the overloaded adipose tissue spills out lipids that spread to ectopic tissues and organs such as the liver, elicits inflammation, and changes its adipokines profile promoting insulin resistance and the metabolic syndrome. Up to 40% of nonalcoholic fatty liver disease (NAFLD) patients are not obese and up to 20% are actually lean. Furthermore roughly 10% of lean subjects have NAFLD. In fact, adiposopathy can occur in patients with normal weight, and it is associated with expansion of metabolically active visceral fat and a qualitatively different adipose tissue that becomes overwhelmed after challenged by a mildly positive energy balance. This defines the concept of personal fat threshold that when exceeded results in metabolic dysfunction. Overweight/obese persons have higher probability of exceeding that threshold, explaining why adiposopathy/metabolic syndrome/NAFLD is more frequent in the obese. In this article, the epidemiology, pathogenesis, and management of patients with lean NAFLD are reviewed with an emphasis on reconciling the concepts of NAFLD in its relationship with adiposity and of NAFLD in lean individuals.

Keywords: Lean nonalcoholic fatty liver disease, metabolically obese normal weight, visceral adipose tissue

Review

Genetic risk factors associated with NAFLD

[Full-Text](#) [PDF](#)

Copy here to cite this article: Kim DY, Park JY. Genetic risk factors associated with NAFLD. *Hepatoma Res* 2020;6:85. <http://dx.doi.org/10.20517/2394-5079.2020.96>

Abstract

Non-alcoholic fatty liver disease (NAFLD) is estimated to affect 25% of the worldwide population, and is the leading cause of chronic liver disease in developed countries. Genetic research on NAFLD has included heritability studies, candidate gene studies, familial aggregation studies, and genome-wide association studies (GWAS). Next-generation sequencing approaches, such as whole-genome sequencing and whole-exon sequencing, are emerging as the post-GWAS era of genetic research. However, GWAS remains more practical for elucidating the genetic factors related to NAFLD, which is affected by thousands of common genetic variants and does not follow Mendelian inheritance. In the present review, we summarize the current knowledge

regarding five GWAS-identified genetic loci that are associated with NAFLD. We also discuss the relationships between NAFLD-predisposing polymorphisms and cardiovascular disease, and potential applications for these identified genetic loci.

Keywords: Genome-wide association study, non-alcoholic fatty liver disease, PNPLA3, TM6SF2, GCKR, MBOAT7, HSD17B13

Review

Current status of laparoscopic repeat liver resection for recurrent hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Hokuto D, Nomi T, Yoshikawa T, Matsuo Y, Kamitani N, Sho M. Current status of laparoscopic repeat liver resection for recurrent hepatocellular carcinoma. *Hepatoma Res* 2020;6:81. <http://dx.doi.org/10.20517/2394-5079.2020.78>

Abstract

Repeat liver resection (RLR) is an effective treatment approach for recurrent hepatocellular carcinoma (HCC) and can provide acceptable long-term outcomes in select patients. Recent randomized controlled trials comparing RLR with radiofrequency ablation revealed that the latter approach was associated with a higher rate of early recurrence compared with RLR. With recent advances in laparoscopic liver resection (LLR), RLR has been increasingly performed using laparoscopy. Several propensity score-matched studies reported that laparoscopic RLR achieved lower blood loss and shorter hospital stays compared to open RLR. However, laparoscopic RLR requires more advanced techniques because of adhesions formed after the previous liver resection, changes in anatomical landmarks, and deformity of the remnant liver. The recently described difficulty classification of laparoscopic RLR is based on five factors including type of previous liver resection (open or laparoscopic), number of previous liver resections, surgical procedure used in previous liver resections, tumor location in previous liver resections, and difficulty score of LLR for recurrent HCC. We reviewed the available literature to summarize available evidence suggesting that laparoscopic RLR might be considered a more minimally invasive surgical treatment approach for recurrent HCC as long as the indication for laparoscopic RLR is carefully determined.

Keywords: Hepatocellular carcinoma, repeat liver resection, laparoscopic repeat liver resection

Review

p53 functional loss, stemness and hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: de Fromentel CC, Levrero M. p53 functional loss, stemness and hepatocellular carcinoma. *Hepatoma Res* 2020;6:80. <http://dx.doi.org/10.20517/2394-5079.2020.77>

Abstract

The tumor suppressor p53 is a key player in the control of genomic integrity and homeostasis in connection with p63 and p73, the two other members of the p53 family. Loss of functional p53 leads to the proliferation and survival of mature cells and progenitor or stem cells that accumulate genetic alterations, thus favoring tumorigenesis. p53 loss of function, observed in a wide variety of human tumor types, is frequently caused by missense mutations more frequently found in the DNA binding domain, but can also be due to the expression of a plethora of viral and cellular

negative regulators. Human hepatocellular carcinoma (HCC) represents a specific situation, first because the *TP53* gene mutations pattern exhibits a “hot spot” rarely found in other tumor types that is linked to Aflatoxin B1 exposure and, second, because many HCCs do not exhibit any *TP53* mutation. Here, we provide an overview of the current knowledge about the inhibition of p53 functions by the N-terminal (Δ N) truncated forms of the family, and their role in the emergence and maintenance of pre-malignant cells with stem cell characteristics and in HCC development. We focus in particular on the Nanog-IGF1R- Δ Np73 axis that is associated with stem-like features in HCC cells and that may provide an attractive new therapeutic target and help to develop new biomarkers for HCC risk stratification, as well as preventive strategies.

Keywords: p53 family, p53 functional inactivation, Δ Np73, hepatic progenitor cells, cancer stem cells, Nanog, hepatocellular carcinoma

Review

Current status of laparoscopic repeat liver resection for hepatocellular carcinoma

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Copy here to cite this article: Morise Z. Current status of laparoscopic repeat liver resection for hepatocellular carcinoma. *Hepatoma Res* 2020;6:79. <http://dx.doi.org/10.20517/2394-5079.2020.76>

Abstract

Although liver resection (LR) is often adopted to recurrent hepatocellular carcinomas, risks of complications and conversion reportedly increase in laparoscopic repeat LR (LRLR). The indication is not agreed upon even with the recent advances of laparoscopic LR. We conducted an international propensity score matching study of LRLR and open repeat LR for hepatocellular carcinoma with 1,582 patients from 42 world centers. Propensity-score matched LRLR patients have smaller blood loss and longer operation time than open repeat LR patients. Median overall survival time was 8.94 years in open and 12.55 years in LRLR; although the difference was not significant, the *P*-value was 0.0855 and the better curve of LRLR is clearly separated from that of open. In our institution, we experienced 34 LRLR and 12 cases of three times or more repeat LR until 2019. There are no significant differences in operation time, blood loss, hospital stay, conversion, and morbidity rates among first, second, and third or higher laparoscopic LR, which is different from the open situation. However, postoperative bile leakage and intraoperative bleeding causing conversion did happen in the cases with repeat extended exposure of Glissonian pedicle. LRLR is feasible for selected patients. However, the procedure is under developing stage and further accumulation of experiences and evaluation are needed.

Keywords: Laparoscopic liver resection, hepatocellular carcinoma, re-do surgery

Review

Prevalence and incidence of intra- and extrahepatic complications of NAFLD in patients with type 2 diabetes mellitus

[Full-Text](#) [PDF](#)

Copy here to cite this article: Mantovani A, Beatrice G, Stupia R, Dalbeni A. Prevalence and incidence of intra- and extrahepatic complications of NAFLD in patients with type 2 diabetes mellitus. *Hepatoma Res* 2020;6:78. <http://dx.doi.org/10.20517/2394-5079.2020.75>

Abstract

Nonalcoholic fatty liver disease (NAFLD) is linked to abdominal obesity, insulin resistance and type 2 diabetes mellitus (T2DM). The association of NAFLD with T2DM is bidirectional. In fact, evidence suggests that abdominal obesity, T2DM and metabolic syndrome play a part in the development and progression of NAFLD. Alternatively, NAFLD is associated with an increased risk of having T2DM and metabolic syndrome. According to this background, it is unsurprising that patients with T2DM patients also have a higher prevalence of NAFLD than those with no T2DM, as well as an increased risk of developing liver-related and extrahepatic complications, mainly cardiovascular and renal diseases. Seeing the relationship of NAFLD with insulin resistance, obesity and T2DM, recent consensus proposes a change in nomenclature from NAFLD to metabolic associated fatty liver disease. In this review, we will discuss the prevalence and incidence of NAFLD (as detected by imaging techniques or liver biopsy) in patients with type T2DM with particular regard to hepatic and extrahepatic complications.

Keywords

Nonalcoholic fatty liver disease, NASH, metabolic associated fatty liver disease, diabetes, type 2 diabetes

Review

Advances in minimally invasive surgery for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Zhang CZ, Li N. Advances in minimally invasive surgery for hepatocellular carcinoma. *Hepatoma Res* 2020;6:77. <http://dx.doi.org/10.20517/2394-5079.2020.74>

Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide. Surgical resection is still regarded as the first choice of treatment for HCC. With advances in technology and techniques, minimally invasive surgery has now become the standard of care in almost every field in general surgery, including hepatectomy surgery. This review focuses on the latest advances in minimally invasive surgical treatment of HCC, including laparoscopic hepatectomy (LH), robotic hepatectomy (RH) and other minimally invasive treatment technologies. Although some limitation in LH or RH exists, these minimally invasive techniques may be performed for hepatectomy with benefits, and have a promising future. With the development of technology and the improvement of surgical operations, patients will benefit from this.

Keywords

Hepatocellular carcinoma, minimally invasive surgery, laparoscopic hepatectomy, robotic hepatectomyCutaneous toxicities of targeted therapies in the treatment of hepatocellular carcinoma

Review

Living donor liver transplantation for patients with advanced hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Cullen JM, Vargas P, Goldaracena N. Living donor liver transplantation for patients with advanced hepatocellular carcinoma. *Hepatoma Res* 2020;6:76. <http://dx.doi.org/10.20517/2394-5079.2020.69>

Abstract

Liver transplantation (LT) is the treatment of choice for patients with hepatocellular carcinoma (HCC) and underlying liver disease. Given the organ scarcity, LT for patients with HCC have been restricted to those patients associated with the highest survivals. However, many patients with extended criteria HCC can still benefit from LT, but due to deceased organ shortage, they are not offered that opportunity. Living donor liver transplantation (LDLT) emerged as a successful strategy to overcome organ shortage around the world and as LDLT experience grows, this technique might offer the opportunity to expand the indications of LT to patients with advanced HCC. Therefore, since LDLT is not competing for deceased donor organs, many patients with extended criteria HCC who could still benefit from transplantation may have access to this treatment option. In this review, we will discuss the role of LDLT for patients with advanced-stage HCC and how LDLT allows for safe expansion of HCC transplant criteria.

Keywords

Living donor liver transplantation, hepatocellular carcinoma, liver transplantation, transplant oncology, clinical outcomes

Perspective

Should selection criteria for HCC be the same (or different) between LDLT and DDLT?

[Full-Text](#) [PDF](#)

Copy here to cite this article: Feier F. Should selection criteria for HCC be the same (or different) between LDLT and DDLT?. *Hepatoma Res* 2020;6:75. <http://dx.doi.org/10.20517/2394-5079.2020.68>

Abstract

Since the Milan Criteria (MC) were adopted in many countries as the allocation policy criteria for patients with hepatocellular carcinoma to be transplanted, many groups started to expand it to provide a chance for patients with tumors outside the MC who could achieve similar survival rates. With the scarcity of deceased donors, Asian countries improved the results with living donor liver transplantation, allowing patients outside MC to be transplanted with a living donor. Newer prognostic models and a more profound understanding of tumor behavior are targeting better patient selection. Currently, patients are unevenly selected for liver transplantation and mostly separated into those fulfilling the MC and transplanted with a deceased donor and those with expanded criteria and transplanted with a living donor. In this paper, insight is brought into this debate.

Keywords

Living donor, hepatocellular carcinoma, alpha-fetoprotein

Review

The role of genetic factors in HBV-related HCC: perspectives from local genetic backgrounds and clinical epidemiology

[Full-Text](#) [PDF](#)

Copy here to cite this article: Tai DI, Tai J. The role of genetic factors in HBV-related HCC: perspectives from local genetic backgrounds and clinical epidemiology. *Hepatoma Res* 2020;6:74. <http://dx.doi.org/10.20517/2394-5079.2020.54>

Abstract

Familial clustering of hepatitis B surface antigen carriers (HBsAg) and hepatocellular carcinoma (HCC) has led to the evaluation of the role of genetics in hepatitis B-related diseases. Consistent reports indicate that the HLA-DP and -DQ loci are associated with persistent hepatitis B virus (HBV) infection. However, for hepatocarcinogenesis, existing studies have low power and conflicting data. Global single nucleotide polymorphism (SNP) data was collected from the 1000 Genomes Project and correlated with local epidemiological information. Southeastern Asia has a higher prevalence of HBsAg than Northeastern Asia; this was used in the evaluation of persistent HBV infection. The higher incidence of HCC in West Africa compared with East Africa was used in the evaluation of hepatocarcinogenesis. The allele frequencies for SNPs were significantly different between East Asians and Africans. Therefore, SNPs that have been identified in persistent HBV infections in East Asia may not be completely applicable in Africa. SNPs in NTCP, CTF19, and the HLA-DQ and -DP loci showed North-to-South allele frequency changes in East Asia. These findings confirm the role of genetics in persistent HBV infection. Some of the SNPs in the HLA loci show a trend of West-to-East allele frequency changes in Africa, indicating they may participate in hepatocarcinogenesis. Among the non-HLA related SNPs, rs2596542 in MICA shows a strong trend of allele frequency changes and is correlated with HCC incidence in Africa. SNPs in KIF1, IL-1A, and STAT4 also show, albeit with low statistical power, allele frequency trends compatible with HCC incidence. Taken together, there are strong correlations between background genetics in HLA-DP and -DQ loci with persistent HBV infection and hepatocarcinogenesis. The correlations were weak-positive in non-HLA loci.

Keywords

Genetic polymorphism, genome-wide associated studies, hepatitis B virus, hepatocellular carcinoma

Review

Cutaneous toxicities of targeted therapies in the treatment of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Silk T, Wu J. Cutaneous toxicities of targeted therapies in the treatment of hepatocellular carcinoma. *Hepatoma Res* 2020;6:73. <http://dx.doi.org/10.20517/2394-5079.2020.61>

Abstract

Liver cancer accounts for 4.7% of all newly diagnosed cancers and 8.2% of cancer deaths annually. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers. There are 2 curative strategies in HCC: resection and transplant. Unfortunately, 50% of patients who undergo resection will relapse in 2 years and many patients on transplant lists become ineligible for transplant due to disease progression. The majority of patients still require systemic therapies. Tyrosine kinase inhibitors have successfully extended the overall survival in patients with hepatocellular carcinoma. However, these treatments have been noted to cause severe side effects including liver toxicity, hypertension, gastrointestinal toxicity and cutaneous adverse effects. This article will focus on the adverse skin reactions seen during the treatment of hepatocellular carcinoma by various tyrosine kinase inhibitors. The focus will be symptomatology, management, and whether the development of cutaneous toxicities can be prognostic.

Keywords: Hepatocellular cancer, tyrosine kinase inhibitors, cutaneous toxicity, hand foot

Original Article

The transcontinental variability of nonalcoholic fatty liver disease

[Full-Text](#) [PDF](#)

Copy here to cite this article: Oliveira CP, Paredes A, Siddiqui M, Serfaty L, Chowdhury A, Stefano JT, Vanni DS, Boyett S, Sanyal AJ. The transcontinental variability of nonalcoholic fatty liver disease. *Hepatoma Res* 2020;6:72. <http://dx.doi.org/10.20517/2394-5079.2020.73>

Abstract

Aim: To compare the phenotype of lean versus overweight (OW) and obese (OB) subjects with non-alcoholic fatty liver disease (NAFLD) across multiple continents.

