

Hepatocellular carcinoma: Advances in diagnosis, management, and long term outcome

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Abstract

Hepatocellular carcinoma (HCC) remains a common and lethal malignancy worldwide and arises in the setting of a host of diseases. The incidence continues to increase despite multiple vaccines and therapies for viruses such as the hepatitis B and C viruses. In addition, due to the growing incidence of obesity in Western society, there is anticipation that there will be a growing population with HCC due to non-alcoholic fatty liver disease. Due to the growing frequency of this disease, screening is

recommended using ultrasound with further imaging using magnetic resonance imaging and multi-detector computed tomography used for further characterization of masses. Great advances have been made to help with the early diagnosis of small lesions leading to potential curative resection or transplantation. Resection and transplantation maybe used in a variety of patients that are carefully selected based on underlying liver disease. Using certain guidelines and clinical acumen patients may have good outcomes with either resection or transplantation however many patients are inoperable at time of presentation. Fortunately, the use of new locoregional therapies has made down staging patients a potential option making them potential surgical candidates. Despite a growing population with HCC, new advances in viral therapies, chemotherapeutics, and an expanding population of surgical and transplant candidates might all contribute to improved long-term survival of these patients.

Key words: Hepatocellular carcinoma; Transplantation; Survival; Locoregional therapy; Resection

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Core tip: Hepatocellular carcinoma (HCC) is a growing malignancy with poor survival. New therapies for the hepatitis C virus may help prevent the development of this malignancy, however the growing obesity epidemic will continue to foster new cases of HCC. With the aid of advances in imaging patients might be diagnosed earlier making them candidates for curative resection or transplantation. In addition, with a growing population of patients undergoing surgery after being down-staged with locoregional therapy, we expect an improvement in long-term outcomes for HCC patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) remains a common malignancy despite the development of many new treatment modalities over the past two decades. Worldwide HCC represents the fifth most common cancer and the second most common cause of cancer related deaths. Primary liver malignancies account for approximately 7% of all cancers and 90% of those are HCC^[1,2]. Unfortunately, this disease has been on the rise, in both developing and developed countries, and despite a multitude of new therapeutic modalities, patients with HCC still have poor long-term survival. In the United States between 1990-2004, there was a 40% increase in HCC related deaths while overall cancer mortality was significantly reduced^[3]. As this disease continues to plague countries worldwide, the United States, despite all its resources, reports a 5-year survival of only 12%, which although quite low, has been improving over recent years^[4].

Much of the pathophysiology of HCC has been attributed to the long-term inflammation associated with a variety of disease processes ultimately resulting in cirrhosis; however roughly 10% of tumors occur in non-cirrhotic patients^[5]. Worldwide, the most common etiology is hepatitis B virus (HBV) that accounts for approximately 50% of all primary HCCs, despite the available therapeutic modalities used to treat and prevent this virus^[6,7]. Chronically HBV infected patients have a 25% chance of developing HCC, however as vaccination rates have increased worldwide the number of patients with HBV is declining^[8]. In contrast to other primary liver diseases, underlying cirrhosis is not necessarily a requirement for the development of HCC in the setting of HBV. Patients infected with HBV who have high levels of viremia (> 2000 IU/mL), high aminotransferases, co-infection of hepatitis D virus and hepatitis C virus (HCV) are more prone to developing HCC. In addition, other risk factors include infection with HBV genotype C as compared to the other genotypes, advanced age, alcohol consumption, smoking, and family history^[9]. The administration of nucleoside and nucleotide analogues helps with HBV suppression in patients infected with the virus and decreases the overall risk for developing HCC. In addition, great strides have been made in liver transplantation, as HBV prophylaxis in the form of lamivudine, a nucleoside analogue, and hepatitis B immunoglobulin (HBIG) have shown to increase HCC recurrence-free survival as compared with HBIG alone or no prophylaxis in patients undergoing transplantation^[10].

