

Current status of therapy for hepatocellular carcinoma

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Abstract: The incidence of hepatocellular carcinoma (HCC) is increasing worldwide. A multi-disciplinary approach is required for its management. Screening high-risk patients allows for earlier diagnosis and the use of potentially curative therapies. Current recommendations for HCC screening for patients with cirrhosis are an abdominal ultrasound and serum alpha fetoprotein level every 6 to 12 months. Treatment choice depends on tumor stage, liver function and the patient's overall functional status. Curative therapies include surgical resection, liver transplantation (LT), transarterial chemoembolization, and radiofrequency ablation (RFA). Surgical resection, either primary resection or LT, is the treatment most likely to result in cure of HCC. Which option to pursue is based on multiple factors. LT has the potential benefit of treating both HCC and the underlying cirrhosis; however, long wait times incur the risk of tumor progression. Firm recommendations regarding the role of living donor LT for HCC are not yet possible because of conflicting data. HCC recurrence after LT is 8–11% and several adjuvant therapies have been investigated to reduce this. Bridging therapy and tumor downsizing are techniques that also may be considered to deal with long waiting periods and qualification for LT, respectively. If neither LT nor primary resection is possible, loco-regional therapies such as RFA and TACE should be considered. Systemic chemotherapies have proved disappointing for the treatment of HCC; however, newer targeted therapies such as sorafenib and cetuximab have provided new hope for the future.

Keywords: hepatocellular carcinoma, ultrasound, resection, liver transplantation, transarterial chemoembolization, radiofrequency ablation, cirrhosis, sorafenib, cetuximab

Introduction

The incidence of hepatocellular carcinoma (HCC) is rising worldwide. The number of therapeutic options for HCC has also increased, making its treatment more complex. The management of HCC requires a multidisciplinary approach including the gastroenterologist/hepatologist, oncologist, interventional radiologist and surgeon. This article will review the current status of HCC with a focus on management and therapeutics.

Epidemiology

HCC is the fifth leading cause of cancer worldwide and has been increasing in incidence over the past four decades [Parkin *et al.* 2001]. In the United States, the incidence has nearly doubled since the 1970s from 1.4 per 100,000 to 2.4 per 100,000 in 1995 [El-Serag and Mason, 1999].

In addition, over this time the mortality rate from HCC has increased by 41%. HCC is currently the leading cause of death among patients with cirrhosis with a mortality rate of 3% per year [Sangiovanni *et al.* 2004; Fattovich *et al.* 1997].

Cirrhosis is present in 90% of cases of HCC. The most common causes of cirrhosis in patients with HCC are hepatitis C, hepatitis B and chronic alcohol use. Routine screening for HCC in patients with cirrhosis with abdominal ultrasound and levels of serum alpha fetoprotein (AFP) has led to the diagnosis of tumors at smaller size and earlier stage. Earlier diagnosis expands the therapeutic options available for HCC treatment.

Screening and diagnosis

While there is limited data demonstrating that screening for HCC in patients with cirrhosis

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reduces mortality, it is generally accepted that screening high-risk patients allows for earlier diagnosis and the use of potentially curative therapies [Bruix *et al.* 2001]. The use of serial ultrasound imaging and measurement of serum levels of AFP allows for the earlier detection of tumors [Zoli *et al.* 1996; Oka *et al.* 1990]. A single, large randomized controlled trial from China demonstrated a 37% reduction in mortality for HCC screening using serial ultrasounds and serum AFP measurements in patients with chronic hepatitis B [Zhang *et al.* 2004]. Current recommendations for HCC screening for patients with cirrhosis are an abdominal ultrasound and serum AFP level every 6 to 12 months [Bruix and Sherman, 2005]. AFP should not be used as the sole screening test unless ultrasound is not available.