Methods: A retrospective study of histologically defined subjects from a single center each in France (Fr), Brazil (Br), India (In) and United States (US) was performed.

Results: A total of 70 lean [body mass index (BMI) < 25 kg/m²] subjects (Fr:Br:In:US: 16:19:22:13) with NAFLD were compared to 136 OW (BMI > 25 kg/m², BMI < 29 kg/m²) (n = 28:33:52:23) and 224 OB subjects (BMI > 29 kg/m²) (n = 81:11:22:103). Lean French subjects had the lowest incidence of type 2 diabetes while those from Brazil (P < 0.01) had the highest. Lean subjects had similar low-density lipoprotein-cholesterol, but higher high-density lipoprotein-cholesterol compared to obese subjects in all regions. In both lean and obese subjects, there were both insulin-sensitive and insulin-resistant subjects. Lean French subjects were most insulin-sensitive while those from Brazil were mostly insulin-resistant. For each weight category, subjects from India were more insulin-sensitive than those from other regions. Disease activity increased from lean to overweight to obese in France but was similar across weight categories in other regions.

Conclusion: The phenotype of NAFLD in lean subjects varies by region. Some obese subjects with NAFLD are insulin-sensitive. We hypothesize that genetics and region-specific disease modifiers account for these differences.

Keywords: Non-alcoholic fatty liver disease, phenotype, epidemiology, demographics

Original Article

Post liver transplant recurrence in patients with hepatocellular carcinoma: not necessarily the end of the road!

[Full-Text](#) [PDF](#)

Copy here to cite this article: Bhangui P, Yadav S, Soin AS. Post liver transplant recurrence in patients with hepatocellular carcinoma: not necessarily the end of the road!. *Hepatoma Res* 2020;6:71. <http://dx.doi.org/10.20517/2394-5079.2020.67>

Abstract

Aim: We analysed outcomes using multimodality therapy in patients with hepatocellular carcinoma (HCC) recurrence post living donor liver transplantation (LDLT).

Methods: Of 2363 LDLT's performed between 2005 to mid 2018, 435 (18.4%) were for HCC within our expanded selection criteria (absence of extrahepatic disease and vascular invasion, irrespective of tumor size and number). Survival after recurrence, and prognostic factors for these patients were studied.

Results: Of 435 LDLT patients, 51% had HCC beyond Milan and 43% beyond UCSF criteria at

the time of LDLT. pre-LT AFP > 100 ng/mL and tumour FDG-18 PET avidity predicted overall survival (OS), whereas pre-LT AFP > 100 ng/mL, UCSF criteria, and FDG-18 PET avidity predicted recurrence-free survival. Hundred patients (23%) developed HCC recurrence at a median time of 16 months (range 2-108 months) post LDLT. Lungs (53%), liver (37%), and bone (21%) were the most common sites of recurrence. Ninety-five patients received tyrosine kinase inhibitors (TKI) after recurrence and 62 received mTOR inhibitors (protocol-based after LDLT, or post recurrence). Surgical resection of metastases was performed in 14 patients, 15 received stereotactic body radiotherapy, and 18 underwent ablation (radiofrequency, microwave ablation, transarterial chemoembolisation, or percutaneous ethanol injection). One- and 3-yr OS after recurrence were 57%, and 24% respectively, with a maximum post recurrence survival of 7.5 years. HCC recurrence within one year after LDLT (P = 0.004, HR = 2.38, 95%CI: 1.325-4.276), AFP > 200 ng/mL at the time of recurrence (P = 0.02, HR = 2.075, 95%CI: 1.121-3.841), and recurrence at multiple sites (P = 0.047, HR = 1.831, 95%CI: 1.009-3.321) were poor prognostic factors for post recurrence survival. Multimodality management of recurrence using combined medical, surgical, ablative treatments and radiotherapy significantly improved survival compared to the use of TKI's or mTORi's alone, or in combination.

Conclusion: In patients accepted for LDLT beyond the conventional size-number criteria, even after HCC recurrence, an aggressive approach using multimodality therapy, when possible, aids in further prolongation of survival.

Keywords: Living donor liver transplantation, hepatocellular carcinoma recurrence, multimodality treatment, outcomes, prognostic factors

Review

Systemic therapy for advanced cholangiocarcinoma: new options on the horizon

[Full-Text](#) [PDF](#)

Copy here to cite this article: Alqahtani SA, Colombo M. Systemic therapy for advanced cholangiocarcinoma: new options on the horizon. *Hepatoma Res* 2020;6:70. <http://dx.doi.org/10.20517/2394-5079.2020.65>

Abstract

Patients with unresectable cholangiocarcinoma (CCA) face a poor prognosis, and there are few effective treatment options for the disease. The standard of care for patients with locally advanced or metastatic CCA is chemotherapy with a gemcitabine-based doublet. Unfortunately, the clinical benefit obtained with these regimens is modest, with a median overall survival of about one year. For CCA that is chemotherapy-refractory or recurs after first-line chemotherapy, the treatment options are even more limited, and no relevant randomized controlled data are available. In recent years, molecular profiling has shed light on the molecular basis of CCA and identified subgroups of patients that might benefit from a personalized treatment approach. These efforts resulted in the recent FDA approval of the fibroblast growth factor receptor (FGFR) inhibitor, pemigatinib, as a second-line treatment for patients with advanced CCA harboring an FGFR2-fusion or rearrangement. Several other targeted agents also are under evaluation in patients with CCA, of which the isocitrate dehydrogenase inhibitor has had the most promising results. Finally, immunotherapy is being explored as a new treatment approach for advanced CCA patients; indeed, the immune checkpoint inhibitor pembrolizumab can already be used to treat CCAs that are mismatch repair deficient. This review is a comprehensive overview of the treatment options for

CCA and offers a glimpse into what the future could hold for these patients.

Keywords: Cholangiocarcinoma, fibroblast growth factor receptor inhibitor, isocitrate dehydrogenase inhibitor, immune checkpoint inhibitor

Review

Beneficial effects of coffee in non-alcoholic fatty liver disease: a narrative review

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Calabrò A, Procopio AC, Primerano F, Larussa T, Luzzza F, Di Renzo L, De Lorenzo A, Gualtieri P, Abenavoli L. Beneficial effects of coffee in non-alcoholic fatty liver disease: a narrative review. *Hepatoma Res* 2020;6:69. <http://dx.doi.org/10.20517/2394-5079.2020.63>

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases and is related to unhealthy lifestyle habits, characterized by a diet rich in sugars and fats leading to excessive calorie intake, and lack of exercise. In recent years, there is a growing incidence of this pathology, raising the attention of hepatologists, endocrinologists, diabetologists, and nutritionists. In this context, the alimentary regimen adopted by patients with NAFLD has become an increasingly scrutinised parameter. Diet is now considered a crucial factor in the treatment of NAFLD since it has been observed that some functional foods play a beneficial role. These include coffee whose health effects have already been amply demonstrated. Here we describe the beneficial effects of coffee consumption reported in the NAFLD literature.

Keywords: Caffeine, steatosis, functional food, liver disease, antioxidant, chlorogenic-acid

Review

Immunotherapy of hepatocellular carcinoma with infection of hepatitis B or C virus

[Full-Text](#) [PDF](#)

Copy here to cite this article: Bonilla CM, McGrath NA, Fu J, Xie C. Immunotherapy of hepatocellular carcinoma with infection of hepatitis B or C virus. *Hepatoma Res* 2020;6:68. <http://dx.doi.org/10.20517/2394-5079.2020.58>

Abstract

Hepatocellular carcinoma (HCC) has one of highest mortalities globally amongst cancers, but has limited therapeutic options once in the advanced stage. Hepatitis B or C virus infection are the most common drivers for HCC carcinogenesis, triggering chronic liver inflammation and adding to the complexity of the immune microecosystem of HCC. The emergence of immunotherapy has afforded a new avenue of therapeutic options for patients with advanced HCC with a history of hepatitis B or C virus infection. This article reviews the change of immunity elicited by hepatitis B or C virus infection, the immune feature of HCC, and the clinical evidence for immunotherapy in advanced HCC and discusses future directions in this field.

Keywords: Hepatocellular carcinoma, hepatitis B virus, hepatitis C virus, immunotherapy

Original Article

Prognostic ability of inflammation-based markers in radioembolization for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Yoneoka G, Bozhilov K, Wong LL. Prognostic ability of inflammation-based markers in radioembolization for hepatocellular carcinoma. *Hepatoma Res* 2020;6:67. <http://dx.doi.org/10.20517/2394-5079.2020.57>

Abstract

Aim: Inflammation-based markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have recently been used as prognostic indicators in hepatocellular carcinoma (HCC). We aimed to determine whether NLR and PLR may predict response to yttrium-90 transarterial radioembolization (TARE) as primary treatment for HCC.

Methods: We performed a retrospective review of a prospectively collected database of HCC cases (1994-2019) and selected patients who received TARE as primary treatment (n = 42). Laboratory studies were used to calculate NLR and PLR. Response to TARE was determined using the modified response evaluation criteria in solid tumors (mRECIST). Patients were classified as non-responders (stable or progressive disease) or responders (partial or complete response) to treatment based on mRECIST.

Results: Receiver operating characteristic curves identified a pre-treatment NLR cutoff of ≥ 2.83 and a pre-treatment PLR cutoff of ≥ 83 for predicting non-response to treatment. Pre-treatment NLR ≥ 2.83 was the only significant predictor of non-response to TARE in multivariate logistic regression analysis (odds ratio 7.83, P = 0.036). On time to progression analysis, both pre-treatment NLR ≥ 2.83 and pre-treatment PLR ≥ 83 were associated with a higher proportion of tumor progression at 6 months post-treatment (43.6% vs. 10.0%, P = 0.014, log-rank) and (38.6% vs. 0%, P = 0.010, log-rank), respectively.

Conclusion: NLR confers prognostic value and may be superior to PLR in determining response to TARE as primary treatment for HCC. Future studies are necessary to validate these findings in a larger cohort.

Keywords: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, transarterial radioembolization, hepatocellular carcinoma

Original Article

Stereotactic body radiation therapy for primary liver tumors with adverse factors

[Full-Text](#) [PDF](#)

Copy here to cite this article: Shimizuguchi T, Imamura J, Hashimoto S, Karasawa K. Stereotactic body radiation therapy for primary liver tumors with adverse factors. *Hepatoma Res* 2020;6:66. <http://dx.doi.org/10.20517/2394-5079.2020.51>

Abstract

Aim: To test the efficacy and safety of liver stereotactic body radiation therapy (SBRT) in patients who harbor adverse factors.

Methods: We retrospectively evaluated the outcomes of liver SBRT in a single cancer center. We invented criteria consisting of two physical factors and two tumor factors to measure the treatment difficulty in each case. The clinical outcomes and toxicity were evaluated by stratification of the harboring factors.

Results: A total of 24 (23 hepatocellular carcinoma and 1 intrahepatic cholangiocarcinoma) patients were eligible for this study, with a median follow-up duration of 18 months. Of all eligible patients, 21 patients (88%) had one or more factors. The local control, progression-free survival, and overall survival rates for all patients at 2 years were 89%, 42%, and 76% respectively. In the

patients with physical and tumor adverse factors, local control/progression-free survival/overall survival rates at 2 years were 100%/42%/69% and 80%/23%/78%, respectively. The subgroup of 11 patients with 2 or more factors showed comparable local control rate at 2 years to the subgroup of 13 patients with 0 to 1 factors (100% vs. 86%, $P = 0.59$). One patient (4.2%) experienced a decline in the Child-Pugh score by 2 points at 3 months after the treatment. Grade 2 to 3 gastrointestinal toxicity was observed in three patients.

Conclusion: SBRT showed a high local control rate with acceptable toxicity for the group of liver cancer patients harboring both physical and tumor adverse factors as long as conducted following patient selection and dose constraints that were used in this study.

Keywords: Hepatocellular carcinoma, stereotactic body radiation therapy, vulnerable patients

Commentary

From nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease: is it time for a change of terminology?

[Full-Text](#) [PDF](#)

Copy here to cite this article: Targher G, Byrne CD. From nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease: is it time for a change of terminology?. *Hepatoma Res* 2020;6:64. <http://dx.doi.org/10.20517/2394-5079.2020.71>

Abstract

Nonalcoholic fatty liver disease (NAFLD) has become the most common cause of liver disease in many parts of the world, causing considerable liver-related (steatohepatitis, cirrhosis, liver failure and hepatocellular carcinoma) and extra-hepatic morbidity and mortality (mainly cardiovascular disease, chronic kidney disease or certain types of extra-hepatic cancers). Recently, based on insights gained from the past two decades, an international panel of experts from 22 countries has taken the initiative to propose a new name and definition for NAFLD in adult individuals - that is, metabolic dysfunction-associated fatty liver disease. This proposed change in nomenclature is not simply a semantic revision, but may facilitate improved diagnosis of this common liver disease for health promotion, case identification, patient awareness, ongoing clinical trials and health services delivery. The aim of this commentary is to discuss the proposal for a change in nomenclature of this common and burdensome liver disease and to address the “pros and cons” for changing the name according to the perspective of different stakeholders.

Keywords: Nonalcoholic fatty liver disease, metabolic dysfunction-associated fatty liver disease, liver fat, commentary

Editorial

Robotic-assisted laparoscopic liver resection in hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Labadie KP, Park JO, Sham JG. Robotic-assisted laparoscopic liver resection in hepatocellular carcinoma. *Hepatoma Res* 2020;6:65. <http://dx.doi.org/10.20517/2394-5079.2020.86>

Review

Viral hepatitis as a risk factor for the development of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Alqahtani SA, Colombo M. Viral hepatitis as a risk factor for the development of hepatocellular carcinoma. *Hepatoma Res* 2020;6:58. <http://dx.doi.org/10.20517/2394-5079.2020.49>

Abstract

Hepatocellular carcinoma (HCC) is the fourth leading global cause of tumor-related mortality. HCC has a high prevalence in patients with chronic liver diseases, and it mostly results from cirrhosis caused by infection with blood-borne viruses. Despite the implementation of various diagnostic and prevention strategies, the rates of new HCC cases and mortality are increasing globally due to the aging and growth of the world population as well as their increased exposure to dominant risk factors like alcohol, hepatitis B and C, and clinical correlates of metabolic syndrome. Modeling studies indicate that sanitation practices, implementation of vaccination programs against hepatitis B, and expanded recognition and treatment of patients with chronic hepatitis B and C could greatly contribute to the eradication of viral hepatitis B and C. While the availability of generic antiviral drugs could partially overcome the bottleneck represented by the lack of resources in low and middle-income countries, where viral hepatitis is the leading cause of liver cancer, the enthusiasm for the prevention of liver cancer through antiviral therapy is mitigated by the risk of cancer in many patients who are treated late in the hepatitis course. The present work aimed to review in detail the various types, epidemiology, and carcinogenesis mechanisms of viral infections that are associated with a significantly increased risk for the development of HCC.

Keywords: Antiviral agents, hepatitis viruses, hepatocellular carcinoma, blood-borne hepatitis, cirrhosis, hepatitis B vaccine

Review

CT and MRI of the liver for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Santillan C. CT and MRI of the liver for hepatocellular carcinoma. *Hepatoma Res* 2020;6:63. <http://dx.doi.org/10.20517/2394-5079.2020.60>

Abstract

Computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used modalities for the imaging based diagnosis and staging of hepatocellular carcinoma (HCC). The Liver Imaging Reporting and Data System (LI-RADS) was initially released in 2011 in an effort to standardize the interpretation and reporting of these studies in patients at increased risk for the development of HCC. With the release of LI-RADS v2018, LI-RADS has reached two important milestones - 10 years since the formation of the American College of Radiology supported LI-RADS committee and integration of LI-RADS into the 2018 American Association for the Study of Liver Disease practice guidance for HCC. In this article, we will discuss recent changes to LI-RADS with v2018, technical recommendations for the performance of CT and MRI in patients at risk for HCC, and critical imaging features in the LI-RADS algorithm.

