Curr Surg Rep (2016) 4:20
DOI 10.1007/s40137-016-0143-4



# Management of Hepatocellular Carcinoma (HCC)

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Published online: 3 May 2016


**Abstract** Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third leading cause of cancer-related death. Historically, HCC has been a problem mostly faced by patients from Asian countries due to the high prevalence of hepatitis B (HBV). Increasing global rates of HBV, hepatitis C, and obesity-related non-alcoholic steatohepatitis has caused a global increased incidence in HCC. Potentially curative therapies for HCC include liver resection, liver transplant, and radiofrequency ablation. More advanced HCC may be palliated with transarterial chemoembolization, transcatheter radioembolization, and sorafenib. Appropriate surveillance for those at risk and accurate clinical staging allows for earlier diagnosis and improved chance for cure. Hepatic resection remains the preferred primary therapy for HCC in the setting of relatively preserved liver function, while liver transplantation is the preferred curative therapy in the setting of small tumor burden with underlying liver disease. The application of locoregional therapies can also cure small lesions and maximize the utility of the limited donor pool by temporizing HCC and reserving livers for those who succumb to their underlying chronic liver disease.

**Keywords** Hepatocellular carcinoma · Liver resection · Liver transplant · Radiofrequency ablation · Transarterial chemoembolization · Transarterial radioembolization

This article is part of the Topical Collection on *Surgical Oncology*.

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## Introduction

Hepatocellular carcinoma (HCC) is one of the single largest drivers of cancer specific mortality globally. Historically a daunting challenge for Asian countries, an exponential rise in the cases of HCC in the US is linked to the increased incidence of inflammatory liver disease in America. According to the American Cancer Society, HCC rates in the US increased 43 % between 2001 and 2011, and the most recent estimates predict an increase in HCC rates this year compared to 2015 in a climate where all other recorded cancer subtypes show steady decreases in frequency. The vast majority of HCC tumors occur in patients with underlying liver disease and cirrhosis from hepatitis B (HBV), hepatitis C (HCV), alcohol related liver disease, and non-alcoholic steatohepatitis (NASH). Worldwide, HBV and HCV account for 75–80 % of HCC cases, but the epidemic of obesity-related liver disease in America suggests that within the next several years, NASH-related HCC will surpass alcohol and viral hepatitis with respect to cancer risk and cancer specific mortality in the US. The chronic inflammation of the four mentioned disease states proceeds from cirrhosis to HCC through accumulated oncogenic mutations [1–4, 5•].

## Screening and Diagnosis

The vast majority of HCC cases develop in an identifiable high-risk patient population amenable to serial screening methods. The disease develops without overt symptoms, so screening patients is critical for early detection [6]. Screening patients has been shown to be cost effective and increase survival [7–9]. Biannual screening using ultrasound has been adopted by many countries. It is non-

invasive, readily available, and associated with a sensitivity of 60–80 % and specificity greater than 90 %. Ultrasound, however, remains highly operator dependent and less sensitive in picking up cancers in severely cirrhotic patients or in the setting of extreme obesity [10]. For this reason, cross-sectional imaging with CT or MRI has been adopted by many as more sensitive, specific, and applicable to a patient population where such technologies are available [11, 12].

Serum alpha-fetoprotein remains the only serologic marker for screening AFP. It is difficult to interpret in the setting of inflammatory liver disease and has become increasing less reliable unless extremely elevated where it is associated with a poor prognosis. AFP as an independent variable does not add to the diagnostic accuracy of ultrasound alone [10, 13].

If a nodule is discovered on ultrasound, further diagnostic recommendations are based on the size of the lesion. A mass less than 1 cm is followed more closely with serial ultrasounds every 3 months to monitor for enlargement. For lesions greater than 1 cm, cross-sectional imaging, either CT or MRI, is utilized to better characterize the lesion. Enhancement on arterial phase imaging with venous or delayed-phase washout is considered diagnostic of HCC in a patient with underlying liver disease. Biopsy is reserved for worrisome lesions without characteristic enhancement. Contrast-enhanced ultrasonography is no longer considered an acceptable diagnostic technique [14].

