

# Hepatoma Research: the beginning of a new forum

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**Received:** 06-02-2015, **Accepted:** 19-02-2015

## INTRODUCTION

Liver cancer, primary hepatocellular carcinoma (HCC) or hepatoma has become the third leading cause of death from cancer worldwide.<sup>[1,2]</sup> In 2008, the GLOBOCAN reported 746,300 new cases of HCC diagnosed worldwide with 695,900 HCC-related deaths and a 1.07 incidence to mortality ratio making it the third most fatal cancer world-wide with the vast majority (84%) of cases concentrated in the developing countries in Asia and Africa.<sup>[2,3]</sup> HCC is a disparate cancer preferentially afflicting the middle to lower socio-economic segment of the world.<sup>[4]</sup> The economic cost of HCC is staggering with global expense estimated at \$895.2 billion a year only followed by cardiac (\$753.2 billion) and cerebrovascular disease (\$298.2 billion).

*Hepatoma Research (Hepatoma Res, ISSN 2394-5079, <http://www.hrjournal.net/>), this new open access online journal, has been created to improve and promote the international exchange of clinical and academic information about HCC. We invite our peers, clinical and research collaborators alike to contribute to this new journal to improve the international exchange of information in real time to meet this global challenge. Our journal will address all aspect of HCC, including cell biology, pathophysiology, genetics, immunology, pharmacology, medical management as well as radiological and surgical interventions.*

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<b>DOI:</b> 10.4103/2394-5079.153290	

## ETIOLOGY

Currently, HCC predominately (78%) arises from two chronic liver infections: hepatitis B virus (HBV) and hepatitis C virus (HCV). HBV represents the etiologic factor in 50% of world-wide HCC cases and was recognized in 1994 by the WHO/IARC with a relative risk ranging from 5 to 98.<sup>[5,6]</sup> Inactive HBV is also an established risk for HCC with a hazard ratio of 4.6. HBV in Asia, especially in China and Korea, has shown a steady decline through HBV immunization programs. Alternatively, the United States and Japan witnessed a rise in HCV acquired from intravenous drug abuse in the 60's and 80's, which was associated with 80-90% of HCC cases in Japan and 40-60% of cases in Italy and the United States with an odds ratio of 1.3-134.<sup>[7-9]</sup> After decades of frustration treating HCV introduction of new protease inhibitors are achieving 80-100% viral eradication, which is associated with a decreased the relative risk for the development of HCC.<sup>[10-12]</sup> Unfortunately complete virologic response does not eradicate the risk of HCC in established HCV-related cirrhosis.

Unfortunately, the progress in viral hepatitis has not addressed the looming cloud of obesity, nonalcoholic fibrotic liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) on our horizon. In a world of advancing technology, the standard of living including food stores has dramatically increased and subsequently the mean body mass index and incidence of obesity. NAFLD/NASH as an etiologic factor results in excess fatty acids, and hepatocellular steatosis, which elicits fatty acid oxidation and reactive oxidative stress thought to produce epigenetic changes.<sup>[13,14]</sup>

## CARCINOGENESIS

No matter what the agent viral hepatitis, fatty liver or diabetes the principle risk factor in HCC is the presence of a pre-neoplastic liver.<sup>[15,16]</sup> In HBV-related HCC, the presence of serum HBV

DNA has been shown to be a predictor of HCC development synergistic with inflammation.<sup>[17]</sup> Viral DNA replication and hepatitis B core antigen expression are halted in HBV HCC, while 20% of cells persist production of hepatitis B surface antigen triggering an immune responses and the secretion of cytokines tumor necrosis factor- $\alpha$ , interferon and interleukin-2, which can down regulate the accumulation of HBV RNAs.<sup>[18-20]</sup>

Development of HCV-related HCC is a multistep process including the up regulation of inflammatory cytokines and induction of oxidative stress from chronic hepatitis, fibrosis, liver regeneration, and cirrhosis.<sup>[21]</sup> The intermediate step is represented by dysplastic nodules with the coexistence of epigenetic and genetic changes that develop into HCC. Multiple pro-inflammatory states appear to be synergistic with HCV including: alcohol, HBV and HIV co-infection, diabetes mellitus, older age, African American race, thrombocytopenia, and smoking.<sup>[21-24]</sup>

Nonalcoholic fibrotic liver disease and NASH is an entity previously classified with cryptogenic cirrhosis with a high relative risk for HCC. Pro-inflammatory states from fatty acids release cytokines, pro-oncogenic signals and stimulate epigenetic changes even in the absence of cirrhosis.<sup>[18]</sup> Subsequently obese type II diabetics are at twice the risk to develop HCC.<sup>[25-27]</sup> Alternatively, African Americans are at a lower relative risk for HCC compared to Caucasians based on fat distribution and metabolism. The estimated yearly incidence of HCC development in NASH-cirrhosis (2.6%) is similar to HCV-cirrhosis (4%).<sup>[28]</sup>