Keywords: Hepatocellular carcinoma, Liver Imaging Reporting and Data System, magnetic resonance imaging, computed tomography

Review

Evaluation and impact of different biomarkers for early detection of hepatocellular

carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Best J, Sydor S, Bechmann LP, Canbay A. Evaluation and impact of different biomarkers for early detection of hepatocellular carcinoma. *Hepatoma Res* 2020;6:62. <http://dx.doi.org/10.20517/2394-5079.2020.56>

Abstract

Worldwide, hepatocellular carcinoma (HCC) is a frequent complication of liver diseases and remains a major cause of cancer-related mortality. In addition, the prevalence of nonalcoholic steatohepatitis (NASH) as prerequisite of hepatocarcinogenesis, even in the absence of cirrhosis, is rising rapidly. The early detection of HCC has been crucial in improving the survival outcomes of those patients. However, in the mostly obese NASH population, diagnostic sensitivity of ultrasound-based HCC screening approaches is limited. On the other hand, biomarkers for HCC show promising potential to improve early detection, providing reproducible, investigator-independent results that can be used either alone or integrated with other biomarkers for scoring models. In the past, validation has been limited due to a lack of prospective longitudinal cohort studies. At present, large-scale retrospective phase-III- biomarker-development- gives hope for the availability of biomarker-based screening approaches in the near future. This review focuses on the potential impact of biomarkers on surveillance strategies, potentially allowing for earlier HCC diagnosis.

Keywords: Nonalcoholic steatohepatitis, hepatocellular carcinoma, alpha fetoprotein, AFP-L3, des-gamma-carboxy-prothrombin, Gender, Age, GALAD-score, Glypican-3, microbiome

Review

Detection of circulating tumor cells in hepatocellular carcinoma: applications in diagnosis, prognosis prediction and personalized treatment

[Full-Text](#) [PDF](#)

Copy here to cite this article: Wang PX, Cheng JW, Yang XR. Detection of circulating tumor cells in hepatocellular carcinoma: applications in diagnosis, prognosis prediction and personalized treatment. *Hepatoma Res* 2020;6:61. <http://dx.doi.org/10.20517/2394-5079.2020.55>

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and is associated with poor clinical prognosis, which is mainly caused by tumor recurrence and metastasis. Circulating tumor cells (CTCs) are tumor cells shed into the bloodstream and regarded as the “seeds” of tumor recurrent or metastatic lesions. Over the past decade, the clinical value of CTC analysis has been extensively explored. CTC analysis is a representative form of liquid biopsy, offering a novel solution that can bypass the problems of invasive biopsy procedures, enabling comprehensive, non-invasive, and real-time disease monitoring. In HCC, CTC analysis has facilitated early detection and prognosis prediction, as well as treatment monitoring and therapeutic intervention guiding. In this review, we summarize available literature and provide an overview of CTC biology, detection technologies, and clinical applications in the diagnosis, prognosis prediction, and personalized treatment of HCC.

Keywords: Hepatocellular carcinoma, liquid biopsy, circulating tumor cells, biomarkers, personalized medicine

Review

Comparison and analysis of the efficacy of drug therapy for liver cancer

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Merle P, Subic M. Comparison and analysis of the efficacy of drug therapy for liver cancer. *Hepatoma Res* 2020;6:60. <http://dx.doi.org/10.20517/2394-5079.2020.52>

Abstract

Hepatocellular carcinoma (HCC) is a poor prognosis tumor when not accessible to potentially curative treatments such as surgical resection, thermal ablations or liver transplantation. Systemic cytotoxic chemotherapies have shown inconsistent clinical benefit. In 2007, sorafenib, a tyrosine kinase inhibitor (TKI), was the first systemic therapy able to significantly improve the outcome of HCC patients non-eligible for curative or loco-regional therapies, despite a modest tolerance and low tumor objective response rate (ORR). Among the newer TKIs approved after 2017, lenvatinib was the first to show a striking ORR and demonstrate non-inferiority vs. sorafenib in the first-line setting. Furthermore, phase 3 trials showed the benefit of other TKIs, regorafenib and cabozantinib, and the anti-angiogenic ramucirumab monoclonal antibody, in systemic second-line therapy. Immune checkpoint inhibitors targeting PD1, achieved striking tumor shrinkage in some patients in monotherapy, seeming to be associated with exciting outcomes. Unfortunately, this occurred in too few patients to improve the median overall survival. More recently, the combination of anti-angiogenic drugs targeting the liver microenvironment with PD-1/PD-L1 inhibitors, such as the combination of bevacizumab and atezolizumab, proved to be substantially effective in phase 3, and other combinations of PD-1/PD-L1 and CTLA-4 inhibitors or TKIs have raised a lot of hopes for the systemic treatment of HCC.

Keywords: Hepatocellular carcinoma, therapy, immune checkpoint inhibitors, tyrosine kinase inhibitors

Review

Alternative approach of hepatocellular carcinoma surveillance: abbreviated MRI

[Full-Text](#) [PDF](#)

Copy here to cite this article: Brunsing RL, Fowler KJ, Yokoo T, Cunha GM, Sirlin CB, Marks RM. Alternative approach of hepatocellular carcinoma surveillance: abbreviated MRI. *Hepatoma Res* 2020;6:59. <http://dx.doi.org/10.20517/2394-5079.2020.50>

Abstract

This review focuses on emerging abbreviated magnetic resonance imaging (AMRI) surveillance of patients with chronic liver disease for hepatocellular carcinoma (HCC). This surveillance strategy has been proposed as a high-sensitivity alternative to ultrasound for identification of patients with early-stage HCC, particularly in patients with cirrhosis or obesity, in whom sonographic visualization of small tumors may be compromised. Three general AMRI approaches have been developed and studied in the literature - non-contrast AMRI, dynamic contrast-enhanced AMRI, and hepatobiliary phase contrast-enhanced AMRI - each comprising a small number of selected sequences specifically tailored for HCC detection. The rationale, general technique, advantages and disadvantages, and diagnostic performance of each AMRI approach is explained. Additionally, current gaps in knowledge and future directions are discussed. Based on emerging evidence, we cautiously recommend the use of AMRI for HCC surveillance in situations where ultrasound is

compromised.

Keywords: Abbreviated magnetic resonance imaging, cirrhosis, Hepatitis B, hepatocellular carcinoma, surveillance, magnetic resonance imaging

Review

Contrast-enhanced ultrasound of focal liver masses

[Full-Text](#) [PDF](#)

Copy here to cite this article: Wilson SR, Merrill C. Contrast-enhanced ultrasound of focal liver masses. *Hepatoma Res* 2020;6:57. <http://dx.doi.org/10.20517/2394-5079.2020.48>

Abstract

Non-invasive imaging is the current method of choice for the characterization of frequently discovered focal liver disease. Although historically, contrast-enhanced computed tomography (CT) and magnetic resonance (MR) scans have been selected for this purpose, contrast-enhanced ultrasound (CEUS) now offers a less expensive and safer method to acquire the same information. Performed with the intravenous injection of a microbubble contrast agent, CEUS provides some unique advantages that make it a valuable addition to an imaging toolbox. CEUS is performed in dynamic real-time, providing superior temporal resolution compared to other modalities and allowing detection of enhancement regardless of its timing or duration. CEUS is performed with a purely intravascular contrast agent, providing accurate depiction of the presence of microbubbles in the circulation in all phases of imaging. This compares with CT and MR contrast agents, which have a well-recognized interstitial phase. Resulting discordant imaging may occur especially in the portal venous phase, when CT and MR may show pseudoenhancement from interstitial contrast, while CEUS will accurately show washout in malignant tumors. Lastly, the contrast specific software used to perform CEUS has an excellent subtraction technique, which produces a contrast only image with high sensitivity to enhancement in thin septations and small nodules. CEUS makes a positive contribution to liver mass characterization in any situation.

Keywords: Contrast-enhanced ultrasound, liver, cancer, diagnosis

Review

Can radiotherapy finally “go live” in the management of liver metastases?

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Copy here to cite this article: John RG, Ho F, Appalanaido GK, Chen D, Tey J, Soon YY, Vellayappan BA. Can radiotherapy finally “go live” in the management of liver metastases?. *Hepatoma Res* 2020;6:56. <http://dx.doi.org/10.20517/2394-5079.2020.37>

Abstract

Liver metastases can present synchronously or at different time points. While systemic therapy continues to be the mainstay of treatment for patients with liver metastases, it is unlikely to completely eradicate the disease. Surgical “metastectomy” for patients with limited metastatic burden, particularly from colorectal cancers, has been shown to improve survival. However, owing to medical co-morbidities or tumour location, not all patients are eligible for surgical resection. In recent years, there has been an increase in the use of non-surgical techniques, including high dose radiation using stereotactic body radiotherapy, or brachytherapy, to ablate liver metastases. The purpose of this narrative review is to describe the role of radiotherapy in the management of liver metastases, both for local ablation and symptom palliation. We will elaborate

on the techniques used, patient selection process, expected outcomes and toxicities based on the current literature.

Keywords: Radiotherapy, stereotactic body radiotherapy, liver metastases, brachytherapy, palliation

Review

Role of imaging in management of hepatocellular carcinoma: surveillance, diagnosis, and treatment response

[Full-Text](#) [PDF](#)

Copy here to cite this article: Osho A, Rich NE, Singal AG. Role of imaging in management of hepatocellular carcinoma: surveillance, diagnosis, and treatment response. *Hepatoma Res* 2020;6:55. <http://dx.doi.org/10.20517/2394-5079.2020.42>

Abstract

Imaging plays a notable role in hepatocellular carcinoma (HCC) surveillance, diagnosis, and treatment response assessment. Whereas HCC surveillance among at-risk patients, including those with cirrhosis, has traditionally been ultrasound-based, there are increasing data showing that this strategy is operator-dependent and has insufficient sensitivity when used alone. Several novel blood-based and imaging modalities are currently being evaluated to increase sensitivity for early HCC detection. Multi-phase computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) should be performed in patients with positive surveillance tests to confirm a diagnosis of HCC and perform cancer staging, as needed. HCC is a unique cancer in that most cases can be diagnosed radiographically without histological confirmation when demonstrating characteristic features such as arterial phase hyperenhancement and delayed phase washout. The Liver Imaging Reporting and Data System offers a standardized nomenclature for reporting CT or MRI liver findings among at-risk patients. Finally, cross-sectional imaging plays a critical role for assessing response to any HCC therapy as well as monitoring for HCC recurrence in those who achieve complete response.

Keywords: Liver cancer, ultrasound, screening, computed tomography, magnetic resonance imaging, contrast-enhanced ultrasound, Liver Imaging Reporting and Data System

Original Article

Validation of novel Japanese indication criteria and biomarkers among living donor liver transplantation recipients with hepatocellular carcinoma - a single center retrospective study

[Full-Text](#) [PDF](#)

Copy here to cite this article: Ichida A, Akamatsu N, Hasegawa K. Validation of novel Japanese indication criteria and biomarkers among living donor liver transplantation recipients with hepatocellular carcinoma - a single center retrospective study. *Hepatoma Res* 2020;6:54. <http://dx.doi.org/10.20517/2394-5079.2020.59>

Abstract

Aim: To validate a novel Japanese indication criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC), i.e., the 5-5-500 criteria (nodule size \leq 5 cm in diameter, nodule number \leq 5, and alfa-fetoprotein (AFP) value \leq 500 ng/mL) and the Japanese double eligibility criteria (DEC) (patients meeting the Milan or the 5-5-500 criteria) in the University of Tokyo cohort. The usefulness of biomarkers in predicting the recurrence of HCC was also verified.

Methods: The overall survival and recurrence rates of patients meeting the Milan, 5-5-500, and the Japanese DEC were compared among 153 patients who underwent living donor LT (LDLT) between 1996 and 2019. A receiver-operating characteristics curve analysis was conducted to evaluate the usefulness of AFP, lens culinaris agglutinin-reactive fraction of AFP, des-gamma-carboxy prothrombin, neutrophil-lymphocyte ratio, and the platelet-lymphocyte ratio to detect recurrence.

Results: The 5-year recurrence rate for all patients, those meeting the Japanese DEC, 5-5-500 criteria, and the Milan criteria was 10.9%, 9.2%, 7.4%, and 7.6%, respectively. Compared with the conventional Milan criteria, the 5-5-500 criteria and the Japanese DEC could increase the number of eligible LDLT candidates by 6.1% and 11.4%. Among five biomarkers, the area under the curve value of AFP was the highest (0.852).

Conclusion: The results suggest that the 5-5-500 criteria and the Japanese DEC are the appropriate selection criteria for patients with HCC in LDLT. Among five biomarkers investigated, AFP was most reliable to predict HCC recurrence, which justified the utilization of AFP in the 5-5-500 criteria and the Japanese DEC.

Keywords: Indication criteria of liver transplantation for hepatocellular carcinoma, the 5-5-500 criteria, the Japanese double eligibility criteria, alfa-fetoprotein, the lens culinaris agglutinin-reactive fraction of alfa-fetoprotein, the des-gamma-carboxy prothrombin, the neutrophil-lymphocyte ratio, the platelet-lymphocyte ratio

Review

Contrast-enhanced ultrasound liver reporting and data system for hepatocellular carcinoma diagnosis

[Full-Text](#) [PDF](#)

Copy here to cite this article: Vezeridis AM, Kono Y. Contrast-enhanced ultrasound liver reporting and data system for hepatocellular carcinoma diagnosis. *Hepatoma Res* 2020;6:53. <http://dx.doi.org/10.20517/2394-5079.2020.36>

Abstract

Contrast-enhanced ultrasound (CEUS) is a powerful imaging modality for the diagnosis of focal liver lesions, including hepatocellular carcinoma (HCC). The American College of Radiology Contrast-Enhanced Ultrasound Liver Reporting and Data System (CEUS LI-RADS®) was created as a standardized reporting system to facilitate consistent and high-quality technique, interpretation, reporting, and data collection for CEUS diagnosis of HCC. This article describes the history and background of CEUS LI-RADS®, its major concepts and algorithm, and the differences between CEUS LI-RADS® and CT/MRI LI-RADS®.

Keywords: Contrast-enhanced ultrasound, LI-RADS, hepatocellular carcinoma, diagnosis

Systematic Review

Global pattern and trend of liver cancer survival: a systematic review of population-based studies

[Full-Text](#) [PDF](#)

Copy here to cite this article: Jiang YF, Li ZY, Ji XW, Shen QM, Tuo JY, Yuan HY, Xiang YB. Global pattern and trend of liver cancer survival: a systematic review of population-based studies. *Hepatoma Res* 2020;6:52. <http://dx.doi.org/10.20517/2394-5079.2020.47>

Abstract

Aim: To describe the global pattern and trend of liver cancer survival, using data from the population-based studies or cancer registration.

Methods: By searching CNKI, Wanfang Data, PubMed, Web of Science, EMBASE and SEER. All population-based survival studies of liver cancer from 1 January 2000 to 30 April 2020 were collected and evaluated by patient gender, time period, and country. The overall or age-standardized five-year relative survival rate was used to describe the pattern and changes in liver cancer survival over the past decades.