In Western countries, HCV remains the most common cause of HCC, however this could be changing

with promising new HCV therapies on the market^[11]. Worldwide, HCV accounts for approximately 30% of HCC, but unlike HBV, underlying cirrhosis is usually present. Interestingly, HCC is the main cause of death in HCV cirrhosis and the first complication experienced in many of these patients as opposed to other complications such as ascites and gastrointestinal bleeding^[12]. Much like HBV, patients with HCV have a higher risk of acquiring HCC with advanced age, alcohol consumption, smoking, infection with HBV and human immunodeficiency virus (HIV), genotype 1b, obesity, as well as diabetes. Patients treated effectively for HCV, not surprisingly, have a significantly decreased incidence of HCC^[13]. In addition to the effect of the chronic processes, there has been implication that the core protein of HCV has the ability to modulate gene transcription, cell proliferation, and cell death associated in the development of HCC^[14].

Therapy for HCV has been evolving over the years, and recently the introduction of new drugs, including polymerase inhibitors such as sofosbuvir, have made significant headway in controlling the virus. Sofosbuvir is a HCV NS5B polymerase inhibitor that acts against HCV, and is used in conjunction most often with ribavirin for genotype 2 and 3. In a randomized control trial ribavirin and sofosbuvir combination therapy showed a 93% and 85% sustained virologic response in genotype 2 and 3, respectively^[15]. Randomized trials looking at double and triple therapy for genotype 1 showed that ledipasvir-sofosbuvir with or without ribavirin showed > 95% sustained virologic responses^[16]. Thus, drugs such as sofosbuvir are changing the face of HCV therapy.

Alcohol is another common cause of cirrhosis globally, making it a major risk factor for the development of HCC. Alcohol consumption of 80 g/d or higher for more than ten years is associated with a five-fold increase in the development of HCC. In patients with HCV cirrhosis, the use of alcohol nearly doubles the incidence of HCC as compared to those who do not use alcohol^[17]. Alcohol consumption is thought to increase oxidative stress due to metabolism of the ethanol and inflammation, which cause chronic changes in the liver leading to cirrhosis and subsequent HCC^[18]. In addition the induction of CYP2E1, a P450 cytochrome, related to alcohol consumption generates reactive oxygen species leading to carcinogenic consequences^[19].

In Western countries, much like alcohol, non-alcoholic fatty liver disease (NAFLD) is a significant cause of chronic liver disease. Unfortunately, obesity rates have been increasing worldwide, and this has become a problem as it increases all disease burdens associated with being overweight, both cancer and non-cancer related. NAFLD is the most common form of liver disease in adults in the United States and has been an increasing indication for liver transplantation as well. NAFLD can be simply mild steatosis or can progress to non-alcoholic steatohepatitis (NASH), which leads to cirrhosis^[20]. It is concerning that NAFLD occurs in 90% of obese patients and 70% of patients with type 2 diabetes mellitus^[21]. In patients with NASH cirrhosis, the reported

risk of developing HCC is as high as 12.8% over 3 years which is alarming given the growing obesity epidemic in both children and adults. The mechanism behind the carcinogenicity of NASH is oxidative stress, insulin resistance, adipocytokine disorder and hyperplasia^[22]. Cytokines such as interleukin-6 and tumor necrosis factor and inflammation are also increased in NASH leading to activation of STAT3, which is has been shown to be an oncogenic transcription factor^[23].

In addition to these more common etiologies, HCC has been associated with increased exposure to aflatoxins such as *Aspergillus flavus* and *Aspergillus parasiticus* more commonly seen in Africa and Asia. Aflatoxins contaminate corn, nuts, soybeans, and legumes. Studies have shows that frequent p53 mutation maybe seen in high aflatoxin exposure which may explain at least part of the tumorigenesis^[19,24].

Other forms of chronic liver diseases have been associated with HCC such as hemochromatosis, hereditary tyrosinemia type I, alpha-1 antitrypsin deficiency, as well as chronic Wilson's disease^[25]. There has been contention regarding the implication of chronic Wilson's disease, however, without chelation therapy, there have been reports of patients developing HCC^[26].