## Staging

Staging of HCC is associated with unique challenges due its variances in epidemiology, risk factors, and concurrence with liver disease. TNM staging requires surgical pathology analysis, but only a fifth of HCC are resected. For this reason, there are several non-pathology-based staging systems used to predict prognosis taking into account both tumor specific and liver specific variables that impact eligibility for treatment and survival [15, 16]. Examples of staging systems more commonly employed in HCC include the Okuda staging system, Chinese University Prognostic Index (CUPI), Japanese Integrated Staging (JIS), French classification, Cancer of the Liver Italian Program (CLIP), and, what is most widely used in the West, the Barcelona Clinic Liver Cancer staging system [17]. The BCLC system takes into account tumor characteristics, liver function as demonstrated by the Child–Pugh classification, health performance status as calculated by the Eastern Cooperative Oncology Group Performance Status (ECOG) tool, as well as clinical parameters such as the presence of portal hypertension, and symptoms [18, 19••].

## Liver Resection

Liver resection remains the standard therapy for patients without documented liver disease. Anatomic resection has been found in some series to be superior to non-anatomic resection, presumably by eliminating occult intrahepatic metastases in the related portal vein tributary [20]. Liver resection in patients with no underlying liver disease is associated with a 1-year survival that exceeds 85 %. Long-term survival remains dependent on the grade of the tumor, size, and the presence or absence of micro- or macrovascular invasion. Liver resection in patients with underlying liver disease is plagued with a 75 % 5-year recurrence rate. Recurrences within 2 years of resection are considered true recurrences or intrahepatic metastases; after 2 years, recurrences are considered *de novo* or late recurrences and linked to the etiology of the liver disease [21]. The patients who do well long term are BCLC stage 0, Child's Pugh class A patients with well-compensated liver disease (normal portal pressures and bilirubin), and a single tumor less than 2 cm [19••]. Resection is considered the standard of care and associated with an overall 5-year survival rate of over 90 % [22, 23•].

## Liver Transplant

Liver transplantation is associated with the ability to eliminate both the existing cancer including the risk of de novo tumor emergence in the at-risk remnant and the underlying liver disease. Liver transplant is the preferred treatment for BCLC stage A or B patients with increased bilirubin and/or portal pressures without other contraindications to transplant. There are several eligibility criteria for transplant of which the Milan Criteria has been adopted nationally and includes patients with a single tumor 5 cm or less in diameter or up to three lesions less than 3 cm, no macrovascular involvement, and no identifiable extrahepatic spread. Strict application of these guidelines result in long-term (>6 years) survival rates of 70–85 % and 5-year recurrence free survival between 83 and 92 % [24••, 25–27]. Given the stark difference in survival between transplant and other treatment modalities, many institutions have adopted broader eligibility criteria without observing a significant decrease in long-term survival. The University of California San Francisco (UCSF) criteria demonstrate similar outcomes to the Milan criteria and include a solitary tumor less than 6.5 cm or 3 or fewer nodules, the largest of which being less than 4.5 cm and with a sum total tumor diameter less than 8 cm. Patients transplanted within UCSF criteria experience survival rates of 90 and 75 % at 1 and 5 years, respectively [28, 29, 30•].

Additionally, Mazzaferro et al., responsible for the Milan criteria, have put forward a new set of criteria called the up-to-seven criteria, which propose that transplant is an acceptable treatment for patients for whom the sum of the tumor with the largest diameter in cm and number of additional tumors is seven or less. These patients have marginally inferior outcomes to the Milan criteria with approximately 88 and 76 % 1 and 5-year overall and tumor-free survival [31, 32]. The ability to broaden eligibility for transplant has allowed for considerably more patients to experience long-term survival.