Histology previously was required to make a definitive diagnosis of HCC. However, this requirement has changed; studies have demonstrated that using a combination of imaging modalities with AFP can correctly diagnose HCC without incurring the risks inherent to a percutaneous needle biopsy, including tumor seeding [Torzilli *et al.* 1999]. The extent of the evaluation needed to make the diagnosis of HCC depends on the size and the characteristics of the suspicious hepatic nodule. HCC has a specific appearance on computerized tomography (CT) and magnetic resonance imaging (MRI) scans performed with intravenous contrast. Normal hepatic parenchyma receives the majority of blood supply from the portal vein; enhancement occurs in the delayed/venous phase of the study. HCC receives its main blood supply from the hepatic artery; enhancement of HCC occurs in the arterial phase of the study (Figure 1), followed by contrast washout during the delayed portal/venous phase (Figure 2). These findings often correspond remarkably well to gross pathology (Figure 3).

This difference in phase enhancement allows for the accurate differentiation between malignant and benign hepatic nodules [Matsui *et al.* 1991; Murakami *et al.* 2001]. For nodules greater than 2 cm, two imaging modalities demonstrating an arterially enhancing lesion, or one imaging modality with an AFP above 200 ng/ml, is diagnostic of HCC [Bruix and Sherman, 2005]. In these instances, biopsy of the lesion is not required. In lesions of 1 cm or greater with an appearance atypical for HCC or with a low AFP, a biopsy is

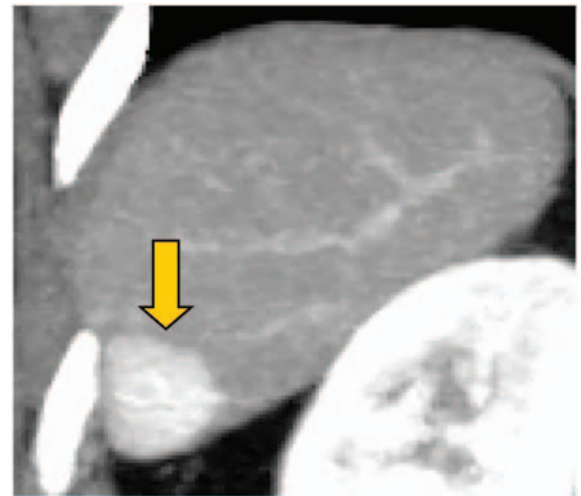


Figure 1. CT scan of the liver in the arterial phase. Note the enhancing lesion (arrow) consistent with hepatocellular carcinoma. Courtesy of Dr Dushyant Sahani.



Figure 2. CT scan of the liver in the portal phase. Note the absence of an enhancing lesion (arrow) seen in Figure 1 with hepatocellular carcinoma. Courtesy of Dr Dushyant Sahani.

recommended for diagnosis. Lesions less than 1 cm should be followed at regular intervals (3–6 months) to evaluate for growth [Bruix and Sherman, 2005].

The differential for liver lesions with arterial enhancement when the AFP is normal includes hepatic adenomas, dysplastic nodules, HCC, cholangiocarcinoma and metastatic adenocarcinoma. Even the interpretation of histology in

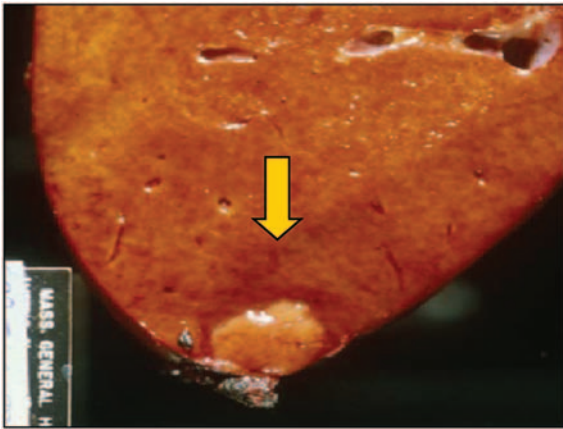


Figure 3. Gross specimen of the liver with the hepatocellular carcinoma nodule seen in Figure 1. Courtesy of Dr Dushyant Sahani.

