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Liver Cancer: From Detection to Treatment

by Michael P. Curry, Sentia Iriani

EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. The majority of disease burden occurs in Asia and sub-Saharan Africa due to endemic hepatitis B (HBV).[1] In the United States, the incidence of HCC has more the doubled over the past two decades and is increasing. This is largely due to the growing number of patients with advanced liver disease from hepatitis C virus (HCV) infection and the burgeoning epidemic of non-alcoholic fatty liver disease (NAFLD). HCC has a strong male preponderance with a male to female ratio estimated to be 2.4. Among both men and women in the United States, death due to liver cancer has increased at the highest rate of all cancers in the past decade.[2] Worldwide, HBV accounts for 54% of all HCC in adults and almost all childhood HCC cases. HCV is the major risk factor for HCC in Europe and North America.[3]

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Hepatocellular carcinoma is 15 to 20 times higher in persons infected with HCV as compared with those without HCV, and most occur in patients with advanced fibrosis or cirrhosis. Cirrhosis is an important risk factor for the development of HCC and approximately one third of patients with cirrhosis will develop HCC over their lifetime.[4] Roughly 30-40% of cases of HCC in Western countries occur in patients without HBV or HCV. These cases are related to alcohol, hemochromatosis, alpha-1-antitrypsin deficiency, autoimmune hepatitis and possibly NAFLD, given the associations between and increased risk of HCC with obesity and diabetes.

Prevention

There are limited effective strategies proven to reduce the risk of HCC. Infant vaccination against HBV has proven to be the most successful preventive strategy for HCC and has been associated with the most dramatic reduction in the incidence of HCC in children ages 6-14 years.[5] The use of antiviral therapy in chronic HBV has also been associated with reduction in HCC development.[6] Historically, achieving a sustained virologic response (SVR) in patients with HCV infection

using interferon has resulted in a decreased risk of future HCC across all stages of liver disease including cirrhosis.[7] There is some controversy about the risk of HCC in HCV patients who have been treated with direct acting antiviral (DAA) therapy. Some studies suggest an increased risk of HCC recurrence and de novo HCC in patients with HCV cirrhosis treated with DAA.[8] The use of HMG-coA-reductase inhibitors ("statins") has been associated with a reduction in the risk of HCC in a meta-analysis of observational studies and randomized trials.[9] Two meta-analyses have demonstrated an inverse relationship between coffee consumption and HCC supporting a reduced risk of liver cancer among individuals with and without a history of liver disease.[10,11] Lastly, the use of metformin has been associated with a reduced risk of HCC in patients with diabetes.

Surveillance

The American Association for Study of Liver Disease (AASLD), the European Association for Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) recommend surveillance for HCC for patients at high risk of HCC development in order to detect tumors at an early stage when they are amenable to curative therapy. The rationale for surveillance is based on data from a randomized study comparing outcomes in HBV patients assigned to screening ultrasound (US) and alpha-fetoprotein (AFP) every 6 months versus no surveillance. In the surveillance group, HCC was detected at an earlier stage and curative treatment successfully resulted in a 37% reduction in mortality. Additional non-randomized studies of screening for HCC in cirrhosis support the role of surveillance for an earlier diagnosis, potential curative therapies and improvement in overall survival (Table 1).[12]

Despite these guidelines, surveillance is underutilized. In a study of patients diagnosed with HCC between 2005 and 2011, only 20% had undergone surveillance. Nineteen percent of patients had unrecognized cirrhosis, 20% had unrecognized liver disease, 38% lacked surveillance orders and 3% failed despite surveillance orders.[13] A more recent study performed in the Veterans Administration health service showed that only 53.5% of patients had received surveillance in the two years prior to HCC diagnosis. However, only 23.1% of patients with NAFLD related HCC received surveillance as compared with 51.8% of HCV-related and 47.4% of alcohol-related HCC suggesting that more work needs to be done educating physicians on the correlation between NAFLD cirrhosis and HCC.[14] In order to improve the effectiveness of HCC surveillance, there will need to be improved recognition of liver cirrhosis in all at risk populations and initiation and compliance with surveillance.

Diagnosis

Hepatocellular carcinoma develops in the background of a field defect of either viral infection or advanced

Table 1. Studies That Have Evaluated the Role of Surveillance in HCC

Author	Tool	Outcome
Wong et al. 2000	US &/or AFP	Survival: 1399 v 234 days
Bolondi et al. 2001	Semi annual US & AFP	Survival 30 v 15 months
Santagostino et al. 2003	US & AFP	No difference in single nodule detection
Sangiovanni et al 2004	Annual US & AFP	Mortality rate per year reduced in treated: 34% - 5%
Santi et al 2010	US with or without AFP	Survival: 6 m: 45 m vs. 30m (12m)
Yeh et al 2014	US	31% reduction in mortality