Results: Globally, the highest age-standardized five-year relative survival rate was observed in Italy (18.0%, 2005-2007) and the highest overall five-year relative survival rate was observed in Korea (34.6%, 2012-2016), when compared to other countries. The most remarkable increase in overall five-year relative survival rate can be seen in Korea (from 10.7% during 1993-1995 to 34.6% during 2012-2016). In general, worldwide, the five-year relative survival rate of younger patients with liver cancer was higher than old people. For most countries, the five-year relative survival rate of liver cancer was slightly higher in women than in men. In China, the overall five-year relative survival rate of liver cancer in Taiwan was higher than that in other areas, while Cixian of Hebei and Qidong of Jiangsu were lower.

Conclusion: Over the past decades, the survival rates of liver cancer have gradually improved, but great variations are also observed globally. Worldwide, younger patients with liver cancer have experienced a better prognosis. Gender disparity in liver cancer survival was not obvious.

Keywords: Primary liver cancer, relative survival rate, prognosis, population-based study, cancer registration

Review

Liver imaging reporting and data system and CT/MRI diagnosis of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Kanmaniraja D, Chernyak V. Liver imaging reporting and data system and CT/MRI diagnosis of hepatocellular carcinoma. *Hepatoma Res* 2020;6:51. <http://dx.doi.org/10.20517/2394-5079.2020.46>

Abstract

The Liver Imaging Reporting and Data System (LI-RADS) is a comprehensive and robust system which provides an algorithmic approach to stratify the probability of hepatocellular carcinoma (HCC) for each observation found in patients at risk for HCC. LI-RADS uses a standardized terminology and approach to improve communication between the radiologist and clinicians. LI-RADS version 2018 is noteworthy for its adoption by the American Association for the Study of Liver Disease into its HCC practice guidance. This manuscript provides an overview of the history of LI-RADS, reviews the Computed tomography/magnetic resonance imaging diagnostic algorithm, highlights the key diagnostic criteria for each category, and discusses the advantage of incorporating LI-RADS in clinical practice.

Keywords: Liver Imaging Reporting and Data System, hepatocellular carcinoma, cirrhosis, hepatocellular carcinoma diagnosis

Review

Risk factors for hepatocellular carcinoma recurrence after liver transplantation

[Full-Text](#) [PDF](#)

Copy here to cite this article: Toniutto P, Fornasiere E, Fumolo E, Bitetto D. Risk factors for hepatocellular carcinoma recurrence after liver transplantation. *Hepatoma Res* 2020;6:50. <http://dx.doi.org/10.20517/2394-5079.2020.40>

Abstract

Liver transplantation (LT) provides an excellent option for the long-term survival of patients with unresectable hepatocellular carcinoma (HCC) based on the Milan criteria. Despite careful selection of patients, HCC may still recur after LT, which represents the most important negative predictor of post-transplant survival. The growing demand for LT in HCC has led to the expansion of patient selection criteria, with a resultant increase in the risk of post-transplant HCC recurrence. Numerous tumor and host factors predict HCC recurrence. The morphological, histological, and serological characteristics of tumors in predicting HCC recurrence have been extensively studied. Furthermore, the type and duration of anticancer response before LT has also been considered a surrogate marker of tumor aggressiveness and is associated with the risk of recurrence. The demographic and clinical characteristics of recipients, as well as the type and duration of exposure to immunosuppressive therapy, represent the main host-related risk factors. Many studies have attempted to describe predictive models for the risk of HCC recurrence, considering evaluable parameters both before and after LT. Although many models have been proposed, relatively few have been externally validated on different patient populations. This paper aims to comprehensively summarize the available data on the predictive factors of HCC recurrence after LT, and to examine and discuss those that have been externally validated.

Keywords: Liver transplantation, hepatocellular carcinoma, tumor recurrence, risk predictive model

Case Report

Combined transarterial chemoembolization and stereotactic body radiation therapy as a bridge therapy to liver transplant for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Bieu BQ, Chau ND, Kien NX, Van Thanh L, Van Quang V, Ky TD, Thinh NT, Bang MH. Combined transarterial chemoembolization and stereotactic body radiation therapy as a bridge therapy to liver transplant for hepatocellular carcinoma. *Hepatoma Res* 2020;6:49. <http://dx.doi.org/10.20517/2394-5079.2020.39>

Abstract

Liver transplant (LT) is the curative treatment for patients with hepatocellular carcinoma (HCC). Bridge therapies are local treatments given to patients on the LT waitlist, to prevent tumor progression and to reduce the dropout rate. Case presentation: We reported a 40-year-old man diagnosed with Barcelona-Clinic Liver Cancer BCLC intermediate stage HCC and Child-Pugh A5 hepatitis B virus cirrhosis who underwent combined bridge therapies to LT. Firstly, the patient received transarterial chemoembolization (TACE) for two times and showed a partial response. Then he underwent stereotactic body radiation therapy (SBRT) with a total dose of 45 Gy in 3 fractions. Three months later, the tumor size and serum protein induced by Vitamin K absence or antagonists-II, alpha fetoprotein levels decreased gradually. In June 2019 a suitable donor was found and his LT was successfully performed. Conclusion: We propose that a combination of

TACE and SBRT was feasible as bridge therapy for HCC patients on the LT waitlist.

Keywords: Transarterial chemoembolization, stereotactic body radiation therapy, bridge therapy, hepatocellular carcinoma, liver transplant

Review

Pathomolecular characterization of HCC in non-cirrhotic livers

[Full-Text](#) [PDF](#)

Copy here to cite this article: Rastogi A. Pathomolecular characterization of HCC in non-cirrhotic livers. *Hepatoma Res* 2020;6:47. <http://dx.doi.org/10.20517/2394-5079.2020.35>

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and usually arises in cirrhotic livers. Increasingly, it is diagnosed in non-cirrhotic livers. A variety of risk factors and etiologies can trigger the development of HCC in non-fibrotic and non-cirrhotic backgrounds. The most important causes are metabolic syndrome and hepatitis B virus infection. Postulated pathogenetic mechanisms are direct carcinogenesis, chronic liver injury and repair cycles, and genetic/epigenetic aberrations. Histopathology has a very important role in the diagnosis of non-cirrhotic HCC. Gross features of non-cirrhotic HCC are quite different from HCC originating in a cirrhotic background. Microscopic characteristics are similar to a classical HCC. However, certain histological variants show a predilection to occur in non-cirrhotic livers. These encompass fibrolamellar, scirrhous, steatohepatic and mixed hepato-cholangiocarcinoma subtypes. Due to the non-cirrhotic background, adenoma, metastasis and most of the other non-neoplastic and neoplastic conditions enter the differential diagnosis. Genomic studies and morpho-molecular classifications of HCC provide further understanding of the molecular pathogenesis of non-cirrhotic HCC. This group however, has rarely been exclusively studied. This review offers an update of etiology, patho-molecular characteristics and differential diagnosis of HCC arising in non-cirrhotic backgrounds.

Keywords: Hepatocellular carcinoma, non-cirrhotic, etiopathogenesis, molecular genetics, pathology, patho-molecular, differential diagnosis

Review

Contrast-enhanced ultrasonography with Sonazoid in hepatocellular carcinoma diagnosis

[Full-Text](#) [PDF](#)

Copy here to cite this article: Minami Y, Kudo M. Contrast-enhanced ultrasonography with Sonazoid in hepatocellular carcinoma diagnosis. *Hepatoma Res* 2020;6:46. <http://dx.doi.org/10.20517/2394-5079.2020.32>

Abstract

With the development of second-generation contrast agents and advancement in contrast harmonic imaging, contrast-enhanced ultrasonography (CEUS) now has the capacity to sensitively and accurately show tumor vascularity. Therefore, marked improvements have been achieved in the diagnosis of focal liver lesions (FLLs), including hepatocellular carcinoma (HCC), by US. In contrast to other agents, Kupffer cells in liver sinusoids take up Sonazoid. Two contrast enhancement phases occur in CEUS with Sonazoid: a vascular phase and Kupffer phase. Images obtained in the Kupffer phase have higher diagnostic sensitivity for hepatic malignancies because the majority of these malignancies do not contain Kupffer cells. Dynamic images obtained in the

vascular phase markedly narrow the clinical differential diagnoses of FLLs. The sustainable detection of inconspicuous HCC, adequate guidance of ablation therapy, and accurate assessment of treatment responses in HCC are all facilitated by Sonazoid. The principles, clinical applications, and techniques of CEUS with Sonazoid in the diagnosis of HCC will be reviewed herein.

Keywords: Contrast-enhanced ultrasonography, focal liver lesion, hepatocellular carcinoma, sonazoid

Case Report

Long-term survival of occult hepatitis B associated hepatocellular carcinoma following surgery and antiviral therapy

[Full-Text](#) [PDF](#)

Copy here to cite this article: Boortalary T, Rosato E, Roth C, Ren XD, Lin SY, Hann HW. Long-term survival of occult hepatitis B associated hepatocellular carcinoma following surgery and antiviral therapy. *Hepatoma Res* 2020;6:48. <http://dx.doi.org/10.20517/2394-5079.2020.38>

Abstract

Occult hepatitis B infection (OBI) is characterized by absent hepatitis B surface antigen (HBsAg), low or undetectable serum hepatitis B viral DNA (HBV-DNA), and detectable DNA in the liver. There is debate over whether OBI increases the risk of hepatocellular carcinoma (HCC). We present a patient with negative HBsAg and a large HCC tumor who underwent a large right hepatic lobectomy. Initially, the etiology of HCC was unknown, but through more sensitive molecular testing, it was believed to be due to OBI. In this case report, we discuss the patient's clinical course, the effect of antiviral therapy, mechanism of carcinogenesis in OBI, and the need for more rigorous HBV DNA assay testing for the detection of OBI.

Keywords: Occult hepatitis B infection, OBI-associated HCC, HBsAg negative HCC

Case Report

First cases of MPV17 related mitochondrial DNA depletion syndrome with compound heterozygous mutations in p.R50Q/p.R50W: a case report

[Full-Text](#) [PDF](#)

Copy here to cite this article: Umetsu S, Inui A, Kobayashi S, Shimura M, Uehara T, Uchida H, Irie R, Sogo T, Komatsu H, Yoshioka T, Murayama K, Kosaki K, Kasahara M, Fujisawa T. First cases of MPV17 related mitochondrial DNA depletion syndrome with compound heterozygous mutations in p.R50Q/p.R50W: a case report. *Hepatoma Res* 2020;6:1. <http://dx.doi.org/10.20517/2394-5079.2019.030>

Abstract

Mutations in MPV17 lead to severe mitochondrial DNA depletion syndrome (MTDPS). All known p.R50W variants in MPV17 are lethal. The homozygous variant p.R50Q in MPV17 among patients with Navajo neurohepatopathy is known to allow longer survival, although heterozygous variants p.R50Q have not been reported. This is the first clinical report in compound heterozygosity MPV17 mutation (p.R50W/p.R50Q). Three siblings were admitted due to multiple hepatic nodules; none presented neurological abnormalities. However, they suffered from severe hypoglycemia and cyclic vomiting. The diagnosis of MPV17-related MTDPS was confirmed by detection of a compound heterozygous MPV17 mutation (p.R50W/p.R50Q), and striking reduction of hepatic mitochondrial DNA. One patient developed pediatric-onset of hepatocellular

carcinoma. Notably, all patients survived for extended periods, including two patients who received liver transplantation, which contrasted the high mortality rate associated with p.R50W mutations, as previously reported. The p.R50Q mutation might be associated with longer survival and improved liver transplantation outcomes.

Keywords: Mitochondrial DNA depletion syndrome, MPV17, compound heterozygous mutation, liver transplantation

Original Article

Interim results from ongoing Phase III placebo-controlled, randomized trial of hepcortespenlisimut-L for advanced hepatocellular carcinoma indication

[Full-Text](#) [PDF](#)

Copy here to cite this article: Bourinbaier AS, Chinburen J, Batchuluun P, Munkhzaya C, Oyungerel D, Dandii D, Kutsyna GA, Tsogkhuu H, Tarakanovskaya MG, Reid AA, Borisova V, Bain AI, Jirathitikal V. Interim results from ongoing Phase III placebo-controlled, randomized trial of hepcortespenlisimut-L for advanced hepatocellular carcinoma indication. *Hepatoma Res* 2020;6:2. <http://dx.doi.org/10.20517/2394-5079.2019.25>

Abstract

Aim: We aimed to further investigate the role of hepcortespenlisimut-L (Hepko-V5 or V5), a new oral immunotherapy developed by us, for hepatocellular carcinoma (HCC) indication.

Methods: The interim data from ongoing Phase III placebo-controlled, randomized trial were evaluated on the initial group of patients in advanced stage of HCC with emphasis on liver function and tumor marker alpha-fetoprotein levels. Additionally, an in vitro study was undertaken to elucidate the mechanism of action of V5 by measuring with flow cytometry the expression of cytokines such as IL-2, INF- γ , and TNF- α and cell activation markers CD69 and Ki67 on CD4- and CD8-positive lymphocytes isolated from peripheral blood of healthy volunteers.

Results: As early as one month after treatment initiation, there was a clear improvement in alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin levels among HCC patients who received daily dose of V5, but not in the placebo group. Additionally, alpha-fetoprotein (AFP) levels among V5 recipients decreased, while in the placebo group they rose. Clinical results are in line with in vitro observations indicating immune activation, as evidenced by many-fold enhancement of CD69, Ki67, and INF- γ expression and at the same time marked anti-inflammatory effect resulting in 10-fold decrease in TNF- α output and lack of influence on IL-2 production.

Conclusion: Hepcortespenlisimut-L, a tableted oral formulation derived from heat-inactivated pooled blood of patients with HCC and viral hepatitis shows beneficial clinical effect, as demonstrated by improvement in liver function and reduction of tumor marker AFP levels. These correlate with in vitro observations showing potent activation of the immune response and pronounced oral tolerance effect.

Keywords: Hepatocellular carcinoma, alpha-fetoprotein, alanine transaminase, aspartate transaminase, IL-2, INF- γ , TNF- α , CD69, Ki67, CD4, CD8, T lymphocytes

Original Article

Response rates to direct antiviral agents among hepatitis C virus infected patients who develop hepatocellular carcinoma following direct antiviral agents treatment

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Burlone ME, Fangazio S, Croce A, Ceriani E, Rapetti R, Rigamonti C, Smirne C, Tonello S, Ravanini P, Minisini R, Pirisi M. Response rates to direct antiviral agents among hepatitis C virus infected patients who develop hepatocellular carcinoma following direct antiviral agents treatment. *Hepatoma Res* 2020;6:3. <http://dx.doi.org/10.20517/2394-5079.2019.37>

Abstract

Aim: Patients with chronic hepatitis C virus (HCV) infection who develop hepatocellular carcinoma (HCC) soon after treatment with direct antiviral agents (DAA) may have been harboring hitherto hidden tumors. If this were true, they should have a lower sustained viral response (SVR) rate, since active HCC hampers DAA efficacy. We aimed to verify this hypothesis.

Methods: We included all patients who attended an HCV clinic, provided that they: (1) had no previous history of HCC; (2) had received at least one DAA dose; and (3) had been followed-up clinically and ultrasonographically for at least six months after concluding DAA.

Results: The study population included n = 789 patients (55% males, median age 62 years). A median of 9.3 months (8.8-11.9) after concluding DAA, n = 19 (2.4%) patients were discovered to harbor HCC. In comparison to all others, patients with HCC were more commonly male (84% vs. 54%, P = 0.009), obese (47% vs. 17%, P = 0.002), and cirrhotic (95% vs. 35%, P < 0.001) and had less commonly achieved an SVR (68% vs. 98%, P < 0.001). Moreover, they had a trend for being less commonly treatment naïve (58% vs. 67%, P = 0.051). Based on multivariate analysis, the independent predictors of HCC were male sex (P = 0.031), cirrhosis (P = 0.004), obesity (P = 0.006), and failure to achieve an SVR (P < 0.001).