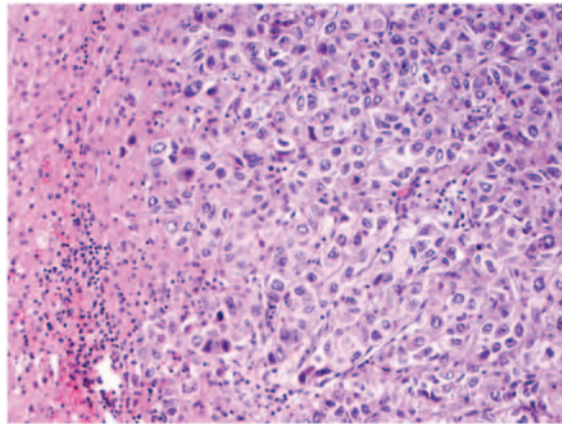


Figure 5. Liver biopsy of poorly differentiated hepatocellular carcinoma. Courtesy of Dr Gregory Y. Lauwers.

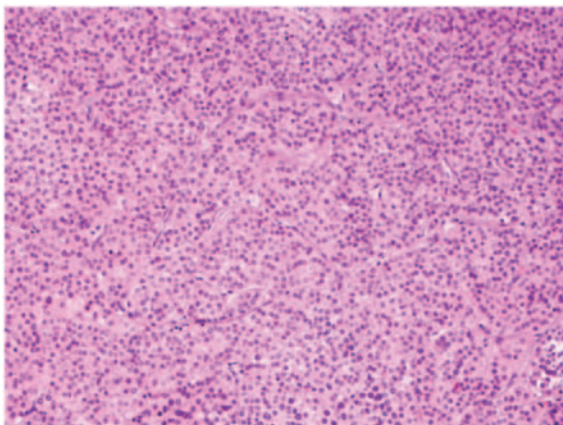


Figure 4. Liver biopsy of well-differentiated hepatocellular carcinoma. Courtesy of Dr Gregory Y. Lauwers.

these cases can present challenges in specific circumstances: well-differentiated HCC (Figure 4) can have an appearance similar to hepatic adenoma while poorly differentiated HCC (Figure 5) can have an appearance similar to metastatic adenocarcinoma [Goodman, 2007]. When the diagnosis of HCC is in doubt, immunostaining can be helpful; polyclonal antiserum to carcinoembryonic antigen (pCEA) and CD34 can be very useful in distinguishing HCC, while AFP and cytokeratin 7 and 20 can be present but are less specific for HCC [Goodman, 2007].

Tumor classification

The Barcelona-Clinic Liver Cancer Classification (BCLCC) is a prognostic staging system for

HCC that links staging to treatment. The BCLCC has been validated in a large cohort study and is the staging system endorsed by the AASLD [Wang *et al.* 2008; Bruix and Sherman, 2005; Llovet and Bruix, 2003]. The BCLCC stratifies patients with HCC into five major categories; very early, early, intermediate, advanced and terminal. Patients in the *very early stage* have a lesion less than or equal to 2 cm and Childs A cirrhosis. In the absence of portal hypertension or hyperbilirubinemia, these patients are potential candidates for curative resection. Patients with *early stage* disease have an isolated nodule that is less than or equal to 5 cm or up to three nodules that are each less than or equal to 3 cm. Patients in this category should also be guided toward curative therapies – surgical resection and liver transplantation (LT). If properly selected, these patients have a 5-year survival of 50–70%.

Patients with *intermediate* stage disease have larger and/or more numerous tumors than the early stage, but they do not have evidence of vascular invasion or extra-hepatic spread of the malignancy, and are asymptomatic. These patients can be considered for locoregional therapy including transarterial chemoembolization (TACE), which has been shown to improve median survival from 16 months without treatment to 20 months with TACE [Llovet *et al.* 2003].