DIAGNOSTICS

There are a multitude of diagnostic modalities available to physicians that may aid in the diagnosis of HCC. The technology has progressed over the years allowing the diagnosis of small HCC's that would otherwise have been missed using more conventional diagnostics. First, patients at risk for HCC, which include non-cirrhotic and cirrhotic HBV patients, chronic HCV, as well as other patients with chronic liver disease and cirrhosis, warrant screening. The American Association for the Study of Liver Disease (AASLD) has created guidelines for the screening of patients at risk for the development of HCC. These were generated in order to define a group of patients who would benefit from screening modalities in a cost-effective manner. These guidelines include patients who have a 1.5% chance of developing HCC or higher while infected with HCV, or a 0.2% chance with HBV infection. The HBV infected patients who meet these criteria include Asian men over the age of 40 years, Asian women over the age of 50 years, patients with HBV and cirrhosis, a family history of HCC, and Africans. In addition, patients who have HCV related cirrhosis, stage 4 primary biliary cirrhosis, hemochromatosis, and alpha-1-antitrypsin related cirrhosis should be screened as well^[27].

In addition it should be noted that those infected with HIV along with either HCV or HBV should be closely monitored, as HCC tends to develop more readily and rapidly in this population. Although these are not included in any defined guidelines, this might become more prevalent as the HIV population has much improved outcomes and are living longer with the disease^[28,29].

Ultrasound is universally the diagnostic choice for

screening, as it remains cost-effective and benign to patients^[30]. Guidelines state that patients at high risk for developing HCC as those mentioned above should undergo surveillance with non-contrast enhanced ultrasound every 6 mo^[31]. In the past, contrast enhanced ultrasound was recommended however the increased number of false positives have led this modality being dropped recently from the diagnostic imaging recommendations for HCC. Lesions that are less than a centimeter should be followed up in 3 mo with repeat ultrasound. If the lesion remains stable it should be watched every 3 mo but if it enlarges, it should be worked up with further imaging. For lesions 1 cm or greater immediate follow up with multi-detector computed tomography (MDCT) or magnetic resonance imaging (MRI) is indicated. Arterial enhancement and delayed phase washout suggests the diagnosis of HCC^[26].

Ultrasound alone has reported sensitivity of 58%-89% and specificity over 90% depending on the source^[32,33]. Ultrasound itself does not subject the patients to any contrast, which may be a concern for many patients with underlying cirrhosis and concomitant renal disease. The accuracy of ultrasound maybe affected by underlying nodular cirrhosis which is present in most of these chronically diseased liver patients^[29,34].

There have been a number of studies that suggest the use of combining alpha-fetoprotein (AFP) with ultrasound as the method of choice for screening the patients at high risk for developing HCC, however the AASLD has not included this in their recommendations due to the lack of sensitivity and specificity^[35]. Sensitivity of AFP alone has been reported to range from 25% to 65% for detecting HCC as a screening tool, and continues to be debated in its combination use with ultrasound^[36]. AFP has, however, been shown to be a poor prognostic factor when it comes to liver transplantation and disease recurrence. Values greater than 1000 mcg/L are associated with high degree of HCC recurrence after transplantation, and although may not be a contraindication, should be heavily weighted while considering for transplant^[37,38].

Multi-detector computed tomography (CT) scanning remains a very useful tool in the diagnosis of HCC. Advances over the last 10 years have seen CT scanners become considerably faster while attempting to limit the radiation dose. The sensitivity of MDCT is reported at 81% as compared to 91% with MRI in a meta-analysis of 15 comparative studies between MRI and MDCT. The specificity of MDCT was 93% compared to 95% in the MRI group. CT scan does afford the ability to perform three-dimensional reconstructions that may help with operative planning which is an advantage over MRI^[39]. Although a rare event, this mode of imaging does however place patients at risk for contrast induced nephropathy^[40].

Although not included in standard diagnostic guidelines, modern advances show that perfusion CT scanning may offer more information regarding liver hemodynamics and blood flow directed toward tumors in the liver^[41]. This may become more useful as transarterial

chemoembolization (TACE) is an evolving therapy for HCC. It also may aid in treatment monitoring. Current perfusion CT does, however, deliver a higher radiation dose as well as lower resolution^[42].