Conclusion: Lack of achieving SVR is a strong independent predictor of development of HCC early after treatment of hepatitis C with DAA. Treatment failure should further alert clinicians to the possibility of this dreadful complication.

Keywords: Chronic hepatitis C, direct antiviral agent, sustained viral response, hepatocellular carcinoma, obesity, cirrhosis

Review

Frailty and Liver resection: where do we stand?

[Full-Text](#) [PDF](#)

Copy here to cite this article: Sioutas GS, Ziogas IA, Tsoulfas G. Frailty and Liver resection: where do we stand?. *Hepatoma Res* 2020;6:4. <http://dx.doi.org/10.20517/2394-5079.2019.43>

Abstract

As the world population is continuously aging, the number of older patients requiring liver surgery is also on the rise. Data have shown that age should not be a limiting factor for liver resection, as it cannot accurately predict postoperative outcomes. Instead, frailty can serve as a more reliable measure of the patient's overall health and functional reserves. Several frailty assessment tools have been implemented for preoperative risk stratification before liver surgery, and higher scores have commonly been associated with postoperative morbidity, mortality, and length of hospital stay. However, no consensus has been reached on the most useful screening tool. Future studies should focus on comparing the currently available assessment tools, constructing a liver resection-specific tool, and assessing the role of frailty assessment tools in preoperative patient

optimization.

Keywords: Frailty, age, elderly, liver resection, liver surgery, morbidity, morbidity, complications

Review

The mechanism of dysbiosis in alcoholic liver disease leading to liver cancer

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Copy here to cite this article:

Méndez-Sánchez N, Valencia-Rodríguez A, Vera-Barajas A, Abenavoli L, Scarpellini E, Ponciano-Rodríguez G, Wang DQH. The mechanism of dysbiosis in alcoholic liver disease leading to liver cancer. *Hepatoma Res* 2020;6:5. <http://dx.doi.org/10.20517/2394-5079.2019.29>

Abstract

Currently, alcoholic liver disease (ALD) is one of the most prevalent chronic liver diseases worldwide, representing one of the main etiologies of cirrhosis and hepatocellular carcinoma (HCC). Although we do not know the exact mechanisms by which only a selected group of patients with ALD progress to the final stage of HCC, the role of the gut microbiota within the progression to HCC has been intensively studied in recent years. To date, we know that alcohol-induced gut dysbiosis is an important feature of ALD with important repercussions on the severity of this disease. In essence, an increased metabolism of ethanol in the gut induced by an excessive alcohol consumption promotes gut dysfunction and bacterial overgrowth, setting a leaky gut. This causes the translocation of bacteria, endotoxins, and ethanol metabolites across the enterohepatic circulation reaching the liver, where the recognition of the pathogen-associated molecular patterns via specific Toll-like receptors of liver cells will induce the activation of the nuclear factor kappa-B pathway, which releases pro-inflammatory cytokines and chemokines. In addition, the mitogenic activity of hepatocytes will be promoted and cellular apoptosis will be inhibited, resulting in the development of HCC. In this context, it is not surprising that microbiota-regulating drugs have proven effectiveness in prolonging the overall survival of patients with HCC, making attractive the implementation of these drugs as co-adjuvant for HCC treatment.

Keywords: Alcoholic liver disease, gut microbiota, dysbiosis, hepatocellular carcinoma

Review

Coffee protection against the development of hepatocellular carcinoma: review article

[Full-Text](#) [PDF](#)

Copy here to cite this article: Carvalho KSD, Cotrim HP. Coffee protection against the development of hepatocellular carcinoma: review article. *Hepatoma Res* 2020;6:6. <http://dx.doi.org/10.20517/2394-5079.2019.027>

Abstract

Coffee, a popular drink around the world, is composed of a complex mix of biologically active molecules, including caffeine, chlorogenic acid, and diterpenes. These compounds have antioxidant, anti-inflammatory, antifibrotic, and anticarcinogenic properties, which may explain observational data showing that coffee drinkers have lower rates of chronic liver disease, including cirrhosis and hepatocellular carcinoma (HCC). Recent studies have also shown that coffee consumption may also increase patient survival before and after liver transplantation. The mechanism by which coffee consumption protects against HCC is not clear; however, its relevant

role has been demonstrated. This literature review article focuses on the role of coffee consumption in protecting against the development of HCC. Methodology: Scientific articles indexed through PubMed, including Medline, Scielo, and Lilacs, published in English were used as search methods. The terms used in English were: “hepatocellular carcinoma” or “Liver cancer” or “HCC” and “coffee”. According to the study design or review article, cross-sectional, longitudinal, or descriptive investigations were included, showing site and year of publication until 2019.

Keywords: Hepatocellular carcinoma, coffee consumption protection, liver cancer

Review

Animal models for hepatocellular carcinoma arising from alcoholic and metabolic liver diseases

[Full-Text](#) [PDF](#)

Copy here to cite this article: Liu K, Chen J, McCaughan GW. Animal models for hepatocellular carcinoma arising from alcoholic and metabolic liver diseases. *Hepatoma Res* 2020;6:7. <http://dx.doi.org/10.20517/2394-5079.2019.39>

Abstract

Hepatocellular carcinoma (HCC) is a major and increasing cause of clinical and economic burden worldwide. Now that there are effective therapies to control or eradicate viral aetiologies, the landscape of HCC is changing with alcoholic and metabolic liver diseases becoming major catalysts. The pathogenesis of HCC is complex and incompletely understood, hampering improvements in therapy. Animal models are essential tools for advancing study on the cellular and molecular processes in HCC and for screening potential novel therapies. Many models of hepatocarcinogenesis have been established using various methods including genetic engineering, chemotoxic agents and dietary manipulation to direct implantation of tumour cells. However, none of these can accurately replicate all features found in human diseases. In this review, we provide an overview of different mouse models of HCC with a particular focus on cancer arising from alcoholic liver disease, non-alcoholic fatty liver disease and hereditary haemochromatosis. We also highlight their strengths and limitations and provide perspectives for future study.

Keywords: Hepatocellular carcinoma, animal models, mouse models, non-alcoholic fatty liver disease, alcohol, haemochromatosis

Review

The interplay between direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C

[Full-Text](#) [PDF](#)

Copy here to cite this article: Yoo SH, Kwon JH. The interplay between direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C. *Hepatoma Res* 2020;6:9. <http://dx.doi.org/10.20517/2394-5079.2019.49>

Abstract

Direct-acting antivirals (DAAs) have been introduced for the treatment of hepatitis C virus, and the sustained virological response rate after DAAs was reported to be over 95%. Because of the high sustained virological response rate, the risk of hepatocellular carcinoma (HCC) was expected to be reduced. However, an unexpected high risk of HCC recurrence after DAA treatment was

reported, and thus the dispute about the association of DAA and HCC arose. The present article reviews the interplay between DAAs and HCC.

Keywords: Chronic hepatitis C, hepatocellular carcinoma, direct-acting antivirals

Review

Association between hereditary hemochromatosis and hepatocellular carcinoma: a comprehensive review

[Full-Text](#) [PDF](#)

Copy here to cite this article: Jayachandran A, Shrestha R, Bridle KR, Crawford DHG. Association between hereditary hemochromatosis and hepatocellular carcinoma: a comprehensive review. *Hepatoma Res* 2020;6:8. <http://dx.doi.org/10.20517/2394-5079.2019.35>

Abstract

Hepatocellular carcinoma (HCC) is a significant global health problem with high morbidity and mortality. Its incidence is increasing exponentially worldwide with a close overlap between annual incidence and death rates. Even though significant advances have been made in HCC treatment, fewer than 20% of patients with HCC are suitable for potentially curative treatment. Hereditary hemochromatosis (HH) is an important genetic risk factor for HCC. HH is an autosomal recessive disorder of iron metabolism, characterised by elevated iron deposition in most organs including the liver, leading to progressive organ dysfunction. HCC is a complication of HH, nearly always occurring in patients with cirrhosis and contributes to increased mortality rates. Identifying the susceptibility of development of HCC in HH patients has gained much traction. This review summarises the current knowledge with regard to the association of HH and HCC in order to encourage further research. In this review, we focus particularly on HFE gene-related HH. Herein, we highlight and discuss emerging clinical research which addresses the prevalence of HCC in HH patients and the coincidence of HH with other risk factors for HCC development. We also focus on the therapeutic tools in the management of HCC associated with HH.

Keywords: Hepatocellular carcinoma, hereditary hemochromatosis, HFE gene, C282Y mutation, H63D mutation, liver cirrhosis

Original Article

Recurrence of hepatocellular carcinoma following deceased donor liver transplantation: case series

[Full-Text](#) [PDF](#)

Copy here to cite this article: Simsek C, Kim A, Ma M, Danis N, Gurakar M, Cameron AM, Philippe B, Garonzik-Wang J, Ottmann S, Gurakar A, Saberi B. Recurrence of hepatocellular carcinoma following deceased donor liver transplantation: case series. *Hepatoma Res* 2020;6:11. <http://dx.doi.org/10.20517/2394-5079.2019.51>

Abstract

Aim: We aimed to study the clinical and pathological characteristics of liver transplant recipients with hepatocellular carcinoma recurrence.

Methods: We reviewed the data for 26 patients who had tumor recurrence after deceased donor liver transplant for hepatocellular carcinoma at the Johns Hopkins Hospital from January 2005 to December 2015.

Results: In total, 88% of recipients were males. The mean age was 59 years. On explant, poor

differentiation was detected in 43%, while 73% had microvascular invasion. Overall, 62% were diagnosed to be outside of Milan criteria. Out of these, 15% met the criteria for downstaging. Twenty (77%) patients had pre-transplant alpha fetoprotein levels ≥ 20 ng/mL. In 54% of patients, the location of hepatocellular carcinoma (HCC) recurrence was extrahepatic, followed by intrahepatic in 31% and both intra- and extrahepatic in 15%. The post-transplant tumor recurrence was diagnosed at a mean of 427 days (range 34-1502). Fifty percent of HCC recurrences were diagnosed within one year following liver transplant. Twenty (77%) patients received treatment for their recurrent HCC: external radiation (n = 10), surgical resections (n = 8; brain 4, spine 2, bone 1, and Whipple surgery 1), sorafenib (n = 7), locoregional therapy (n = 5). Overall, 24 out of 26 (92%) recipients died within four years after the transplant.

Conclusion: HCC recurrence after liver transplant is infrequent. More than fifty percent of HCC recurrences following liver transplant are extrahepatic. Despite better recipient selection for liver transplant, the curative options are limited in recurrent cases and associated with extremely poor outcomes.

Keywords: Hepatocellular carcinoma, liver transplant, liver resection, locoregional therapy

Original Article

Microwave ablation of hepatocellular carcinomas in octogenarians

[Full-Text](#) [PDF](#)

Copy here to cite this article: Freedman J. Microwave ablation of hepatocellular carcinomas in octogenarians. *Hepatoma Res* 2020;6:10. <http://dx.doi.org/10.20517/2394-5079.2019.32>

Abstract

Aim: To evaluate whether it is safe and meaningful to treat octogenarians with microwave ablation for hepatocellular carcinoma. With an ageing population being healthier than previous generations, old limits for treating disease founded on patient age need to be revised. One of the most common tumour related death causes is hepatocellular carcinoma (HCC). With the development of minimally invasive therapies with curative potential, new ground is being broken offering treatments to older patients in the hope of achieving prolongation and better quality of life.

Methods: In this retrospective single centre study of patients having a first microwave ablation therapy for HCC in a national referral centre for ablative liver treatments, septuagenarians (n = 161, age 70-80) were compared with octogenarians (n = 32, age 80-90).

Results: Octogenarians selected for microwave ablation of HCC at a regional multidisciplinary team conference have similar outcomes as their younger control group. Survival, complications and length of stay are not different.

Conclusion: Octogenarians who are fit for ablative treatment of HCC should not be disqualified on grounds of age, recognising that this group has an obvious immortality, or lead-time, bias as well as a probable selection bias in part explaining their good results.

Keywords: Microwave, ablation, hepatocellular carcinoma, octogenarians, survival, complications

Review

Prehabilitation in elderly patients scheduled for liver resection and protocol for Recovery Of Surgery in Elderly

[Full-Text](#) [PDF](#)

Copy here to cite this article: Mohan R, Huey CWT, Junnarkar S, Low JK, Shelat VG. Prehabilitation in elderly patients scheduled for liver resection and protocol for Recovery Of Surgery in Elderly. *Hepatoma Res* 2020;6:13. <http://dx.doi.org/10.20517/2394-5079.2019.53>

Abstract

Ageing population of first world economies pose unique challenges to surgical community. Enhanced recovery after surgery protocols and pathways do not attempt to optimize or enhance physical function of patients by customized program of physical activity. Increasingly, prehabilitation programs (PP) have gained momentum in orthopaedics, urology, colorectal surgery and hepatopancreaticobiliary surgery. Current evidence of PP in various elective surgical procedures have shown improved outcomes with minimal to none drawback or harm. There is emerging evidence of role of PP in elective liver resection. The aim of this paper is to review the basis of PP and share local multidisciplinary team protocol specifically customized to frail and elderly population - Recovery Of Surgery in Elderly.

Keywords: Prehabilitation, liver resection, hepatocellular carcinoma, pre-operative exercise, ageing

Original Article

Distinctive magnetic resonance imaging findings of hepatocellular carcinoma after hepatitis C virus eradication with direct-acting antivirals

[Full-Text](#) [PDF](#)

Copy here to cite this article: Shimizu T, Tsuchiya K, Kurosaki M, Yasui Y, Kirino S, Watakabe K, Osawa L, Okada M, Wang W, Higuchi M, Takaura K, Kaneko S, Tamaki N, Nakanishi H, Itakura J, Takahashi Y, Hisamatsu T, Izumi N. Distinctive magnetic resonance imaging findings of hepatocellular carcinoma after hepatitis C virus eradication with direct-acting antivirals. *Hepatoma Res* 2020;6:12. <http://dx.doi.org/10.20517/2394-5079.2019.48>

Abstract

Aim: The aim of the present study was to evaluate the characteristics of the magnetic resonance imaging features of hepatocellular carcinoma (HCC) that developed early after the eradication of hepatitis C virus (HCV) by direct-acting antiviral (DAA) treatment.

Methods: This study included 26 patients who achieved sustained viral response with DAA and developed HCC thereafter within one year (DAA-SVR HCC). The radiologic characteristics of these patients were evaluated by contrast-enhanced magnetic resonance imaging, including diffusion-weighted imaging (DWI) and T2-weighted imaging (T2WI). For comparison, 80 HCC patients with positive HCV RNA (HCV-positive HCC) were included. Among 42 patients where tumor biopsy was available, histological grade and radiologic findings were compared.

Results: The rates of high intensity on DWI and T2WI were significantly higher in DAA-SVR HCC compared to HCV-positive HCC (DWI: 100% vs. 67.5%, $P < 0.001$; T2WI: 92.6% vs. 67.5%, $P = 0.01$). HCC with high intensity on DWI or T2WI was more likely to have moderately or poorly differentiated HCC compared to well-differentiated HCC (DWI: 69.7% vs. 30.3%, $P = 0.02$; T2WI: 66.7% vs. 27.3%, $P = 0.03$).

Conclusion: High intensity on DWI and hyperintensity on T2WI were distinctive features of HCC that developed within one year after the end of DAA treatment.