Patient in the *advanced* category have cancer-related symptoms, vascular invasion or extra-hepatic spread of HCC. Treatment options for

this group are limited with only a 10% 3-year survival. Patients with *terminal* HCC have severe physical impairment, Childs C cirrhosis or Okuda stage 3 (tumor involving more than 50% of the liver and/or the presence of decompensated cirrhosis). Their median survival is 3–4 months and treatment is strictly palliative.

While the BCLCC is used by some to help guide treatment, it is not a prognostic index to be used for individual patients. The most widely used prognostic index is the Cancer for Liver Italian Program (CLIP) score. The CLIP score was derived from a retrospective analysis of 435 patients with HCC. Using Childs classification, tumor morphology (defined by a single nodule *versus* multiple nodules and less than or greater than 50% of liver involved), presence of portal vein thrombosis and AFP (less than or greater than 400 mg/dl) an individual's CLIP score can be derived. A lower CLIP score correlates with a higher median survival, performs better than the Okuda and Childs classification for predicting median survival, and has been validated prospectively [2000, 1998].

Treatment

A myriad of treatment options exist for HCC. The proper choice depends on tumor stage, liver function and the patient's overall functional status. Curative therapies including surgical resection, LT, TACE, and radiofrequency ablation (RFA), are possible in 20–40% of patients who present with HCC [Siegel *et al.* 2008; Llovet *et al.* 2003].

Resection

Surgical resection, either primary resection or liver transplantation, is the treatment most likely to result in cure of HCC. The choice of which option to pursue is based on multiple factors (Figures 6–9). Primary resection is the best option for patients without cirrhosis found to have a single tumor without gross vascular invasion or extrahepatic spread. The utility of primary resection in patients with cirrhosis is limited by the postresection residual hepatic mass and function. Patients with Childs B or C cirrhosis are at a prohibitively high risk of hepatic decompensation after primary resection. Assuming they are otherwise a reasonable candidate, these patients should be evaluated for LT. For patients with Childs A cirrhosis and tumors less than 5 cm, either primary resection

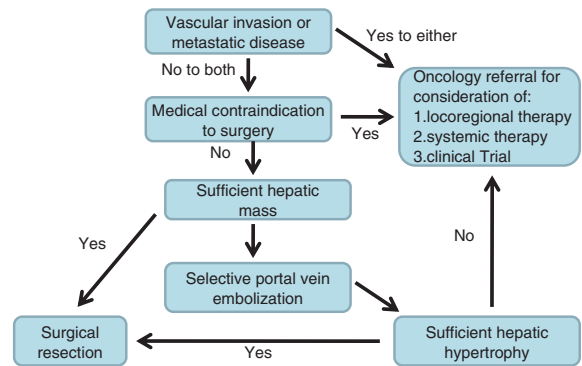


Figure 6. Hepatocellular carcinoma algorithm for a single lesion in patients without cirrhosis.

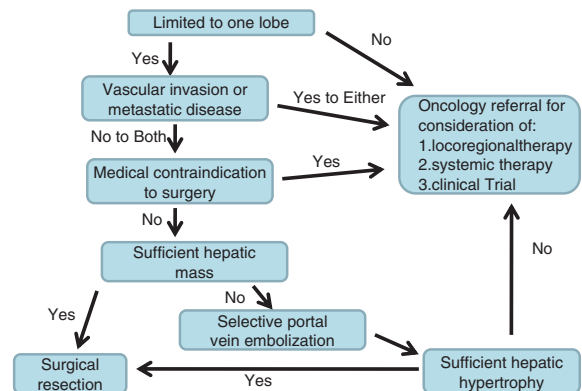


Figure 7. Hepatocellular carcinoma algorithm for more than one lesion in patients without cirrhosis.

or LT may be reasonable options. While primary resection has been shown to be superior to percutaneous ethanol injection (PEI) or TACE, there are no randomized trials comparing primary resection with LT [Arii *et al.* 2000]. LT has the potential benefit of treating both HCC and the underlying cirrhosis. However, the long wait times associated with LT incurs the risk of tumor progression; this may ultimately prohibit both LT and resection. The following paragraphs summarize the data related to this debate.