MRI has been used extensively in the diagnosis of HCC and advances in imaging continue to improve its diagnostic capability. The contrast most commonly used for MRI is gadolinium-based; however newer contrasts are more hepatocyte specific. Gadoxetate dimeglumine is one of these newer agents used and has demonstrated improvement in distinguishing small HCCs including those less than 1 cm. It has also been shown to be effective in distinguishing HCC vs benign liver lesions as compared to other contrasts. Nearly half of this contrast is taken up by hepatocytes and subsequently excreted into the bile in comparison to roughly 5% by standard gadobenate dimeglumine, which supports the improved accuracy in diagnosing liver malignancies^[43,44]. The use of gadolinium based contrast agents should however be used with caution in patients with renal failure given the risk of nephrogenic systemic fibrosis which is a rare disorder associated with fibrosis of the skin, joints, eyes, as well as internal viscera^[45]. The other disadvantage to MRI is the relatively long time it takes to complete the study which maybe a challenge for critically ill transplant candidates who need more detailed imaging before listing for transplant.

Some newer non-imaging modalities for prognosticating HCC, once diagnosed, have been developed over the last ten years, which may pave the way for a tailored approach to treating this malignancy. They also may define populations that either may benefit from more aggressive therapies or a more conservative or palliative approach. More recently microRNA expression in HCC has become a possible prognosticating marker for outcomes in HCC. Looking at HCC and benign liver disease, Jiang *et al*^[46], found that miR-199a, miR-21, and miR-301 all were expressed differentially in HCC tumors. They specifically looked at expression of microRNA's and found that patients could be potentially prognosticated based on specific microRNA expression^[46,47].

Another study looking at gene expression in resected HCC specimens identified 5 genes that could be used for prognosticating HCC. These genes, *HN1*, *RAN*, *RAMP3*, *KRT19*, and *TAF9*, were chosen based on correlations with disease-specific survival (HR = 3.5; 95%CI: 1.9-6.6; $P < 0.0001$). This 5-gene score was found to be associated with disease-specific survival, which upon multivariate was independent of many of the tumor features^[48].

In addition to gene-score and micro-RNA, Kamiyama *et al*^[49] evaluated N-glycosylation of glycoproteins in regards to HCC. They analyzed 369 presumed curative hepatectomies for HCC, and found that the G2890 and G3560 N-glycans were associated with recurrence and prognosis. In fact these two glycans were found to correlate with tumor number, size, and vascular invasion. These biomarkers maybe useful in prognosticating resected patients in the future^[49].

THERAPY

Therapeutic options for HCC have grown considerably over the last few decades. Initially resection was the only option, but now transplantation has emerged as an effective intervention as well as the growing number of locoregional therapies which have been proven quite effective. Rahman performed a large meta-analysis looking at resection vs transplantation looking at comparable early cirrhotic patients. This study found that at 5 years there was a higher disease free survival in patients undergoing transplantation (OR = 0.39; 95%CI: 0.24-0.63; $P < 0.001$) although similar 5-year overall survival. However, at 10-years this study demonstrated a clear overall and disease-free survival for patients undergoing liver transplantation. They did however demonstrate a higher short-term mortality for transplant patients^[50].

Resection remains the first line therapy in patients who have preserved liver function and can be completely resected. In patients with no underlying liver disease, roughly 70%-80% of the hepatic parenchyma can be resected safely due to the ability of the liver to regenerate. Ratio of remnant liver volume to body weight should be $\geq 0.8\%$ according to most literature to avoid post-resection major complications including post-resection liver failure^[51,52]. In cirrhotic patients it is thought that only 60% of the parenchyma can be resected leaving at a minimum 40% of functioning liver^[53,54].