Keywords: Hepatocellular carcinoma, direct-acting antivirals, sustained viral response, contrast enhanced magnetic resonance imaging

Review

Ion channels in liver diseases and hepatocellular carcinoma: potential tools for diagnosis, prognosis, and therapy

[Full-Text](#) [PDF](#)

Copy here to cite this article: de Guadalupe Chávez-López M, Cruz-Díaz A, Tlapalcoyoa-Apanco KN, Pérez-Carreón JI, Camacho J. Ion channels in liver diseases and hepatocellular carcinoma: potential tools for diagnosis, prognosis, and therapy. *Hepatoma Res* 2020;6:14. <http://dx.doi.org/10.20517/2394-5079.2019.023>

Abstract

Cancer is a major cause of death worldwide. Hepatocellular carcinoma (HCC) is one of the malignancies with the highest mortality-to-incidence ratio (> 0.9), and in some countries this value is up to 1. Unfortunately, many patients are diagnosed at advanced stages of the disease. Therefore, HCC early markers, as well as novel therapeutic approaches, are urgently needed. HCC is the main type of liver cancer and it is associated with different factors including alcohol use, viral infections, and fatty liver disease. A significant percentage of HCC patients previously had liver cirrhosis. Several ion channels have been proposed as novel potential markers and therapeutic targets for diverse cancers including HCC. Here, we review most of the findings associating ion channel expression with HCC and its etiological factors, as well as some possible pro-tumorigenic mechanisms of action for ion channels in HCC. Novel therapies for HCC treatment and prevention are also discussed. Ion channel targeting offers a plethora of opportunities for HCC prevention, early diagnosis, and therapy that may help to reduce the extremely high mortality-to-incidence ratio of this malignancy.

Keywords: Ion channels, hepatocellular carcinoma, hepatitis virus, cirrhosis, liver disease, alcohol

Review

Direct acting antivirals therapy and hepatocellular carcinoma risk in patients with hepatitis C virus

[Full-Text](#) [PDF](#)

Copy here to cite this article: Pazgan-Simon M. Direct acting antivirals therapy and hepatocellular carcinoma risk in patients with hepatitis C virus. *Hepatoma Res* 2020;6:17. <http://dx.doi.org/10.20517/2394-5079.2019.52>

Abstract

The estimated number of people with active hepatitis C virus infection worldwide is about 70 million. The estimated number of people with active hepatitis C virus infection worldwide is about 70 million. Approximately 30% of infected individuals develop cirrhosis, whilst some develop liver cancer, the fifth most common cancer worldwide. Currently available treatments, high-efficacy antiviral agents mostly short-term (8-12 weeks) and pangenotypic, have efficacy rates of over 96%. Some patients, especially those with cirrhosis, develop primary liver cancer even after effective hepatitis C virus treatment. In order to diagnose hepatocellular carcinoma early, patients at risk should be enrolled in a surveillance program.

Keywords: Hepatitis C virus, direct acting antivirals treatment, oncogenesis

Review

Cytotoxic immune cell-based immunotherapy for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Li J, Tao L, Wang X. Cytotoxic immune cell-based immunotherapy for hepatocellular carcinoma. *Hepatoma Res* 2020;6:15.

<http://dx.doi.org/10.20517/2394-5079.2019.34>

Abstract

Hepatocellular carcinoma (HCC) is one of the most common solid tumors with poor clinical prognosis. Novel therapeutic regimens are urgently required for patients with advanced HCC. Both pre-clinical and clinical studies suggest immunotherapy as an attractive alternative for advanced HCC treatment. Natural killer (NK) cells and CD8⁺ T cells are the most important cytotoxic immune cells involved in cancer treatment and elimination. Reinvigorating the anticancer activity of NK and CD8⁺ T cells is the fundamental guarantee for the success of immunotherapy in advanced HCC treatment. Therefore, in this review, we aim to summarize the characteristics and roles of NK and CD8⁺ T cells in HCC development, describe the frontiers of immunotherapy for advanced HCC based on immune checkpoint inhibitors and adoptive cell transfer, and discuss their limitations and scope for future improvement.

Keywords: Hepatocellular carcinoma, immunotherapy, natural killer cells, CD8⁺ T cells

Original Article

Treatment efficacy for patients with chronic hepatitis C and preexisting hepatocellular carcinoma by directly acting antivirals

[Full-Text](#) [PDF](#)

Copy here to cite this article: Dai CY, Huang CF, Hsieh MH, Huang CI, Yeh ML, Tsai PC, Lin CC, Lee MS, Yang JF, Hsu PY, Wei YJ, Hsu CT, Liang PC, Lin YH, Huang JF, Chuang WL, Yu ML. Treatment efficacy for patients with chronic hepatitis C and preexisting hepatocellular carcinoma by directly acting antivirals. *Hepatoma Res* 2020;6:16.

<http://dx.doi.org/10.20517/2394-5079.2019.40>

Abstract

Aim: Despite the high cure rate of interferon-free directly acting antivirals (DAAs) for chronic hepatitis C (CHC) patients, the treatment efficacy for patients with preexisting hepatocellular carcinoma (HCC) remains undefined. We aimed in the present study to address the issue by using novel DAAs in treating CHC patients who were adherent to treatment in Taiwan.

Methods: CHC patients with or without HCC were consecutively enrolled. The primary objective was sustained virological response (SVR) defined as undetectable HCV RNA throughout 12 weeks of a post-treatment follow-up period (SVR12). Only patients with available SVR12 were enrolled for final analysis.

Results: A total of 1237 patients (1113 non-HCC, 101 inactive HCC and 23 active HCC) were enrolled. The overall SVR12 rate was 98.9%, and was similar between HCV patients with and without pre-existing HCC (98.4% vs. 98.9%, $P = 0.64$). While HCC patients were classified as those who had active or inactive HCC, the SVR12 was also similar between patients with and without active HCC (95.7% vs. 99.0%, $P = 0.34$). Among the 101 patients without viable HCC at the time of DAA initiation, eighty-four patients exhibited curative therapy and the other 17 patients experienced HCC recurrence before DAAs. Among the 23 patients with viable HCC at

the time of DAA treatment, 10 patients had received curative therapy for HCC whereas the remaining 13 patients had HCC that was never cured. The SVR12 rates were also similar among the four subpopulations, being 98.8% (83/84), 100% (17/17), 90% (9/10) and 100% (13/13) respectively.

Conclusion: CHC patients with HCC who were adherent to potent DAAs achieved similar SVR12 rate compared to those without HCC and could be effectively treated.

Keywords: Directly acting antiviral, chronic hepatitis C, hepatitis C virus, hepatocellular carcinoma, sustained virological response

Review

Epidemiology of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a western perspective

[Full-Text](#) [PDF](#)

Copy here to cite this article: Farrell A, Ryan M, Howell J. Epidemiology of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a western perspective. *Hepatoma Res* 2020;6:18. <http://dx.doi.org/10.20517/2394-5079.2019.019>

Abstract

Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease worldwide, and represents an increasingly important cause of hepatocellular carcinoma (HCC). As the prevalence of NAFLD has increased, the burden of NAFLD-related HCC has been rising in parallel. This is particularly evident in Western countries, where NAFLD is estimated to account for 10%-59% of all HCC. NAFLD-related HCC can occur in the presence or absence of cirrhosis, and, while those with cirrhosis remain at the greatest risk, factors such as steatohepatitis, age, genetic polymorphisms, type 2 diabetes mellitus and obesity also appear have an impact on the risk of developing HCC in NAFLD. In this review, we present the epidemiology of NAFLD-related HCC from a Western perspective, highlighting gaps in current knowledge and future directions for research in this field.

Keywords: Non-alcoholic fatty liver disease, steatohepatitis, cirrhosis, hepatocellular carcinoma, epidemiology

Review

Diagnosing non-hepatocellular carcinoma malignancies on CT/MRI and contrast enhanced ultrasound: the Liver Imaging Reporting and Data System approach

[Full-Text](#) [PDF](#)

Copy here to cite this article: Fowler KJ, Cunha GM, Kim TK. Diagnosing non-hepatocellular carcinoma malignancies on CT/MRI and contrast enhanced ultrasound: the Liver Imaging Reporting and Data System approach. *Hepatoma Res* 2020;6:19. <http://dx.doi.org/10.20517/2394-5079.2020.21>

Abstract

The Liver Imaging Reporting and Data System (LI-RADS) provides a stepwise algorithmic approach that is proven to be highly accurate in diagnosing hepatocellular carcinoma (HCC) in patients at risk. An essential and early step in the algorithm is the diagnosis of malignancies other than HCC, such as cholangiocarcinoma and combined tumors, by application of LR-M features and criteria. The LR-M category captures most non-HCC malignancies and some atypical HCCs.

The exclusion of non-HCC malignancies is important for maintaining the high specificity of the LR-5, definite HCC category. This review provides an overview of the approach to diagnosing non-HCC malignancies using LI-RADS CT/MRI and contrast enhanced ultrasound algorithms.

Keywords: Magnetic resonance imaging, computer tomography, contrast-enhanced ultrasound

Review

The advancement of immunotherapy in hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Ni L, Feng Y, Dong C. The advancement of immunotherapy in hepatocellular carcinoma. *Hepatoma Res* 2020;6:25. <http://dx.doi.org/10.20517/2394-5079.2020.14>

Abstract

Most patients diagnosed with hepatocellular carcinoma (HCC) present with advanced or metastatic disease. The lack of therapeutic options in the treatment of advanced HCC accounts for its high mortality and recurrence rate. HCC is known as an immunogenic tumor, which develops in chronically inflamed livers. Anti-PD-1/PD-L1 antibodies (immune checkpoint inhibitors, ICB) were approved by the FDA to treat advanced HCC in patients previously treated with sorafenib as a second line. This has opened up a new era of anticancer treatment, although the response rate of HCC to anti-PD-1/PD-L1 antibodies is only around 20%. Other than ICB treatment, adoptive cell transfer, dendritic cell-based vaccines and oncolytic therapy are currently under clinical trials. In this review, different immunotherapy approaches for HCC is presented. Current knowledge on the mechanisms of action for each approach is discussed and relevant, ongoing clinical trials are presented. We also discuss the future of immunotherapy and combination treatment for HCC patients.

Keywords: Hepatocellular carcinoma, immunotherapy, anti-PD-1/PD-L1 antibodies

Review

Recent advances regarding tumor microenvironment and immunotherapy in hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Qin W, Cao ZY, Liu SY, Xu XD. Recent advances regarding tumor microenvironment and immunotherapy in hepatocellular carcinoma. *Hepatoma Res* 2020;6:24. <http://dx.doi.org/10.20517/2394-5079.2020.04>

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors of the liver, with poor prognosis and high mortality. Traditional treatments for patients with HCC have shown poor efficacy especially for advanced liver cancer. Compared with other organs, the liver has more natural immune cells such as Kupffer cells, natural killer cells and natural killer T cells. Immunotherapy for liver cancer has become the focus in current research. The theoretical basis of immunotherapy rests on immune tolerance and suppression in the tumor microenvironment. Common immunotherapy methods include vaccines, cytokines, adoptive cell therapies, immune checkpoint inhibitors, and oncolytic viruses. Compared with traditional treatment, immunotherapy can enhance the body's immune function, delay tumor progression, and prolong survival. This article reviews the HCC microenvironment and immunotherapy both in the clinical and basic

research aspects.

Keywords: Immunotherapy, hepatocellular carcinoma, microenvironment, immune

Review

Personalized T-cell therapy in liver transplanted patients with hepatitis B virus related hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Hafezi M, Bertoletti A, Tan A. Personalized T-cell therapy in liver transplanted patients with hepatitis B virus related hepatocellular carcinoma. *Hepatoma Res* 2020;6:23. <http://dx.doi.org/10.20517/2394-5079.2020.02>

Abstract

Hepatocellular carcinoma (HCC) is a deadly malignancy which typically occurs in the context of chronic liver inflammation. Chronic hepatitis B virus (HBV) infection is considered a major global cause of HCC development. At the moment, liver transplantation is the only curative modality for HBV-associated HCC. However, some patients develop HBV-HCC recurrence after liver transplantation, leaving them with very limited therapeutic options. Adoptive cell therapy with HBV-specific T cell receptor (TCR) that redirects T cells against HCC relapses has shown promising results in such HBV-HCC patients. In this mini-review, we discuss the application of this personalized T cell therapy, and highlight mRNA electroporation as an efficient tool for engineering safe and efficient TCR-redirectioned T cells for the treatment of liver transplant patients with HBV-HCC metastasis.

Keywords: HBV, TCR-T cells, mRNA, HCC metastasis, adoptive cell therapy

Review

Direct-acting antivirals and risk of hepatocellular carcinoma: from genetic signature to metabolic risk factors

[Full-Text](#) [PDF](#)

Copy here to cite this article: Gitto S, Villa E. Direct-acting antivirals and risk of hepatocellular carcinoma: from genetic signature to metabolic risk factors. *Hepatoma Res* 2020;6:22. <http://dx.doi.org/10.20517/2394-5079.2019.50>

Abstract

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related death. Hepatitis C virus and mainly hepatitis C virus-related cirrhosis is the chief risk factor for HCC. Many direct-acting antivirals are available for the eradication of hepatitis C virus with remarkable results in terms of virological response and with optimal safety profile. Notably, some authors have suggested that viral eradication due to these new drugs might favor both occurrence and recurrence of HCC. The exact biological mechanisms of carcinogenesis in this specific setting have not been well identified, but it has been suggested that adjustments in immune surveillance and increase in vascular endothelial growth factor expression could have a chief role. Remarkably, after publication of many large studies and meta-analyses, we can affirm that there is no increased risk on a population basis. Nonetheless, on an individual basis, sustained virological response due to direct-acting antivirals may facilitate HCC onset in some specific subgroups of patients. Among them, we could point out patients with activated neoangiogenesis but also subjects with particularly severe metabolic imbalance.

Keywords: Direct-acting antivirals, hepatocellular carcinoma, carcinogenesis

Review

The impact of direct-acting antivirals on hepatitis C associated hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Lee TP, Bernstein D. The impact of direct-acting antivirals on hepatitis C associated hepatocellular carcinoma. *Hepatoma Res* 2020;6:21. <http://dx.doi.org/10.20517/2394-5079.2019.44>

Abstract

The increased incidence of hepatocellular carcinoma (HCC) in the last several decades in the United States and worldwide has partly resulted from an increase in hepatitis C virus (HCV) infection. HCV carcinogenesis is speculated to be indirectly related to multiple steps from inflammation to fibrosis and advanced fibrosis/cirrhosis over 20 or more years. However, the direct carcinogenic potential from HCV may explain HCC occurring in non-cirrhotic HCV patients. Highly potent direct-acting antivirals (DAAs) in recent years have changed hepatitis C treatment significantly and have resulted in the sustained virologic response (SVR) rate exceeding 90%. Although initial reports concerned the increase in de novo and recurrent HCC associated with DAAs, more recent studies showed that DAA-induced SVR on the contrary reduced risk of HCV-associated HCC without increasing its recurrence. The International Consortium of Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) database and other resources of HCV patients treated with DAA collectively in the near future most likely will be able to show definitive evidence on the risk of HCC occurrence and recurrence after DAA with SVR. The long-term risk of HCC in chronic hepatitis C patients with advanced fibrosis or cirrhosis remains high after DAAs with SVR. Thus, HCC surveillance on this sub-group of patients is important for early detection and intervention of HCC.