A trial of 37 patients with Childs A cirrhosis and early HCC demonstrated a 5-year survival rate of 71% for patients who underwent LT compared with 36% for those who underwent primary resection [Bigourdan *et al.* 2003]. However, patients in this trial had a mean waiting time for LT of only 24 days (range 5–84 days), a time that is significantly less than mean waiting

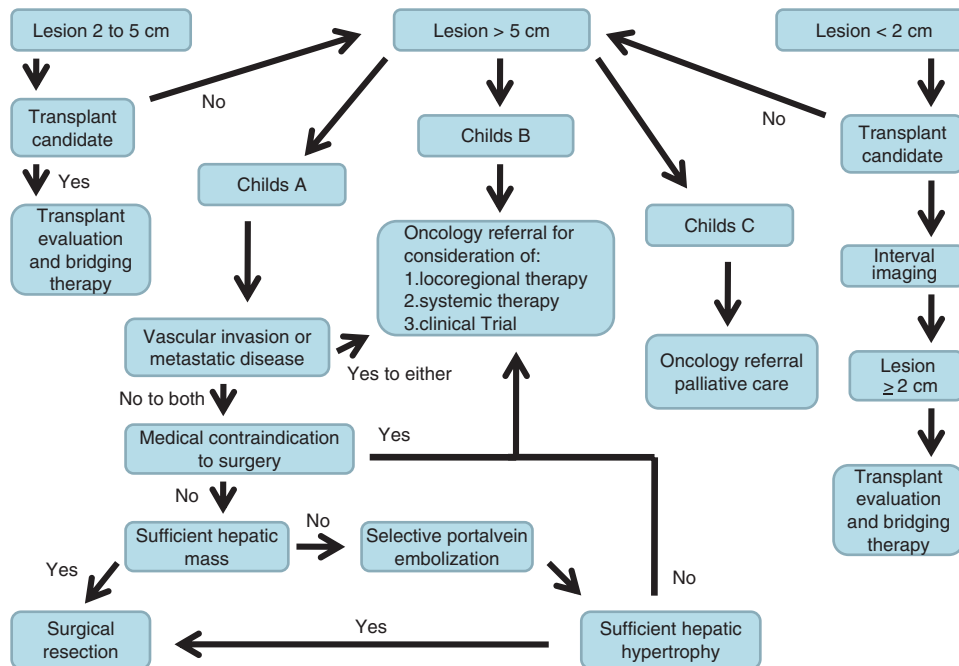


Figure 8. Hepatocellular carcinoma algorithm for single lesion in patients with cirrhosis.