CT volumetrics are used to help in planning resection, however in cases where there is not enough predicted remnant liver, portal vein embolization (PVE), originally reported by Makuuchi *et al*^[55] in 1990, may be utilized to increase the predicted hepatic reserve post-resection. Two-stage hepatectomies in which patients undergo PVE have been compared to one-stage hepatectomies by Schadde *et al*^[56], and showed that they were comparable in outcomes. Two-stage hepatectomy was developed over 10 years ago to allow for more extensive R0 resections while allowing enough remnant liver. The groups were comparable and no significant differences were seen in complications with a relative risk of 0.9 ($P = 0.79$). There were also no significant differences in post-resection liver failure or mortality when comparing two-stage vs one-stage hepatectomy. This technique has expanded the ability to resect patients who would otherwise not be candidates for resection^[56-58].

Unfortunately only 20%-30% of patients who present with HCC are candidates for resection due to either multifocal unresectable tumors or their underlying chronic liver disease. In Western countries only 5% of patients develop HCC without underlying liver disease as compared to that of 40% of Asian countries^[30]. In well-selected candidates without chronic liver disease, survival rates at 5 years approach 70% or higher with surgical resection with margins greater than 1 cm and tumors less than 5 cm^[59,60]. Furthermore, a randomized

control trial showed that 2 cm margins show decreased recurrence rate and improved survival when it comes to solitary tumors^[61].

Selecting patients with chronic liver disease for resection remains a very difficult treatment decision when planning therapy for HCC. Operative mortality is increased in patients with cirrhosis as compared with non-cirrhotics. Determining who is an adequate candidate is difficult however. It is thought that Childs-Pugh A patients are suitable candidates, however these patients may also go into post resection failure, unexpectedly. Both the Childs-Pugh scoring system and model of end stage liver disease have been evaluated to aid in the selection criteria for resection candidates, however neither have been deemed reliable. When evaluating patients in the office a platelet count of 100000 or less, a history of esophageal varices and documented splenomegaly should be factored into the equation regarding liver resection as they all suggest significant portal hypertension. Furthermore, a hepatic venous pressure gradient of greater than 10 mmHg is also a poor prognostic factor for resection as it is a sign of significant liver disease although is very rarely available when initially working up a resection candidate. In patients with underlying liver disease a normal bilirubin, hepatic venous pressure gradient ≤ 10 mmHg, and a small isolated tumor (≤ 3 cm) portends the best outcomes^[3,62]. In patients who have preserved liver function without cirrhosis, anatomic resections should be performed if possible, as they have been associated with improved outcomes. This may not always be possible given certain locations of lesions as well as the patients overall liver function^[63].

More recently laparoscopic and even robotic liver resections have become more common across the world. Not every HCC is amenable to minimally invasive approaches, but smaller, more peripheral lesions that have some distance from major hepatic vasculature can often be resected safely^[64]. Major hepatectomies in 210 patients were performed either completely laparoscopic or hand-assisted and were described in one study that included six major hepatobiliary centers across the world. They reported both right and left formal hepatectomies and converted only 12% of cases to laparotomies. In addition to being able to be performed safely, laparoscopic liver resections have been shown to have less blood loss, in some studies less transfusion requirements, less overall intravenous narcotic usage, and decreased length of stay. In regards to HCC, patients who eventually underwent liver transplantation who had previous laparoscopic resection had shorter hepatectomy and operative times, less blood loss, and less blood transfusions as compared with those who underwent open resection prior to transplant^[65]. In addition to laparoscopic procedures, some centers are performing robotic resections for a variety of cases from segmentectomies to major hepatectomies. Most of the comparative studies show similar blood loss in robotic vs laparoscopic resection, with slightly longer operative

times in the robotic groups but data is mixed^[66,67]. Although minimally invasive resections have been shown to be safe and have some benefit, these procedures should be done concomitantly with laparoscopic ultrasonography and should only be done by surgeons with vast laparoscopic and open experience.