Keywords: Direct-acting antivirals, hepatitis C virus infection, risk of hepatocellular carcinoma

Review

Hepatocellular carcinoma and hepatitis C virus infection in Latin America: epidemiology, diagnosis and treatment

[Full-Text](#) [PDF](#)

Copy here to cite this article: Galicia-Moreno M, Monroy-Ramirez HC, Campos-Valdez M, Sanchez-Meza J, Sanchez-Orozco L, Armendariz-Borunda J. Hepatocellular carcinoma and hepatitis C virus infection in Latin America: epidemiology, diagnosis and treatment. *Hepatoma Res* 2020;6:20. <http://dx.doi.org/10.20517/2394-5079.2019.36>

Abstract

Hepatocellular carcinoma (HCC) is the most common cancer associated with chronic liver disease and cirrhosis. The most common cause of HCC is chronic hepatitis C virus infection and many studies in Europe, Asia and North America have focused on its etiology, epidemiology, diagnostic tools, and therapeutic options. However, little is known about these issues in Latin America. The aim of this review is to address these aspects of HCC in Latin America. The main risk factors associated with developing HCC in this region are: age, concomitant cirrhosis, hepatitis C infection, obesity and hereditary disease such as hemochromatosis. On the other hand, screening tests and diagnostic methods of HCC are mostly serum alpha fetoprotein quantification, liver

ultrasound, computed tomography, magnetic resonance, and histopathology. Novel diagnostic methods include gut microbiota analysis and the use of nanotechnology and they continue to be tested. Finally, according to the Barcelona Clinic Liver Cancer, curative treatments used in HCC patients are mainly liver resection, liver transplantation, and local ablation, each with advantages and disadvantages. In conclusion, clear strategies are urgently needed to understand the extent of HCC and related problems in this part of the world. This review provides greater knowledge of HCC for the proper design of preventive programs by taking into consideration specific characteristics of our population. Also, this review allows for an understanding of individualizing treatments according to the patient's needs.

Keywords: Liver, hepatitis C, epidemiology, diagnosis, treatment, hepatocellular carcinoma, Latin America

Review

Treatment options for recurrence of hepatocellular carcinoma after surgical resection: review of the literature and current recommendations for management

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Copy here to cite this article: Pasini F, Serenari M, Cucchetti A, Ercolani G. Treatment options for recurrence of hepatocellular carcinoma after surgical resection: review of the literature and current recommendations for management. *Hepatoma Res* 2020;6:26. <http://dx.doi.org/10.20517/2394-5079.2019.47>

Abstract

The recurrence rate after primary resection for hepatocellular carcinoma (HCC) has been reported to be up to 80%. There is no consensus or guideline about the best treatment option for such recurrent HCC (rHCC). It is therefore of paramount importance to select patients for suitable treatment due to the high risk of associated morbidity and mortality. In this paper, we review the literature on treatment for rHCC and propose a strategy based on the best evidence available. Even in rHCC, it is still possible to achieve cure and good survival rates through careful patient selection. Repeat hepatectomy is recognized as a feasible and safe procedure even in cirrhotic patients and should be considered as the best option with curative intent when the patient is fit enough. Greater adoption of minimally-invasive liver surgery could have the potential to increase the number of candidate patients with rHCC for repeat resection in the next few years. Liver transplantation offers longer disease-free survival compared to repeat resection, curing the underlying cirrhosis, but is not widely available due to organ shortage. When surgery is not feasible, locoregional treatments such as radiofrequency ablation and transarterial chemoembolization have an important role for patients who cannot tolerate repeat hepatectomy and are not suitable for transplantation. For advanced cases, systemic therapy could be considered.

Keywords: Recurrence, hepatocellular carcinoma, hepatic resection, second resection

Review

Mechanisms and immunotherapies of HBV- and NAFLD-related hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Song XJ, Ma CH. Mechanisms and immunotherapies of HBV- and NAFLD-related hepatocellular carcinoma. *Hepatoma Res* 2020;6:27. <http://dx.doi.org/10.20517/2394-5079.2020.05>

Abstract

Hepatitis B virus (HBV) infection remains the most important risk factor for hepatocellular carcinoma (HCC) worldwide and nonalcoholic fatty liver disease (NAFLD) has developed as major etiology of chronic liver diseases, cirrhosis and eventually HCC in the last decades. Although nucleos(t)ide analogs are recommended as the first-line drug for patients with chronic hepatitis B, incomplete eradication of HBV serves as an obstacle for effective cure of chronic hepatitis B and even HCC. NAFLD refers to a spectrum of hepatic metabolic disorders, compromised with multi-system diseases. Considering the specificity of hepatocytes and enrichment of immune cells in liver, this review aims to summarize the mechanisms of direct pro-tumorigenesis to hepatocytes induced by HBV infection and abnormal lipid metabolism, and indirect oncogenic processes mediated by immune cells. We also discuss similarities and differences of immune cells between HBV- and NAFLD-HCC and finally focus on the novel immunotherapies concerning preclinical and clinical studies for liver cancer.

Keywords: Hepatitis B virus, nonalcoholic fatty liver disease, hepatocellular carcinoma, immune cells, immunotherapy

Review

Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients?

[Full-Text](#) [PDF](#)

Copy here to cite this article: Ramadori G. Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients?. *Hepatoma Res* 2020;6:28. <http://dx.doi.org/10.20517/2394-5079.2020.43>

Abstract

The COVID-19 pandemic has led to the greatest worldwide health crisis in decades. The number of infected patients with severe SARS-CoV-2 (COVID-19) disease has overwhelmed the capacity of almost all health care systems around world. Hypoalbuminemia has now been reported in patients with severe disease seeking help in the emergency room because of COVID-19 infection. In the past, hypoalbuminemia was considered to be a negative prognostic marker, not only in patients with chronic liver disease, but also in patients with SARS and MERS infections. Albumin is the major serum protein synthesized by the liver. A low serum albumin level is an ominous clinical sign. Introduction of amino acids to a patient's diet is of fundamental importance to hepatic albumin synthesis in different clinical situations. This highlights the importance of nutritional support during the early phases of COVID-19-infection. Furthermore, albumin synthesis in the hepatocyte is downregulated at a pretranslational level by the direct interaction of the major acute-phase cytokines which are released into the circulation during the cytokine "storm" induced by the viral effects on the lungs. Both mechanisms contribute to severe hypoalbuminemia which, combined with massive fluid losses due to the fever, is responsible for severe hypovolemia and shock commonly observed in patients with COVID-19 in critical care settings.

Keywords: Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, COVID-19, albumin synthesis, nutrition, acute-phase reaction, cytokines, liver, extrahepatic organs

Review

Epidemiology of hepatocellular carcinoma in metabolic liver disease

[Full-Text](#) [PDF](#)

Copy here to cite this article:

Bellentani S. Epidemiology of hepatocellular carcinoma in metabolic liver disease. *Hepatoma Res* 2020;6:29. <http://dx.doi.org/10.20517/2394-5079.2020.10>

Abstract

Nonalcoholic fatty liver disease and its evolutive form nonalcoholic steatohepatitis (NASH) are nowadays the second/third cause of chronic liver disease worldwide, and their prevalence and incidence are rapidly increasing in parallel to the burden of diabetes and obesity. Hepatocellular carcinoma (HCC) due to NASH (HCC-NASH) has become the major cause of HCC and is now one of the major indications for liver transplant in Western countries, after that due to HCV infection. NASH occurs both in the presence and absence of liver cirrhosis. In this review, we describe the epidemiology of HCC related to metabolic liver disease: not only NASH-HCC but also type 2 diabetes mellitus and obesity-related HCC. Some new practical guidelines for screening and surveillance of patients with metabolic diseases at risk for HCC are also discussed.

Keywords: Nonalcoholic steatohepatitis, hepatocellular carcinoma, metabolic syndrome, obesity, type 2 diabetes mellitus

Review

Imaging biomarkers for predicting poor prognosis of hepatocellular carcinoma: a review

[Full-Text](#) [PDF](#)

Copy here to cite this article: Zhang Y, Huang ZX, Chen J, Shi YJ, Jiang HY, Cao LK, Song B. Imaging biomarkers for predicting poor prognosis of hepatocellular carcinoma: a review. *Hepatoma Res* 2020;6:30. <http://dx.doi.org/10.20517/2394-5079.2020.17>

Abstract

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver with a high mortality rate. Heterogeneity is the main biological characteristic of HCC, which manifests through the different biological behaviors of each phenotype and ultimately, affects patient prognosis and treatment efficacy. Various aggressive biological behaviors are considered to be associated with the poor prognosis of HCC patients including poor differentiation, microvascular invasion, intracellular fat accumulation, invasive growth, bile duct invasion or tumor thrombosis, and tumor spread and metastasis, and have been reported as prognostic biomarkers. In addition, HCC results from multifactor synergistic damage, and various factors related to genetics, molecular pathology and immunohistochemistry such as β -catenin, Ki67, cytokeratin-19, and epithelial cell adhesion molecule have an impact on HCC differentiation and prognosis. This article is an overview of the biological behaviors that lead to poor prognosis of HCC, and the roles of morphological and quantitative noninvasive imaging biomarkers in the evaluation and prediction of these behaviors. Some common biomarkers related to genetics, molecular pathology and immunohistochemistry are also briefly summarized. It is hoped that this review will provide clinicians and radiologists with an update on the development of liver imaging, and provide directions for the combination of radiology, genetics, molecular pathology and histopathology to better predict the prognosis of HCC patients.

Keywords: Hepatocellular carcinoma, poor prognosis, biological behaviors, imaging biomarkers, genetics, molecular pathology, immunohistochemistry

Review

Impact of direct-acting antivirals on *de novo* occurrence of hepatocellular carcinoma in hepatitis C virus patients

[Full-Text](#) [PDF](#)

Copy here to cite this article: Yang M, Ma R, Huang Y, Wei L. Impact of direct-acting antivirals on *de novo* occurrence of hepatocellular carcinoma in hepatitis C virus patients. *Hepatoma Res* 2020;6:31. <http://dx.doi.org/10.20517/2394-5079.2019.45>

Abstract

Hepatitis C Virus (HCV) infection constitutes a significant burden to world health, leading to liver cirrhosis and hepatocellular carcinoma (HCC). In the past decades, pegylated interferon combined with ribavirin has been used extensively for HCV treatment, and interferon (IFN) is thought to have antitumor property. Direct-acting antivirals (DAAs) have fundamentally changed HCV therapy, due to their high efficacy and tolerability. However, recent studies have reported relatively high rates of HCC occurrence, and recurrence, following successful HCV treatment using DAAs. These studies were grossly underpowered due to their retrospective design, lack of untreated or IFN controls, small sample size, and limited patient follow-up time. From then, many retrospective and prospective cohort studies with larger size and longer follow-up duration after DAAs therapy have been published. These studies showed that treatment with DAAs can reduce the risk of HCC compared to no treatment, didn't increase the risk of HCC compared to IFN-based therapy after adjusting for the potential confounders of these two groups, and DAAs-induced sustained virological response decreased the risk of HCC compared to DAAs treatment failure. In conclusion, DAAs treatment doesn't appear to increase the development of HCC, even in cirrhotic patients. However, cirrhotic patients should be monitored for the development of HCC during and after DAAs treatment.

Keywords: Sustained virological response, hepatocellular carcinoma, liver cirrhosis

Review

Intraarterial and intravenous contrast enhanced CT and MR imaging of multi-step hepatocarcinogenesis defining the early stage of hepatocellular carcinoma development

[Full-Text](#) [PDF](#)

Copy here to cite this article: Kobayashi S, Kozaka K, Gabata T, Matsui O, Minami T. Intraarterial and intravenous contrast enhanced CT and MR imaging of multi-step hepatocarcinogenesis defining the early stage of hepatocellular carcinoma development. *Hepatoma Res* 2020;6:36. <http://dx.doi.org/10.20517/2394-5079.2020.24>

Abstract

Liver cancer is the second leading cause of cancer deaths in men worldwide, and the 6th and 7th cause of cancer deaths in men and women in developed countries. 70%-90% of primary liver cancer is hepatocellular carcinoma. Hepatitis B or C viruses and chronic inflammation due to alcohol intake are the main risk factors for hepatocellular carcinoma. One of the key approaches for the early detection of hepatocellular carcinoma is to understand the specific imaging findings of liver nodules in the multi-step hepatocarcinogenesis process. In this article, we review the imaging findings of multistep hepatocarcinogenesis, with a focus on the early detection of malignant, cirrhotic nodules with CT and MRI.

Keywords: Hepatocellular carcinoma, multistep hepatocarcinogenesis, early hepatocellular carcinoma, dysplastic nodule, CT, MRI

Review

Predictive factors for hepatocellular carcinoma recurrence after curative treatments

[Full-Text](#) [PDF](#)

Copy here to cite this article: Marasco G, Ravaioli F, Vestito A, Rossini B, Dajti E, Colecchia L, Gjini K, Renzulli M, Golfieri R, Festi D, Colecchia A. Predictive factors for hepatocellular carcinoma recurrence after curative treatments. *Hepatoma Res* 2020;6:33. <http://dx.doi.org/10.20517/2394-5079.2020.01>

Abstract

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide. Recurrence of HCC after resection or loco-regional therapies represents an important clinical issue as it affects up to 70% of patients. This can be divided into early or late, if it occurs within or after 24 months after treatment, respectively. While the predictive factors for early recurrence are mainly related to tumour biology (local invasion and intrahepatic metastases), late recurrences are mainly related to de novo tumour formation. Thus, it is important to recognize these factors prior to any treatment in each patient, in order to optimize the treatment strategy and follow-up after treatment. The aim of this review is to summarize the current evidence available regarding predictive factors for the recurrence of HCC, according to the different therapeutic strategies available. In particular, we will discuss the role of new ultrasound-based techniques and biological features, such as tumor-related and circulating biomarkers, in predicting HCC recurrence. Recent advances in imaging-related parameters in computed-tomography scans and magnetic resonance imaging will also be discussed.

Keywords: Liver resection, trans-arterial chemoembolization, radiofrequency ablation, liver stiffness measurement, indocyanine green retention test

Meta-Analysis

Role of laparoscopic and robotic liver resection compared to open surgery in elderly hepatocellular carcinoma patients: a systematic review and meta-analysis

[Full-Text](#) [PDF](#)

Copy here to cite this article: Brolese A, Rigoni M, Vitale A, de Pretis G, Avancini I, Pravadelli C, Frisinghelli M, Rozzanigo U, Luppi G, Dionisi F, Marcucci S, Viel G, Beltempo P, Prezzi C, Frisini M, Brolese M, Nollo G, Ciarleglio FA. Role of laparoscopic and robotic liver resection compared to open surgery in elderly hepatocellular carcinoma patients: a systematic review and meta-analysis. *Hepatoma Res* 2020;6:34. <http://dx.doi.org/10.20517/2394-5079.2020.15>

Abstract

Aim: This study aimed to compare mini-invasive liver resection (MILR) (laparoscopic/robotic approach) and open liver resection (OLR) for hepatocellular carcinoma (HCC) in elderly patients with regard to clinical and oncological outcomes through a comprehensive systematic review.

Methods: The MEDLINE and Cochrane Library electronic databases were systematically searched from 2009 to December 2019 to identify relevant English written studies comparing MILR and OLR. The main endpoints were Child-Pugh score, serum total bilirubin level, comorbidity, presence/absence of cirrhosis, minor/major resection, challenge segment approach,

operative time, estimated intraoperative blood loss, liver failure rate, morbidity according to the Clavien-Dindo classification, length of hospital stay (LOS), postoperative mortality, number of lesions, tumor size, readmission rate, recurrence rate and survival at 1, 3 and 5 years after operation. Meta-analyses provided pooled relative risks and mean differences for these outcomes. Cut-off for “elderly age” was set at 65 years old.

Results: Eight studies that evaluated 3051 patients who underwent liver resection for HCC, with 950 undergoing MILR and 2101 OLR, were included after the screening process. Blood loss, morbidity, and LOS showed statistical significance in favor of MILR. In particular, with respect to OLR, MILR decreased on average blood loss by 161.43 mL (95%CI: 250.24-72.61), risk of morbidity by 42% ($P < 0.01$), LOS by 4 days (95%CI: 7-2), postoperative mortality risk by 47% (although not significantly, $P = 0.06$). Major resections were significantly more common in the OLR group ($P < 0.0001$). Recurrence, although not significant ($P = 0.06$), must also be emphasized. The two surgical approaches were comparable with regard to the other outcomes investigated.