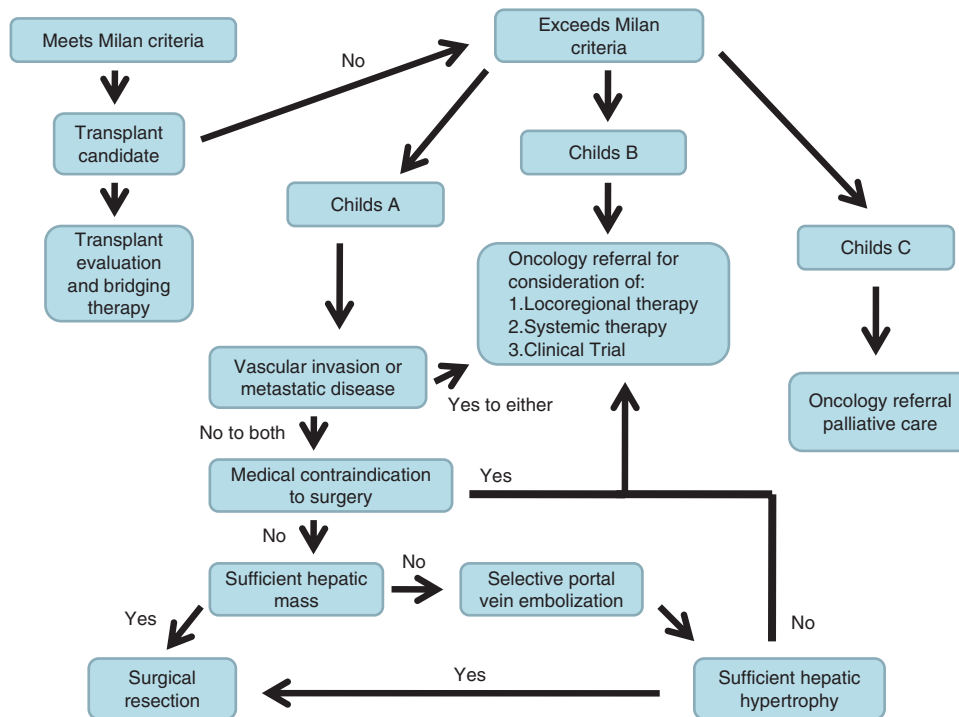


Figure 9. Hepatocellular carcinoma algorithm for more than one lesion in patients with cirrhosis.

times in the United States. This short waiting time was the reason why none of the patients waiting for LT died or had disease progression pretransplant. A second study compared primary

resection to LT on an intention-to-treat basis in 164 patients with early stage HCC [Llovet *et al.* 1999]. The groups being compared were not identical; patients with well preserved liver

function, defined as a hepatic venous portal gradient (HVPG) ≤ 10 , underwent resection ($n=77$) and those without well preserved liver function were considered for LT ($n=87$). LT patients had an average wait time of 110 days (range 1–485) and a 5-year survival of 69% while the surgical resection group had a 5-year survival of 53%, a difference that was not statistically significant even when the LT group was compared to only Childs A patients (5-year survival of 71%). Eight patients dropped out because of tumor progression or progression of end stage liver disease. During the study, wait time for transplantation in the LT group increased significantly from a mean of 62 days to a mean of 162 days. All dropouts occurred during this later portion of the study and survival for patients undergoing LT (2-year survival of 47%) was significantly lower than for those undergoing resection (2-year survival of 91%). This study suggests that patient with early stage HCC and Childs A cirrhosis who can undergo LT after a short wait have a survival comparable to primary resection; however, a longer wait for LT is associated with worse outcomes compared with primary resection.

Tumor recurrence is an issue after primary resection. There have been a number of new techniques to allow the surgeon to pursue a complete resection. Selective portal vein embolization is employed when the extent of resection required is greater than that deemed safe based on calculated residual hepatic reserve. Embolization of the branch of the portal vein supplying the tumor-containing-segment leads to atrophy of this area and compensatory hypertrophy of the remaining liver [Makuuchi and Sano, 2004]. This technique has been successful employed in patients without cirrhosis and patients with Childs A cirrhosis, although the likelihood of success is lower in the patients with cirrhosis.

Liver transplantation

LT provides the benefit of treating both HCC and underlying cirrhosis. Acceptance of LT as a treatment for HCC occurred after Mazzafero and colleagues demonstrated that selected patients with unresectable tumors who underwent LT had a recurrence-free survival at 4 years of 83% and an actuarial survival of 75%. Patients who benefited had either two or three tumors, each less than 3 cm in diameter, or a single tumor less than 5 cm in diameter. These are the

so-called Milan criteria. These results have been confirmed and are used to identify HCC patients eligible for transplantation in the United States [Figueras *et al.* 2001].