Transplant as an option for treatment of HCC is complicated by the shortage of organs. In the United States, the Organ Procurement and Transplant Network (OPTN) via the United Network for Organ Sharing (UNOS) is responsible for the allocation of organs, and does so by prioritizing livers for the sickest patients. OPTN uses the MELD score to rank patients. For the purposes of prioritizing HCC, OPTN employs the American Liver Tumor Study Group (ALTSG) modification of the TNM classification. Patients who are stage 2 (T2), which means they have either one nodule, 2–5 cm or two or three nodules, all $\leq$3 cm, are given an automatic priority and started with a MELD of 22. Every 3 months, these patients are given additional points, reflecting a 10 % increase in mortality, but cap at a MELD of 34. This is because stage 2 patients have a 15 % 3-month mortality and risk tumor progression beyond Milan criteria. 10–20 % of patients drop out before being able to receive a liver mostly due to death or increase in tumor stage. Patients with smaller or larger tumors than stage 2 may be listed but do not receive this automatic priority [33–37].

Due to the risk of progression of HCC while waiting for transplant and the finite donor pool, strategies have evolved to maximize limited organ availability. The use of a living donor liver transplant (LDLT) is a potential alternative to cadaveric liver transplantation but remains controversial as it puts a donor potentially at risk of death. Nonetheless, LDLT provides a high-quality organ available for an elective transplant schedule. This allows for optimal timing of the transplant and minimizes the risk of tumor progression. It also has the advantage of decreasing the number of patients on the waitlist. There are three major issues related to LDLT that lessen enthusiasm for this approach: (1) the inherent risk to the donor, (2) the theoretical risk that the regenerative response in the recipient is associated with up-regulation of growth factors that may promote occult tumor growth, and (3) the risk of graft failure and the need for salvage transplant as a priority-one, bumping a patient who was previously on the general waitlist to the top of the list [38–43].

Salvage liver transplant is a transplant performed for in response to HCC recurrence after liver resection. Viability of this option has been explored to allow resection of larger tumors while a patient remains on the waitlist. The goal is to prevent disease progression while waiting for transplant. As with LDLT, salvage transplant is debated as some publications have demonstrated significantly greater mortality after salvage transplant compared to primary transplant and suggest salvage should be reserved for highly selected patients with small tumors and minor comorbidities [44, 45].

As waitlist times have lengthened, therapies to bridge patients prior to transplant are being utilized more frequently. The goal of these therapies is to prevent or delay tumor progression through locoregional therapy while patients await availability of a liver transplantation. Current modalities include radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and stereotactic body radiotherapy (SBRT) [37]. Depending on the waitlist drop-off rates of a given region or institution (studies point to a monthly dropout rate of 4 %, consisting of 1 % from worsening liver disease and 3 % from tumor progression), bridging therapy may be more or less relevant. There is general consensus that some form of liver directed therapy is appropriate in T2 patients who will wait longer than 6 months for liver transplant. T1 patients generally do not require bridging therapy but at a minimum require radiographic surveillance every 3 months and AFP monitoring. This recommendation is based on the odds that T1 patients progress to T2 at a rate of 2.1 % at 3 months and 5.3 % at 6 months. Elevated AFP greater than 200 ng/mL indicates a higher risk of progressive disease [46, 47]. While international consensus does not recommend a particular modality for bridging [48], RFA appears to be the most effective modality for solitary tumors, especially those less than 3 cm in size. Pathologic examination of explants shows RFA to result in greater tumor necrosis than TACE. An additional benefit of RFA when done laparoscopically is that it provides the ability to stage the tumor more accurately [49, 50]. TACE is effective for larger lesions and the presence of multiple nodules. Preliminary studies have shown benefit in combining these therapies, but further investigation is needed.

Down-staging refers to reduction in the stage of HCC using locoregional therapies from tumors outside accepted criteria for transplantation (i.e., T3 or higher), to T2. There are single institution series suggesting equal survival in patients down-staged into transplant criteria compared to those transplanted within criteria [51–54]. However, such studies lack the prospective clinical trial data that would eliminate the bias inherent to retrospective series, so down-staging remains controversial and limited to highly selected patients with favorable tumor biology. For example, patients with markedly elevated AFP and tumors outside

criteria, patients with infiltrative tumors, and patients with macrovascular invasion are currently not eligible for transplant even with down-staging. Studies show liver resection after down-staging can be performed between 6 and 17 % of the time with 5-year survival of between 25 and 60 %. Liver transplant rates for down-staging in intention to treat analyses range from 25 to 90 % and 3-year survival between 71 and 76 % with a 3-year recurrence rate of 11 % and 3-month dropout rate of 3.5 % [51, 55].