Genes involved in hepatocarcinogenesis include *p53*, *PIKCA*, and  *$\beta$ -catenin*. In addition, there are two signaling pathways for cellular differentiation that are frequently disrupted: (1) *Wnt- $\beta$ -catenin* and (2) *Hedgehog*. WNT signaling appears to be associated with a higher incidence of transformation and pre-neoplastic adenomas.<sup>[29]</sup>

## SURVEILLANCE

The American Association for the Study of Liver Diseases advocates bi-annual ultrasound surveillance for high-risk patients.<sup>[30]</sup> Cost-effectiveness is met with two criteria: (1) annual incidence > 1.5% per year and (2) threshold of \$50,000 per quality-adjusted life year (QALY). Several economic analyses confirm Child-Pugh Class A patients increase life expectancy with cost effectiveness of \$26,000 and \$55,000 per QALY. The best data on surveillance comes from a prospective Chinese trial.<sup>[31-35]</sup> Surveillance is recommended for all cirrhotics, HBV carriers if they are Africans older than age 20 years, Asians older than 40 years or have a family history of HCC. However, debate on the utility of AFP continues.

Unfortunately ultrasound is highly operator dependent with a variable sensitivity of 30-70%, and most importantly < 20% of patients compliant with biannual exams.<sup>[36-38]</sup>

## DIAGNOSIS

Hepatocellular carcinoma is diagnosed by contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI). Early arterial phase enhancement is seen in the tumor followed by venous phase dropout. These characteristics carry result in 90% sensitivity and 95% specificity for lesions greater than one centimeter.<sup>[39]</sup> In 2013, the American College of Radiology introduced the Liver Imaging Reporting and Data System to standardize the reporting and data collection of CT and MRI for HCC.<sup>[40]</sup> In efforts to improve lower cost technology, contrast-enhanced ultrasound was introduced with a 90% sensitivity, 99% specificity and 89% diagnostic accuracy.<sup>[41]</sup> The diagnostic accuracy of MRI has been improved by dual contrast agents like Eovist<sup>®</sup>, which is a hepatobiliary excretion and vascularization markers used to diagnosis HCC.<sup>[42]</sup> Despite these advances in technology, diagnostics are still encumbered by operator variability and inadequate diagnostic resolution in tumors under 2 cm. The deficiencies in diagnostic screening and sensitivity are seen by the mean tumor size of HCC with the state of Louisiana being 6.5 cm well above Milan Criteria.

## STAGING AND PROGNOSIS

Multiple staging systems exist for HCC, but the Barcelona Clinic Liver Cancer (BCLC) staging, and prognostic system appear to be the most widely accepted. BCLC incorporates tumor stage, cirrhosis stage, and functional performance status and links stage with a treatment algorithm.<sup>[43-45]</sup> Despite multiple valid staging systems, the most attractive system would be the staging of HCC on genomic finger printing directing therapy and resource allocation such as liver transplants.

Very early stage HCC (Stage 0) are tumors < 2 cm have the best prognosis but are hard to identify on imaging. Early stage HCC (Stage A) is solitary lesions or up to three lesions < 3 cm with preserved liver function (Child-Pugh Class A or B) and reasonable functional status (PS 0-2) with. Their 5-year survivals reach 50-75%. Intermediate stage HCC (Stage B) is multi-nodular with preserved liver function (Child-Pugh Class A or B) and good functional status (PS 0), and no cancer-related symptoms or evidence of vascular invasion. Advanced stage HCC (Stage C) demonstrates vascular invasion or extra-hepatic spread with compromise of functional status (PS 1 or 2) due to HCC. Terminal stage HCC (Stage D)

have tumor marked with vascular invasion and extra-hepatic spread with decompensated cirrhosis (Child-Pugh Class C), poor functional status (PS > 2).

## TREATMENT OPTIONS

Surgical resection is an excellent option but has a limited utility due to advanced cirrhosis and is employed in < 5% of patients.<sup>[46]</sup> Candidates for resection include: (1) Child-Pugh Class A; (2) hepatic venous pressure gradient < 10 mmHg; (3) platelet count > 100,000; (4) future remnant > 25% (non-cirrhotic); and (5) 50% (cirrhotic) resulting in a 70% 5-year survival.<sup>[47,48]</sup> The future remnant can be augmented by pre-operative portal vein embolization. Unfortunately, the majority of patients develop either new HCC or recurrent tumor within 5-year exceeding 70% but if the tumor burden remains within Milan they are candidates for salvage transplant.<sup>[49,50]</sup>

Liver transplantation is reserved for unresectable or decompensated cirrhotics with HCC within the Milan criteria: (1) One lesion ≤ 5 cm and (2) three lesions ≤ 3 cm could provide a > 70% 5-year survival.<sup>[51]</sup> Current organ allocation in the United States is performed utilizing Model for End-stage Liver Disease with HCC receiving exception point varying from 22 to 34 points while patients that exceeding Milan are required to be downstaged by pre-transplant locoregional to reduce dropout and potentially post-operative recurrence.<sup>[52,53]</sup> European centers take an alternative approach whereby laparoscopic resection is liberally employed, and those patients with the highest risk for recurrence are sent for the liver transplant. These factors include lymphovascular invasion and nonencapsulated tumors.