There have been efforts to prove that liberalizing these guidelines will not adversely affect patient outcomes. Researchers at the University of California at San Francisco (UCSF) have shown that patients that fit into expanded criteria, the so-called UCSF criteria, can still have excellent outcomes despite increased tumor burden [Yao *et al.* 2007, 2002, 2001] The investigators found that in patients with a single lesion less than or equal to 6.5 cm or three or fewer nodules, each less than or equal to 4.5 cm, had 1- and 5-year survival rates of 91.3% and 72.4%, respectively, rates that are similar to those seen with the Milan criteria. A recent evaluation of expanded indications for living donor liver transplantation (LDLT) also suggested survival rates similar to Milan and UCSF rates. Patients ($n=186$) with no more than six nodules, a maximum single nodule size of 5 cm, and an absence of gross vascular invasion underwent LDLT. The overall 5-year survival rate in this group was 76.3%, comparable to both the Milan and UCSF criteria [Lee *et al.* 2008].

As a result of these studies, there have been calls to re-evaluate the criteria currently used for HCC and LT. However, it is important to note that the majority of these studies were retrospective in nature and HCC size and number of nodules was determined in explant pathology. Explant pathology often correlates poorly with pretransplant radiologic staging. The 2007 study by Yao and colleagues is the only prospective trial and it does suggest that expanded indications may allow for survival rates comparable to the Milan criteria [Yao *et al.* 2007]. However, additional prospective studies are needed before expanded indications can be widely accepted given the continued shortage of cadaveric organs for transplantation and the ethical issues surrounding the performance of LDLT in patients that exceed Milan criteria.

Living donor liver transplantation

A report from the Adult-to-Adult Living Donor Liver Transplantation (A2LL) cohort has suggested that patients with HCC may have a higher rate of recurrence with living donor liver transplants (LDLT) for deceased donor liver

transplantation (DDLT) [Kulik *et al.* 2005]. It is theorized that the longer wait time associated with DDLT compared with LDLT allows for the identification of biologically aggressive tumors and the removal of these patients from the transplant list. Patients with tumors that have less aggressive biology and a lower risk of recurrence do not progress during time on wait list. These patients go on to transplantation and have low recurrence rates. The A2ALL researchers reported a 3-year recurrence rate of 0% in patients with HCC undergoing DDLT and a 42% recurrence rate in those undergoing LDLT. It should be noted that there was a trend toward more advanced tumors in the LDLT group which may confound these results.

Chao and colleagues investigated whether time on the waiting list correlates with outcomes in patients transplanted for HCC. They evaluated 100 patients who underwent LT for HCC; 90 underwent DDLT and 10 underwent LDLT [Chao *et al.* 2007]. There was no difference in survival or 5-year recurrence rate of HCC for those patients waiting less than 3 months, those waiting 3–6 months, and those waiting more than 6 months for LT. Similar findings were found in an analysis of 274 patients with HCC who underwent LDLT or DDLT; there was no difference in 1- and 2-year HCC recurrence between the two groups [Hwang *et al.* 2005]. Firm recommendations regarding the role of LDLT for HCC are not yet possible in light of this conflicting data.

Bridging therapy

Long waiting periods for LT can result in tumor progression and removal from the transplant list. The goal of treating HCC while patients are on the LT wait list is to halt disease progression so patients remain within Milan criteria. There is conflicting data regarding whether TACE performed on patients awaiting LT for HCC have reduced HCC recurrence and improved survival [Decaens *et al.* 2005; Graziadei *et al.* 2003; Oldhafer *et al.* 1998; Troisi *et al.* 1998; Venook *et al.* 1995; Spreafico *et al.* 1994].

Troisi and colleagues [1998] evaluated 20 patients with HCC awaiting transplant. Fourteen patients received pre-LT TACE and PEI, six did not. Those receiving TACE plus PEI had a significant reduction in tumor size (37–28 mm) and serum AFP level. All patients underwent LT within 26 months. 80% of those

who underwent TACE had 100% tumor response. No recurrences were noted in the TACE/PEI group while two recurrences occurred in the non-treatment group. The rate of actuarial disease-free survival at 48 months was 82% in the TACE/PEI group and 65% in the untreated group.