## Locoregional and Other Adjuvant Therapies

RFA is an effective technique for small, early-stage tumors (less than 3 cm) as a bridge to transplant or as primary treatment when transplant and resection are not options. Larger tumors are more difficult to treat with this technique, and the risk of marginal recurrences at the periphery of the treatment zone increases with the size of the lesion being ablated. RFA can be performed percutaneously, laparoscopically, or during open surgery using ultrasound guidance. Laparoscopic and open surgical approaches have the benefit of allowing for improved staging with lymph node analysis and identification of small extrahepatic metastases that would otherwise be missed on imaging. Up to a quarter of tumors are not suitable for RFA due to location [49, 56, 57]: subcapsular tumors, as well as those adjacent to the gall bladder, or major vessels risk complications and heat sink phenomenon [58]. For BCLC stage 0 tumors, RFA is curative, with 97 % response rate and 70 % 5-year survival. This implies that if combined with close surveillance, RFA could obviate the need for resection or transplant, unless transplant becomes indicated for liver failure from progression of cirrhosis. Since it has the additional benefit of sparing liver parenchyma, RFA decreases the chance of hepatic decompensation. Serious consideration should be given to making RFA first line therapy for BCLC stage 0 tumors. RFA alone, however, fails to be as effective as resection for tumors less than 3 cm [56, 59•, 60, 61]. Prior to development of RFA, PEI was widely used but eventually found to be inferior to RFA. Studies predominantly from Asian centers have demonstrated that combined PEI–RFA is more effective than RFA alone at achieving tumor necrosis, has improved long-term outcomes, is well tolerated, has negligible complications, and may be as effective as resection for tumors less than 3 cm [62–64].

TACE involves localized arterial injection of a mixture of chemotherapeutic agent, generally doxorubicin or epirubicin, and lipiodol, which is selectively retained in hepatomas. Recently, the PRECISION V trial introduced drug-eluting beads as a superior treatment to conventional TACE [65]. TACE has shown effectiveness for patients outside of Milan criteria, identified as BCLC stage B. TACE provides a survival benefit, increasing median survival time to 20 months from 16 with 49 % 2-year survival. Decompensated liver disease with ascites or jaundice is contraindications [66, 67]. TACE and RFA work well in concert with each other, especially in treating solitary tumors up to 5 cm in size. Combination treatment decreases 3-year recurrence rates from 39 % with RFA alone to 6 % [68].

Transarterial radioembolization (TARE) with yttrium-90 (Y90), a pure beta emitter, is an alternative catheter based technique delivered into the tumor bed via the hepatic artery [69, 70]. There is currently no published prospective head-to-head comparison between DEB-TACE and Y90, but there is a clinical trial underway [71]. Retrospective studies suggest that TACE and Y90 are equivalent [72], but that in selected patients with portal vein thrombosis, Y90 is better tolerated and associated with less post-embolization symptoms [69, 72, 73].

Stereotactic body radiation therapy (SBRT) delivers a limited number of high dose radiotherapy fractions to the tumor. The largest series describing SBRT for HCC is 93 patients from Asan Medical Center in Seoul Korea. They treated a combination of Child–Pugh A and B patients with tumor sizes ranging from 1 to 6 cm in diameter in patients otherwise not candidates for resection. They reported a complete in-field response rate of 16 % and in-field progression-free survival at 3 years of 92 %. Most failures were in tumors larger than 3 cm [74]. SBRT has promise as a therapy to complement other locoregional options in patients who are not candidates for other ablative therapies, such as patients with tumor vascular thrombus. It remains to be seen if survival is improved with SBRT as it has been demonstrated with other modalities [75–77]. Currently, a clinical trial comparing SBRT to sorafenib is underway.