Conclusion: Meta-analyses confirmed the advantages of MILR in terms of short perioperative outcomes, where it may promote the extension of liver resection to HCC patients with borderline liver function. MILR may be considered an important treatment option with significant benefits in the elderly and fragile patients. However, large well-designed prospective comparative studies or randomized controlled trials would be necessary to further confirm our conclusions.

Keywords: Hepatocellular carcinoma, HCC, mini-invasive liver resection, laparoscopic liver surgery, robotic liver surgery, open liver surgery, meta-analysis

Review

Non-invasive tests for the prediction of post-hepatectomy liver failure in the elderly

[Full-Text](#) [PDF](#)

Copy here to cite this article: Marasco G, Colecchia A, Milandri M, Rossini B, Alemanni LV, Dajti E, Ravaioli F, Renzulli M, Golfieri R, Festi D. Non-invasive tests for the prediction of post-hepatectomy liver failure in the elderly. *Hepatoma Res* 2020;6:32. <http://dx.doi.org/10.20517/2394-5079.2019.54>

Abstract

Post-hepatectomy liver failure (PHLF) is associated with great morbidity and mortality after resection of hepatocellular carcinoma. Previous studies have underlined that advanced age could be a potential factor influencing post-operative complications and long-term survival.

In the past, candidates for resection were based on the Child-Pugh classification, the predictive value of which was rather low. The selection of patients undergoing resection in Western countries is based on the assessment of portal hypertension (PH), which is clinically assessed by measurement of the hepatic venous pressure gradient, an invasive and costly process. Thus, there have been several attempts to identify the best non-invasive test (NIT) to accurately predict PHLF. Most biochemical NITs for the prediction of PHLF are focused on evaluation of underlying liver cirrhosis and PH. Amongst them, FIB-4, which also includes the patient’s age, seems to have more robust supporting results. In Europe and the USA., the most tested and reliable NIT for predicting PHLF is the evaluation of liver stiffness measurement, which is also influenced by age. Imaging parameters are promising tools which are used only in specialized centers however, and when available. Liver volume parameters, as well as contrast-enhanced data, demonstrate good accuracy

in predicting PHLF. In this scenario, the evaluation of sarcopenia and bone mineral density through contextual imaging allows the delineation of PHLF in at-risk elderly patients. Further studies focused on parameters for the evaluation of PHLF in elderly patients are needed.

Keywords: Post-hepatectomy liver failure, liver resection, elderly, liver stiffness measurement, indocyanine green retention test

Review

Emerging risk factors for nonalcoholic fatty liver disease associated hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Benhammou JN, Lin J, Hussain SK, El-Kabany M. Emerging risk factors for nonalcoholic fatty liver disease associated hepatocellular carcinoma. *Hepatoma Res* 2020;6:35. <http://dx.doi.org/10.20517/2394-5079.2020.16>

Abstract

Worldwide, nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions and in parallel, hepatocellular carcinoma (HCC) has become one of the fastest growing cancers. Epidemiological studies have not only shed light on the prevalence and incidence of the disease but have also unmasked important environmental risk factors, including the role of diabetes and dyslipidemia in disease pathogenesis. Genetic association studies have identified single nucleotide polymorphisms implicated in NAFLD-HCC, many of which are part of lipid metabolism pathways. Through these clinical studies and subsequently, translational and basic research, the role of statins as a chemoprotective agent has also emerged with ongoing clinical trials assessing their utility in HCC prevention and treatment. In this review, we summarize the recent epidemiological studies describing the burden of NAFLD-HCC in different patient populations and countries. We discuss the genetic and environmental risk factors for NAFLD-HCC and highlight the chemoprotective role of statins and aspirin. We also summarize what is known about NAFLD-HCC in the cirrhosis and non-cirrhosis populations and briefly address the role of surveillance in NAFLD-HCC patients.

Keywords: Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, hepatocellular carcinoma, statins, metabolic syndrome

Letter to Editor

For dietary advice in end-stage liver cirrhosis resting metabolic rate should be measured, not estimated

[Full-Text](#) [PDF](#)

Copy here to cite this article: Bot D, Droop A, Tushuizen ME, van Hoek B. For dietary advice in end-stage liver cirrhosis resting metabolic rate should be measured, not estimated. *Hepatoma Res* 2020;6:45. <http://dx.doi.org/10.20517/2394-5079.2020.62>

Review

Imaging assessment after SBRT for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

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<http://dx.doi.org/10.20517/2394-5079.2020.30>

Abstract

The use of stereotactic body radiotherapy (SBRT) in hepatocellular carcinoma (HCC) has increased over the past few decades. Thus, accurate evaluation of post-SBRT treatment response is essential to avoid over-treatment of responders as well as missing the opportunity to salvage non-responders. There are some intricate imaging differences after liver SBRT compared to those observed after conventional fractionated radiotherapy and other locoregional treatment. We aim to review the imaging changes that occur following SBRT for HCC and their potential clinical implications.

Keywords: Imaging, liver, stereotactic body radiotherapy, hepatocellular carcinoma

Review

Comprehending the therapeutic effects of stereotactic body radiation therapy for small hepatocellular carcinomas based on imagings

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Copy here to cite this article: Zeng ZC, Fan J, Zhou J, Zeng MS, Chen YX, Wu ZF, Sun J, Zhang JY, Hu Y, Zhao QQ. Comprehending the therapeutic effects of stereotactic body radiation therapy for small hepatocellular carcinomas based on imagings. *Hepatoma Res* 2020;6:43. <http://dx.doi.org/10.20517/2394-5079.2020.29>

Abstract

Surgical resection or radiofrequency ablation (RFA) is considered first-choice treatment for small hepatocellular carcinomas (HCCs). When a patient has a small HCC that is inoperable or unsuitable for RFA, what are alternative treatments? Some oncologists recommend transarterial chemoembolization (TACE), chemotherapy, molecular-targeted therapy, or immunotherapy. However, these treatments have minimally beneficial effects in small HCCs. Stereotactic body radiation therapy (SBRT) is a liver-directed radical therapy for small HCCs, with treatment outcomes similar to those for surgical resection or RFA, but many oncologists do not comprehend its efficacy or accept this therapy. We herein discuss 11 typical patients who received SBRT for various indications: refusal to undergo resection or RFA; surgical resection or RFA considered difficult or unfeasible; residual cancer after surgical resection or RFA or incomplete iodized oil retention after TACE; or tumor recurrence after resection or RFA. We describe each case, including the radiation field, tumor radiation dose, and response to SBRT in both the tumor and liver parenchyma. These clinical data should help readers understand this new therapeutic technique. We also conducted a literature review and found evidence to support survival benefit with SBRT, including good three- and five-year overall survival rates. The purpose of this article is to encourage readers to accept the concept that SBRT is a low-toxicity and effective therapeutic option for patients with small HCCs, which offers substantial local control and improved overall survival, especially for patients with a tumor that is unresectable or unsuitable for RFA, residual tumor after local therapy, or intrahepatic recurrent tumor.

Keywords: Small hepatocellular carcinomas, stereotactic body radiation therapy, treatment outcomes, toxicity, imaging changes

Review

Genetics of alcohol-related hepatocellular carcinoma - its role in risk prediction

[Full-Text](#) [PDF](#)

Copy here to cite this article: Liu K, Verset G, Trepo E, Seth D. Genetics of alcohol-related hepatocellular carcinoma - its role in risk prediction. *Hepatoma Res* 2020;6:42. <http://dx.doi.org/10.20517/2394-5079.2020.25>

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, with increasing incidence worldwide. Alcohol-related cirrhosis (AC) accounts for 30% of the global incidence of HCC and HCC-related deaths. With the decline of hepatitis C virus (HCV) and decreasing HCV-related HCC, AC will soon become the leading cause of HCC. Excess alcohol consumption (> 80 g per day for > 10 years) increases the risk of HCC by 5-fold. However, only up to 35% of excessive drinkers develop cirrhosis and its associated HCC risk. Individual variation in susceptibility to HCC is known, but there is limited information to predict who among the patients is at high risk of progressing to HCC. Clinical risk factors for HCC include male gender, older age, severity of cirrhosis, obesity and presence of type 2 diabetes. In addition to ethnic variability in HCC risk, genetic variants are known to alter the risk of alcohol-related HCC. For example, single nucleotide polymorphisms in *PNPLA3* (rs738409, C>G) and *TM6SF2* (rs58542926, C>T) increase the risk of AC-related HCC, whereas *HSD17B13* (T>A) reduces the risk for HCC. Studies have also confirmed *PNPLA3* and *TM6SF2* to be independent risk factors for AC-related (but not HCV-related) HCC. Combining genetic risk factors with phenotypic/clinical risk factors has been explored for stratification of patients for HCC development. Risk allele rs378409-G in *PNPLA3* when combined with phenotypic/clinical risk factors (BMI, age, sex) has enabled HCC risk stratification of AC patients into low-, intermediate- and high-risk subgroups. Similarly, a combination of the two genetic variants *PNPLA3*-G and *TM6SF2*-T has been independently associated with risk of HCC onset. Using a polygenic risk score approach of incorporating several genetic variants, prognostic performance of polygenic risk score that included *PNPLA3* rs378409 and *TM6SF2* rs58542926 improved HCC prediction better than with either variant alone. Incorporating new variants and risk factors has the potential to build better algorithms/models to predict onset, early diagnosis and treatments for AC-related HCC. However, clinical usefulness of these approaches is yet to be determined.

Keywords: Alcohol-related cirrhosis, *PNPLA3*, *HSD17B13*, *TM6SF2*, risk prediction

Original Article

β -catenin in intranuclear inclusions of hepatocellular carcinoma

[Full-Text](#) [PDF](#)

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Abstract

Aim: β -catenin activation is known to promote liver regeneration and play a role in the pathogenesis of liver cancer. Recently, we detected intranuclear inclusions (NI) in hepatocellular carcinoma (HCC) containing degenerated cell organelles and lysosomal proteins and delimited by a completely closed nuclear membrane. The presence of NI was positively associated with patient survival. The aim of the current study was to investigate a possible association between proteins of the Wnt/ β -catenin pathway with NI morphology and survival.

Methods: We examined NI in 72 paraffin-embedded specimens of HCC. Immunohistochemistry (IHC) and immunofluorescence (IF) were performed to investigate the content and shape of NI. β -catenin gene (*CTNNB1*) mutations were analyzed by next generation sequencing.

Results: We detected the accumulation of β -catenin and glutamine synthetase (a target gene of β -catenin) proteins within NI. Further, we found immunopositivity for the lysine demethylase KDM2A in NI. KDM2A is known to be involved in β -catenin degradation. We detected significant associations between the presence of β -catenin and autophagy-associated proteins in NI. Double-IF revealed co-localization of β -catenin and p62 in the same NI. Kaplan-Meier survival analysis showed that the presence of NI containing KDM2A protein accumulations displayed a significant benefit in overall survival.

Conclusion: We detected accumulations of β -catenin and proteins associated with the Wnt/ β -catenin pathway partly together with autophagy-associated proteins in the same inclusion. Our finding that KDM2A immunopositivity within NIs was associated with favorable clinical outcomes and suggests a biological significance of NI.

Keywords: Wnt/ β -catenin pathway, KDM2A, intranuclear inclusions, hepatocellular carcinoma

Review

The advances in immunotherapy for hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Zhang F, Li Y. The advances in immunotherapy for hepatocellular carcinoma. *Hepatoma Res* 2020;6:40. <http://dx.doi.org/10.20517/2394-5079.2020.20>

Abstract

Hepatocellular carcinoma (HCC) is one of the malignant tumors with higher incidence and mortality worldwide. Recently, significant progress has been made in uncovering immunotherapy in HCC, for instance programmed death-1, cytotoxic T-lymphocyte antigen 4, chimeric antigen receptor T-cell therapy, T cell receptor T cell therapy, dendritic cell vaccine, and cytokine-induced killer cells. This paper reviews the advances in immunotherapy and focuses on the results of many of preclinical studies and clinical trials in the field, as well as some of the promising therapeutic strategies for HCC in the future.

Keywords: HCC, PD-1, PD-L1, CTLA-4, CAR-T, T cell receptor, DC, CIK

Review

Stereotactic body radiation therapy for the management of HCC

[Full-Text](#) [PDF](#)

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Abstract

Hepatocellular carcinoma (HCC) is a common malignant tumor in China. After years of efforts, there has been great progress in the management of liver cancer, but overall, it is still not ideal. At present, there are many therapies for liver cancer, including surgical resection, transcatheter arterial chemoembolization (TACE), ablation, molecular targeted therapy, stereotactic body radiation therapy, chemotherapy, immunotherapy, and so on. Studies have reported that TACE combined with radiotherapy can shrink the tumor, and some of the remainder will be resectable, resulting in cure. For HCC with tumor thrombus, the tumor thrombus was reduced and then

resected after neoadjuvant radiotherapy. The survival time of the patients with portal vein tumor thrombus was significantly longer than that of the patients without neoadjuvant radiotherapy. Large liver cancer will be reduced to small liver cancer after comprehensive treatment, which can be transformed into stereotactic radiotherapy or radiofrequency ablation, and can also be palliative to radical treatment. Individualized and multidisciplinary therapy for liver cancer is the direction of future development. More clinical evidence-based level of radiotherapy treatment of liver cancer should be done in the future.

Keywords: Hepatocellular carcinoma, stereotactic body radiation therapy, tumor thrombus, combined therapy

Review

Conventional type 1 dendritic cells in protective antitumor immunity and its potential in hepatocellular carcinoma

[Full-Text](#) [PDF](#)

Copy here to cite this article: Qu C, Chen K, Cheng SY. Conventional type 1 dendritic cells in protective antitumor immunity and its potential in hepatocellular carcinoma. *Hepatoma Res* 2020;6:38. <http://dx.doi.org/10.20517/2394-5079.2020.12>

Abstract

Immunotherapy is revolutionizing the clinical management of cancer patients by modulating T cells and natural killer cells. Dendritic cells (DCs) have the capacity to orchestrate the expansion and function of these effector cells both in lymphoid and non-lymphoid tissues of cancer patients. Distinct subtypes of DCs have various capacities to prime and activate different T cell responses. Here, we review conventional type 1 dendritic cells (cDC1s) and their crucial role in protective anti-tumor immunity. Targeting cDC1s as a cancer vaccine against the development of hepatocellular carcinoma will be discussed.

Keywords: Conventional type 1 dendritic cells, antitumor immunity, hepatocellular carcinoma, cancer vaccine

Review

Risk factors of portal vein thrombosis after splenectomy in patients with liver cirrhosis

[Full-Text](#) [PDF](#)

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Abstract

Portal vein thrombosis (PVT) is a common complication after splenectomy, causing a possible negative impact on the prognosis of patients with liver cirrhosis. However, the risk factors of PVT are not completely clear. Many factors are related to the occurrence of postoperative PVT, such as hemodynamic changes, splenomegaly, splenectomy, coagulation and anticoagulation disorder, liver cirrhosis, platelet count, D-dimer level, infection, inflammation, and other factors. Hemodynamic changes are mainly caused by thicker portal and splenic vein diameters, larger spleen, slower portal vein blood flow rate, lower portal vein pressure before and after surgery, etc. It is timely detection and advanced prevention that really matter in reducing PVT incidence and improving patient prognosis. We systematically reviewed the researches on the risk



factors and therapies of PVT to provide useful information on a comprehensive understanding for researchers.

Keywords: Liver cirrhosis, splenectomy, portal vein thrombosis, risk factors, treatments, prophylaxis