Liver transplantation remains the mainstay therapy for patients with Childs-Pugh class B and C or moderate and severe cirrhosis with HCC, as well as those individuals who have unresectable tumors within Milan or UCSF criteria. The oncologic advantage to liver transplantation includes the ability to completely remove all previously identified tumors as well as any premalignant or non-radiologically present tumor. HCC is frequently a multifocal disease process, and often times patients are found to have numerous small HCC's upon explant of the liver during liver transplantation that were not otherwise seen on modern-day advanced imaging^[68]. Initial results were poor as compared to patients transplanted for non-malignant liver disease, but in 1996 the Milan group defined a group of patients who could achieve excellent survival of 75% at four years. The group initially defined the Milan Criteria as single tumor < 5 cm, three lesions or less with none greater than 3 cm, with no distant metastasis, lymph node involvement, or lymphovascular invasion^[69]. Since then, groups have expanded their criteria for transplant showing that good outcomes can be achieved. The UCSF criteria was based off their study in 2001 which showed a 75% survival at 5 years, and includes a single tumor ≤ 6.5 cm, three or fewer tumors all ≤ 4.5 cm with a total tumor diameter of ≤ 8 cm. Patients outside the UCSF criteria had less than a 30% 5 year survival rate^[37].

In addition to the Milan and UCSF criteria, the Barcelona Clinic Liver Cancer Group created criteria including: 1 tumor < 7 cm, 3 tumors < 5 cm, 5 tumors < 3 cm, or down-staging to Milan criteria with pretransplant adjuvant therapies. They achieved excellent results with these expanded criteria with over 50% 5-year survival^[70-72]. The Hangzhou group created a criteria as well consisting of total tumor diameter less ≤ 8 cm; total tumor diameter more than 8 cm, with histopathologic grade I or II and preoperative AFP level less than or equal to 400 ng/mL, simultaneously. With these criteria they achieved a 71% 5-year overall survival^[73]. The European Metro Group created the Metroticket criteria, which consists of nodule size plus tumor number ≤ 7 and they also, achieved a 71% 5-year survival as well^[74,75].

Liver transplantation and resection are both curative approaches to HCC, however in comparable patient populations, transplantation has been shown to increase recurrence-free survival as compared with liver resection. In one study, even outside of the Milan criteria there was a trend toward improved survival in liver transplantation although not statistically significant. This study had a 51.5% recurrence rate in liver resection as compared with only 29.5% in the transplant group ($P < 0.001$). Of note patients who were in the resection group were

primarily Child's class A cirrhotics with only 13.1% being Child's class B. The rationale behind transplantation being a superior treatment in these cirrhotic patients is that one has their tumor eradicated and cirrhosis is cured as well^[76].

Although results have improved over the years making transplant an excellent option for those with HCC and significant liver disease, lifelong immunosuppression has its drawbacks, including infection, renal failure, diabetes, neurotoxicity, amongst many more. Over the history of liver transplantation for HCC, immunosuppression has improved significantly. The introduction of mTOR inhibitors for immunosuppression such as rapamycin, also known as sirolimus, which is thought to have anti-tumor properties related to its ability to decrease cell proliferation and angiogenesis. Some studies suggest better survival without major differences in complications in HCC patients who underwent liver transplantation, although further studies are necessary to further validate this treatment modality^[77,78].

Tumor biology is an important part in the outcomes after liver transplantation, however often times is unavailable at time selection of transplant candidacy. There is a reported incidence of 3% of seeding biopsy tracts, making biopsy undesirable in many cases especially given the accuracy of present imaging modalities^[79]. Poor differentiation and lymphovascular invasion are both poor predictive markers for outcomes following OLT, however these factors are not always available for transplant patient selection. As mentioned above, most criteria for HCC in liver transplantation are based on size and number of tumors, however there is evidence that poor differentiation predicts higher rate of recurrence than being outside the Milan criteria^[80].

In addition to tumor biology AFP and protein-induced vitamin k absence or antagonist II have been shown to be markers in the prognosis of HCC but results have been variable^[81]. The combination of markers is associated with tumor recurrence and worsened survival after any treatments for HCC, and might be useful in monitoring for recurrence. This combination may also be used in some settings to predict treatment outcomes in certain groups of patients undergoing local therapies such as ablation or TACE^[82].