HCC tends to be resistant to chemotherapy. Several studies have evaluated the role of systemic adjuvant chemotherapy without demonstration of benefit [19••, 42]. Sorafenib, an orally active, multi-targeted tyrosine kinase inhibitor is the standard therapy for advanced HCC and currently the most potent systemic therapy available. This medication inhibits the vascular endothelial growth factor receptor (VEGFR) intracellular kinase pathway, and its effect is likely due to inhibition of tumor angiogenesis through interruption of this pathway [78]. The Sorafenib HCC Assessment Randomized Protocol (SHARP) Trial compared sorafenib to placebo in Child–Pugh A cirrhotic patients with inoperable HCC. Overall survival was 10.7 months in the sorafenib group compared to 7.9 months in the placebo group. Radiologic progression was slower in the sorafenib group as well, taking 5.5 months in the sorafenib group versus 2.8 months in the

**Table 1** A summary of indications and outcomes for HCC treatment strategies

| Treatment | Indication | 1-year survival (%) | 3-year survival (%) | 5-year survival (%) | Median survival (months) |
|---|---|---|---|---|---|
| Liver resection | Tumor <2 cm, no underlying liver disease | – | – | 90 [23•, 24••] | – |
| | Milan or UCSF criteria (meld <10) | 84–98 [61] | 57–84 [61] | 43–76 [61] | – |
| Liver transplant | Milan criteria | – | – | 75 [24••] | – |
| | UCSF criteria (but not meeting Milan) | 71 [30•] | – | 57 [30•] | – |
| | Down-staged with adjuvant therapy | – | – | 25–60 [51–54] | – |
| Radiofrequency ablation | Tumor <3 cm | – | – | 70 [56, 59•] | – |
| Transarterial chemoembolization | BCLC stage B | – | – | 22.5 [66, 67] | 20 [66, 67] |
| Transarterial radioembolization | BCLC stage B | – | – | – | 15–22 [69, 73] |
| Stereotactic body radiation therapy | <5 cm | 67–75 [77] | – | – | – |
| | <3 cm | – | 73 [77] | – | – |
| Sorafenib | BCLC stage C | – | – | – | 10.7–14.5 [79•, 80] |

placebo group. Sorafenib is generally well tolerated with diarrhea and hand–foot skin reaction representing the majority of side effects experienced [79•]. Meta-analysis shows that combination of sorafenib with TACE was also modestly effective at improving time to progression from 7.1 to 9 months but did not prevent progression [80].

## Conclusion

Management of HCC continues to improve as newer therapies combined with resection and transplant become more precise and better tolerated in even patients with more advanced liver disease (Table 1). Better surveillance has allowed for early detection and allow treatments to have a higher rate of cure. In early-stage disease, the difference in outcome between surgical and non-surgical methods, like RFA, is minimal. There is ample evidence that RFA can be curative in small lesions, and this therapy will continue to challenge the role of resection as the primary therapy for BCLC stage 0 tumors. Since many patients who present with HCC have moderate to severe liver insufficiency, liver transplant remains a critical method to eliminate the cancer and cure the underlying liver disease. For this reason, patients with vulnerable liver disease and cancer are better served in an institution that provides transplant services or is affiliated with such a program; such infrastructure maximizes the number of patients who benefit long term from transplant and allows for aggressive use of locoregional therapies in patients while on the waitlist to diminish drop-off rates due to tumor progression. Improved survival for patients treated with Sorafenib for advanced disease increases enthusiasm for additional therapies for HCC. With improvements in surveillance, early detection of cancer will allow for treatment at a stage where locoregional treatments are effective and transplantation is reserved for patients likely to succumb to progressive liver insufficiency rather than cancer.

**Acknowledgments** This work was supported by a Grant from the Lilly Endowment for the Biomedical Sciences.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Drs. Milgrom, Maluccio, and Koniaris declare no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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