Table 2. Criteria and Outcome for HCC Patients Undergoing Liver Transplantation

Transplantation criteria	Post Transplant Survival	Comments
MILAN CRITERIA • 1 ≤ 5cm/3 ≤ 3cm	85% 4 years	Based on size and number
UCSF • 1 ≤ 6.5cm/3 ≤ 4.5 with TTD ≤ 8cm	80.% 5 years	Based on size
UP-TO-7 CRITERIA • Sum of Max TD and # < 7	Beyond Milan but within up to 7 71.2% 5 years	Based on size
TOTAL TUMOR VOLUME (TTV) • TTV ≤ 115 cm3 • AFP ≤ 400 ng/mL	Beyond Milan but within TTV/AFP 74.6% 4 years	Size and number and biological marker (AFP)
EXTENDED TORONTO CRITERIA • No limit size / number • No vascular invasion • No extrahepatic spread • No cancer related symptoms • Not poorly differentiated	Beyond Milan but within ETC 68% 5 years	No size and number limit but biological behavior (cancer-related symptoms and tumor differentiation)
KYOTO CRITERIA • Number ≤ 10 tumors • Size ≤ 5cm • DCP ≤ 400AU/ml	Beyond Milan but within Kyoto 65% 5 years	Size and number and biological marker

fibrosis or cirrhosis.[15] Hepatocarcinogenesis should be considered as a continuum with dedifferentiation from regenerative nodule through dysplastic nodule to early and subsequently overt HCC. Unlike regenerative and dysplastic nodules, which have portal and arterial blood supply, unpaired hepatic arteries solely supply HCC.[16] This results in the characteristic vascular pattern on arterial enhancement and portal venous phase washout on cross sectional multiphase imaging. In 2005, the AASLD and EASL panel of experts adopted a new HCC radiological algorithm, which has been validated. The diagnostic accuracy of a single dynamic technique showing intense arterial uptake followed by ''washout'' of contrast in the venous-delayed phases has been demonstrated. Non-invasive diagnosis was established by one imaging technique in nodules above 2 cm showing the HCC radiological hallmark and two coincidental techniques with nodules of 1–2 cm in diameter (computed tomography (CT) and magnetic resonance imaging (MRI)). Recent updated AASLD guidelines have proposed that one imaging technique (CT or MRI) showing the HCC radiological hallmark suffices for diagnosing tumors of 1–2 cm in diameter.[17] For tumors that meet radiological criteria, biopsy is no longer indicated. However, liver biopsy is recommended by AASLD, EASL and the National Comprehensive Cancer Network (NCCN) for nodules > 1cm if radiological criteria are not present on multiphasic imaging. The NCCN guideline also allows for repeat cross sectional imaging at a 3-month interval for nodules between 1-2cm to determine if the tumor characteristics have changed.[3,17,18]

Histological assessment of tissue obtained by needle biopsy of a nodule allows for assessment using a number of techniques to establish the diagnosis of HCC. The presence of an increase in clear to cytoplasm (N:C) ratio and degree of cellular atypia can provide clues to the presence of HCC. Disruption of the normal reticulin pattern adds additional evidence. The use of immunohistochemical assessment to demonstrate positive staining for HepPar1 and polyclonal CEA can establish origin of the cells and lastly the use of

Table 3. Common Modalities Used for Loco-Regional Destruction of HCC

Therapy	Mechanism of Injury	Technical Notes	Best for:
Thermal ablation	Thermal coagulation/ heat fixation	RF or MW devices	Small <3 cm, fewer number (<3) Better tolerated in liver dysfunction
Chemoembolization	Ischemia + chemotherapy	Lipiodol Drug-eluting beads	Large >3 cm* Multifocal Selective TACE with T bili > 2.0
SIRT / Y90	High dose B radiation	Glass or Resin beads	Infiltrative with portal vein invasion Limit to T bili <2.0

glypican 3, gluthamine synthase and heat shock protein 7 which are relatively sensitive for HCC can help in the definitive diagnosis.

Staging

Clinical staging of HCC is an essential part of the evaluation to assess prognosis and to guide therapeutic interventions. Numerous staging systems have been developed and are employed. The Chinese University Prognostic index (CUPI) and the Cancer of the Liver Italian Program (CLIP) have been validated, include prognosis based on tumor stage and sub-classify patients at advanced stages of liver cancer.[19,20] The Japanese Integrated Staging (JIS) has been modified to include the biomarkers AFP, AFPL-3 and des-gamma-carboxy prothrombin (DCP).[21] While there is no worldwide consensus as to which system should be used, the AASLD and EASL recommend use of the Barcelona-Clinic Liver Cancer (BCLC) staging system. The BCLC divides patient into 5 stages (0, A, B, C and D) according to established prognostic variables and allocates therapies based on tumor stage, functional capacity and degree of liver dysfunction.

Treatment

Treatment of HCC requires that due consideration be given to the tumor burden, stage of liver disease and the patient's performance status. This is best assessed by a multidisciplinary team approach that includes hepatologists, surgeons, oncologists, radiologists and interventional radiologists, pathologists and radiation oncologists.