It is also important to note that patients who are outside of criteria for liver transplant candidacy maybe down-staged. Resection in many of these cirrhotic patients is not an option, but locoregional therapy allows destruction of focal lesions without much damage to the uninvolved liver parenchyma. Many options are available to physicians including percutaneous ethanol injection (PEI) with 95% ethanol or 50% acetic acid (PAI), radiofrequency ablation (RFA), TACE, transarterial radioembolization (TARE). Many of these methods have been used in the attempted down staging of HCC for liver transplantation, and results have shown that response to these therapies may predict post-transplant outcomes. When successful, these therapies may induce complete tumor necrosis, and are associated with better

recurrence free survival. In the more advanced tumor populations with stage III/IV HCC, the small group of patients down-staged to within Milan had similar survival to those with lesser-advanced tumors^[83].

The use of locoregional therapies is very effective in down staging, and disease control for liver transplantation, but also has a role outside transplantation. Given the multitude of therapies it is important to be educated to know what modality should be used in each specific situation. In patients who are not candidates for curative measures including liver transplantation and surgical resection, percutaneous ablation is the best therapeutic option in small tumors less than 3 cm. There are a host of ways to approach ablation, usually done under ultrasound guidance, including those mentioned above such as injection of alcohol, acetic acid, microwaves, laser, cryoablation, and the most commonly used radiofrequency^[84].

Percutaneous ethanol injection has limited use, as it often does not perform well in setting of fibrosis and with larger tumors. This method is relatively low cost, however often times requires multiple treatment sessions with relatively poor outcomes in tumors greater than 2 cm. In small tumors less than 2 cm there are reports of complete tumor response. The approach of percutaneous RFA has been used however with more success in numerous studies, and the rationale is that this method delivers a thermal energy insult to the tumor and a small area of non-tumor hepatic parenchyma which may induce necrosis of small satellite lesions not seen on imaging. A meta-analysis looking at the comparison of RFA and PEI, demonstrated statistically significant improved overall survival in the RFA group with OR of 2.32 as compared with 1.92 in the PEI group^[85]. In addition, RFA was associated with a greater rate of complete tumor response, decreased number of treatments, and decreased local recurrence^[86]. RFA is recommended for tumors ≤ 3 cm with up to three lesions treated simultaneously, a single lesion ≤ 5 cm who are not surgical candidates, and can be used in both Child-Pugh Class A and B liver disease relatively safely. These modalities must be monitored as recurrent or inadequately treated tumors maybe retreated, and recommendations are to re-image with MDCT or MRI within 1 mo^[87].

Percutaneous ablation has become a frequently used and extremely effective modality for patients who either need to be down-staged or who are not candidates for transplant or resection; however, its use in larger tumors has been unsuccessful. TACE is the treatment of choice in larger and later staged tumors. The rationale behind its use is that after the initial stage of HCC when the blood supply comes from the portal vein, the hepatic artery becomes the main feeder to the tumor. This procedure requires percutaneous access to the arterial system, and subsequent access to the hepatic artery and ultimately in the segmental branches to deliver treatment directly to the tumor limiting damage to surrounding normal hepatic parenchyma. The catheter

directed therapy delivers chemotherapeutics such as doxorubicin, mitomycin-C, cisplatin, amongst others and then uses vascular embolization material to cease blood flow and induce cellular injury to the tumor^[88]. Unlike RFA, which has shown fairly consistent results, TACE has shown variable results with some studies showing limited benefit as compared to supportive therapies. This treatment modality has been shown to have higher morbidity from the ischemic insult, which places patients with more advanced liver disease at higher risk of post-procedure liver failure. The general recommendations for the use of TACE is for lesions < than 8 cm, > 3 lesions, with no evidence of extrahepatic extension or lymph node involvement, and with patients with relatively preserved liver function including Child-Pugh Class A and B liver disease. Mortality from this procedure is reported at less than 2% assuming appropriate candidacy of patients^[1,89].