Locoregional therapies include: (1) percutaneous ethanol injection; (2) cryotherapy; (3) radiofrequency ablation; (4) microwave therapy; (5) irreversible electroporation (IEP); and (6) yttrium. Percutaneous ethanol is the least expensive and frequently performed in the office with ultrasound. Thermal ablation is more complex but very effective in smaller tumors (2-3 cm): 70-80% and intermediate tumors (3-5 cm): 50%. Radiofrequency ablation, microwave ablation, and IEP all result in thermal injury, tissue necrosis and apoptosis propagation.<sup>[54,55]</sup>

Several drug delivery systems have been introduced including ThermoDox<sup>®</sup> and Delcath<sup>®</sup> a percutaneous intrahepatic, hepatic perfusion device. ThermoDox<sup>®</sup> is a liposomal delivery system for doxorubicin triggered by heat delivered by an ablation device.<sup>[56]</sup> The Delcath<sup>®</sup> device delivers high doses of chemotherapy to the liver in an isolated circuit under hyperthermic conditions.

Radioembolization or Y-90 is the radiation delivered through microembolization beads. Two versions of Y-90 exist, smaller

beads for end capillary embolization and the larger for arterial embolization both designed to deliver up to 150 Gy of beta radiation.<sup>[57]</sup> Both have relative complications related to their size, embolization stasis methods and radiation intensity. Elevated bilirubin and portal vein thrombosis have become relative contraindications using selective and super-selective approaches. Y-90 has a median survival of 17.2 months in Child-Pugh A cirrhotics and 7.7 months in Child-Pugh B cirrhotics.<sup>[58]</sup>

Trans-arterial chemoembolization (TACE) is a widely adopted therapy for HCC embolizing tumor's arterial supply with or without doxorubicin. TACE has a survival advantage at 1 year (82% vs. 63%) and 2 years (63% vs. 27%) compared to controls.<sup>[59,60]</sup> Increased bilirubin (> 2.5 mg/dL) and portal vein thrombosis are no longer an absolute contraindications utilizing a selective or super-selective approach to tumors.<sup>[61]</sup> Drug-eluting beads have been developed to provide stable and prolonged delivery to decrease doxorubicin toxicity resulting in higher rates of complete response.<sup>[62,63]</sup> Chemoembolization results in the tumor ischemia and hypoxia, which stimulate angiogenic growth factors including vascular endothelial growth factor (VEGF), which potentially-induce tumor angiogenesis and tumor recurrence.<sup>[64]</sup>

Sorafenib is a tyrosine kinase inhibitor that was shown to have a survival benefit over best supportive care in two pivotal studies: (1) sorafenib in patients with advanced HCC and Asian Pacific trials in patients with Child-Pugh Class A cirrhosis, and (2) advanced HCC compatible with Stage C.<sup>[65,66]</sup> Sorafenib is currently the primary chemotherapeutic agent for the treatment of unresectable or recurrent HCC. Multiple adjuvant trials are under way to evaluate the synergistic effects of sorafenib post-resection and ablative therapies. Brivanib is an oral selective dual inhibitor of the fibroblast growth factor and the VEGF pathway, which is being evaluated as a second-line therapy for the management of VEGF stimulation.<sup>[67]</sup> Other agents under investigation include: erlotinib, bevacizumab, lapatinib, gefitinib and cetuximab.

## CONCLUSION

Hepatocellular carcinoma is the third leading cause of cancer mortality world-wide preferentially afflicting lower socioeconomic patients. Dramatic advances have been made to reduce the incidence of HBV and HCV including HBV immunization strategies and the introduction of new direct acting antiviral drugs for the treatment of HCV. With eradication strategies for HBV and HCC, NAFLD and NASH will become the principle etiology for HCC. HCC will become a disease of the obese.

Obesity itself will complicate HCC management particularly surgical interventions including resection and liver transplantation. Concentrated efforts should be placed on early diagnosis. Early diagnosis not only improves patient survival and is far more cost

effective than any late intervention. Several diagnostic strategies lie in the future with the potential identification of circulating tumor cells or identification of a premalignant signature like epigenetic changes. Despite our best efforts to diagnose HCC in earlier stages, this will not be feasible in most. Therapeutic efforts should be redoubled into the development of new drug delivery systems and platforms to improve chemotherapeutic monotherapy or platform assisted surgery with agents such as nanoparticle and liposomal delivery systems.

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**How to cite this article:** Buell JF. *Hepatoma Research: the beginning of a new forum.* *Hepatoma Res* 2015;1:1-5.

**Source of Support:** Nil. **Conflict of Interest:** None declared.