Surgical resection and liver transplantation are the mainstays of HCC treatment as they offer the best outcomes in patients with early disease stage and afford patients a five-year survival of 60-80%. Liver resection is the treatment of choice for patients with non-cirrhotic HCC. Improved outcomes for patients with cirrhosis and HCC has occurred as a result of refinements in surgical technique and appropriate selection of candidates. Some selection criteria to enroll appropriate patients for liver resection include a hepatic venous pressure gradient (HVPG) of < 10mmHg and a platelet count of > 100,000.mm3. Adjuvant and neo-adjuvant therapies have not been conclusively shown to decrease the risk of or recurrence of de-novo tumor in patients undergoing surgical resection for HCC.

Loco-regional therapy is considered first line treatment for patients not suitable for surgical resection. Additionally, this therapy may be utilized by transplant programs to "bridge" patients to transplantation or to downstage patients who are outside acceptable criteria for liver transplantation. Loco-regional therapies include local ablation of the tumor by chemical or thermal destruction, chemoembolization with conventional chemoembolization or drug eluting beads and radio embolization. Radiofrequency ablation (RFA) and transarterial chemotherapy are most commonly used for loco-regional therapy of HCC (Table 3). Percutaneous ethanol injection (PEI) and RFA are suggested for patients with BCLC stage A disease and tumors up to 3 cm. Transarterial chemoembolization (TACE) is the recommended treatment for intermediate stage HCC. Conventional TACE (cTACE) and drug eluting bead TACE (deb-TACE) are both used in patients with intermediate stage disease. Deb-TACE is better

Table 4. The AFP Model for Prediction of HCC Recurrence After Liver Transplantation

Variables	b coefficient	Hazard ratio	Points
Largest diameter,cm	0	1	0
< 3	0.272	1.31	1
3-6	1.347	3.84	4
>6			
Number of nodules	0	1	0
1-3	0.696	2.10	2
>4			
AFP level , ng/ml	0	1	0
< 100	0.668	1.95	2
100-1000	0.945	2.57	3
>1000			

tolerated, however cTACE may offer better long term results. Radioembolization can be used in patients with intermediate stage disease who do not respond to, or have contraindications to TACE. It can also be applied in the setting of portal vein thrombosis or tumor thrombosis.

Liver transplantation (LT) is considered for patients with compromised liver function and small multifocal tumors or single tumors of modest size. Liver transplantation has the added advantage of curing the tumor as well as the underlying liver cirrhosis. However, in the equitable distribution of liver grafts, patients receiving liver transplantation for HCC should have the same outcome in as those patients undergoing liver transplantation for non-HCC indications. The Milan criteria, proposed in 1996, established the tumor size and number criteria for patients with HCC that demonstrated a similar survival as compared to non-HCC liver transplant recipients.[22,23] Several other sets of criteria have been published and are utilized to select suitable candidates with HCC for liver transplantation in different geographic locations around the globe (Table 2).

Recurrence after Liver Transplantation

Although many single center studies have shown excellent post-transplant outcome for HCC using Milan or modestly expanded criteria for patient selection, registry data that reflect more global experience with liver transplantation have continued to show inferior results with HCC compared to non-HCC indications. There is an urgent need to identify reliable factors that can predict recurrence of HCC so that these patients can be excluded from liver transplantation. MacDonald et al. analyzed 11 pre-transplant recipient and donor variables in 1074 patients with HCC meeting Milan criteria to detect association with post-liver transplant tumor recurrence or mortality.[24] Recurrence of HCC was seen in 6% of patients. Univariate analysis identified AFP at listing and at last time point prior to transplantation was associated with higher rate of recurrence. The last AFP prior to liver transplantation was associated with disease recurrence. The optimal cut off of last AFP was a value of > 300ng/dL with the highest odds ratio (OR) for HCC recurrence of 2.52.[24,] A model has been developed and independently validated to predict recurrence of HCC based on pre transplant characteristics. The AFP model contains 3 independent pre- transplant predictors of tumor recurrence (tumor size, tumor number and AFP level at the time of listing for liver transplant). A score calculated by addition of points for each variable can differentiate patients a low (≤ 2 points) and high risk (>2 points) of recurrence and survival after transplantation (Table 4).[25,26]

Systemic Therapies

Sorafenib is currently the only approved first line systemic therapy for the treatment of advanced HCC not amenable to surgical resection. This drug has shown survival benefits of three months.[27] A subsequent trial demonstrated that sorafenib was associated with over survival (OS) times of > 20 months.[28] Regorafenib, a second line multi-kinase inhibitor, has been shown to prolong survival in patients with advanced stage HCC that has progressed despite sorafenib.[29] A number

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of immunotherapies are currently in clinical trial for patients with HCC. Nivolumab has demonstrated efficacy in providing durable responses in both regorafenib naïve and experienced patients with HCC.[30]

CONCLUSIONS

Hepatocellular carcinoma continues to be a significant cause of morbidity and mortality in patients with chronic liver disease. Despite the improvements in imaging and therapeutics, only tumors diagnosed in early stages effectively respond to treatment. Surveillance rates for HCC are low due to unrecognized cirrhosis. Locoregional therapies, surgical resection and transplantation allow for improved survival. For patients with advanced stage disease, there is a need for novel and effective therapies. ■

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