More recently the use of TACE with drug eluting beads (DEB) has been utilized with some improved side-effect profiles and perhaps a trend toward improved outcomes as compared to TACE alone in more advanced liver disease. The beads allow for the controlled release of the chemotherapeutic agents over a one-week period creating a longer tumor treatment period as well as also increasing local drug concentrations. Studies have demonstrated increased tumor concentration of the chemotherapeutics and decreased systemic concentrations, subsequently decreasing both liver toxicity and cardiac toxicity with the use TACE with DEB as compared to TACE alone^[90,91]. The use of TACE with DEB maybe better suited in patients who have more advanced liver disease and are borderline candidates for TACE alone.

Unlike the therapies mentioned so far, external beam radiation has little role in the treatment of HCC due to its toxic effect on the diseased liver. There have, however, been major advances with the use of TARE with the use of microspheres coated with Yttrium-90 (Y₉₀). Y₉₀ is delivered to the tumor much like the chemotherapeutics distributed in TACE, allowing for localized radiation therapy limiting subsequent hepatic toxicity as compared to external beam radiation. Distribution of Y₉₀ is a form of brachytherapy that allows for internal radiation of the tumor alone, permitting for higher doses of radiation than standard external beam doses^[85]. In addition, this modality has been shown to be safe in patients who have portal vein thrombosis (PVT) with no significant increases in post treatment liver failure, however there was a significantly decreased median survival for patients with PVT as compared to those without^[89].

Although, no large randomized control trials are completed, there have been comparative studies looking at TARE vs TACE with a trend toward higher treatment response in the TARE group at 49% vs 35% ($P = 0.052$), and significant increase in time to disease progression at 13.3 mo compared with 8.4 mo, in the TARE and TACE groups, respectively. Much like other

therapies, abdominal imaging with CT or MRI should be done to evaluate efficacy of treatment^[85,92].

CHEMOTHERAPY

HCC has been known as one of the most chemo-resistant tumors encountered by physicians all over the world. Many agents have been attempted yet with little tumor response and survival benefit. Currently sorafenib is the only drug recommended in the treatment of HCC. Sorafenib is a multi-tyrosine kinase inhibitor used in the treatment of a number of cancers but has time and time again shown improved outcomes in HCC. It functions to inhibit Raf-1 and B-Raf serine-threonine kinases, and receptors of tyrosine kinases of vascular endothelial growth factor receptors 1, 2, 3, and platelet derive growth factor receptor- β . The means by which this drug works is that *via* these pathways, it inhibits tumor-cell proliferation and angiogenesis, while increasing rate of apoptosis. The SHARP trial was a randomized double-blind, placebo controlled trial which showed a median time to radiologic progression of 5.5 mo in the sorafenib arm and 2.8 mo in the placebo arm. The median survival demonstrated a survival advantage in the sorafenib group as compared to the placebo group at 10.7 mo and 7.9 mo respectively ($P < 0.001$)^[93].

Sorafenib has also been studied looking at adjuvant therapy in high-risk patients undergoing liver transplantation. A retrospective review looked at a small group of patients who underwent post-OLT sorafenib therapy suggesting its safety and potential benefit in regards to HCC recurrence and extending disease free and overall survival in high-risk transplant recipients^[94]. Yoon *et al*^[95] also looked at a small number of patients who were treated with sorafenib post-OLT and found similar results, although prospective data, which is ongoing, is required to determine the true potential benefit.

CONCLUSION

The incidence of HCC has been increasing worldwide, and despite a multitude of diagnostics, established treatment modalities, and new innovative viral therapies and prophylaxis, it still remains an aggressive tumor and one of the more common causes of cancer related-death. However, with advanced surgical techniques including resection, liver transplantation, and percutaneous interventions, this malignancy can be cured in appropriately selected patients. The hope is that with new innovative therapies being developed for HCV, the incidence of HCV related HCC might decline, however we must educate western societies regarding weight reduction as the increasing degree of obesity and subsequent development of NASH will continue to increase HCC incidence. With the continuing advancement of newer imaging modalities, pathologic studies, surgical approaches, and improved patient selection, there is

optimism to improve outcomes for this deadly disease.

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