A prospective trial evaluated the use of TACE in 63 patients awaiting LT for HCC; 48 patients met Milan criteria while 15 exceeded Milan criteria but had a greater than 50% necrosis response to TACE [Graziadei *et al.* 2003]. Of the patients initially meeting Milan criteria, 95.9% had a complete or partial response (>50% necrosis) to TACE and none experienced post-LT recurrence. Five-year actuarial survival rate in these patients was 95%. The outcomes in the patients who initially exceeded Milan criteria were much poorer. These patients had a recurrence rate of 30%. This study suggests that patients who are within the Milan criteria and achieve a complete or partial response to TACE, have low HCC recurrence rates survival rates that are comparable with patients without HCC.

Several studies have contradicted these results, finding that pre-LT TACE had no impact on post-LT survival or recurrence [Decaens *et al.* 2005; Graziadei *et al.* 2003]. However, in both these studies the rates of complete/partial response to TACE ranged from 50–66%, far lower than reported in the prior trials. This suggests that the completeness of the response to TACE may correlate with post-LT recurrence and survival.

Work by Otto and colleagues also suggests that treatment with TACE can decrease HCC recurrence and that response to TACE may predict the risk of recurrence [Otto *et al.* 2007, 2006]. These studies have demonstrated that patients who do not have progression of HCC after TACE have significantly lower rates of post-LT HCC recurrence compared with patients who have tumor progression despite TACE. Responsiveness to TACE may be a marker of a biologically less aggressive tumor.

Tumor downstaging

Downstaging is the process of using locoregional therapies such as TACE and RFA to shrink tumors that exceed Milan criteria so they meet

Milan criteria. By meeting Milan criteria these patients are able to be listed for LT. Otto and colleagues examined the role of TACE to down-stage tumors that initially exceed the Milan criteria. Sixty-two patients who exceed the Milan criteria underwent TACE. Thirty-four of these patients had sufficient tumor regression to meet Milan criteria and were listed for LT. There was no significant difference in 5-year disease-free survival between those patients initially meeting Milan criteria and those patients who only met Milan criteria after TACE. This suggests down-staging of tumors can allow for the successful transplant of patients who otherwise would not be candidates.

Recurrence

The HCC recurrence rate after transplantation is 8-11%. (26, 30). A Predicting Cancer Recurrence Score (PCRS) has been developed to predict the risk of HCC recurrence. One point is assigned for a tumor larger than 4.5 cm, 2 points for tumor in both lobes of the liver, three points for macroinvasion of the vasculature and three points were subtracted for well differentiated tumors. (43) The PCRS was validated in several cohorts and found that a score of zero correlated with a low rate of recurrence (0-3%) while a score of 1-2 had a moderate rate of recurrence and those with a score of three or greater had a high rate of recurrence (75-100%) [Chan *et al.* 2008].

Adjuvant therapies to reduce recurrence

Fifty percent of patients who undergo a curative liver resection for HCC have microscopic lesions that eventually manifest as disease recurrence [Yamamoto *et al.* 1996]. Adoptive immunotherapy has been studied as adjuvant therapy for patients with HCC. Adoptive immunotherapy uses autologous lymphocytes and activates them in-vitro with recombinant interleukin-2 and antibody to CD-3. The lymphocytes have activity against HCC cells. A randomized, controlled trial of 150 Japanese patients demonstrated that use of adoptive immunotherapy reduced recurrence rates from 77% to 59% at a median follow-up of 4.4 years [Takayama *et al.* 2000]. The mean time to recurrence was greater in the immunotherapy group (2.8 years) compared to the control group (1.6 years) and recurrence free survival was 37% in the immunotherapy group compared to 22% in the control group.

A second adjuvant protocol for post-resection HCC uses intra-arterial iodine-131-labelled lipiodol [Lau *et al.* 1999]. Lipiodol is a fatty acid ethyl ester from poppyseed oil. It contains a high concentration of iodine which allows the lipiodol to be converted in to iodine-131 lipiodol, a radioactive compound. Lipiodol is taken up by HCC cells after intra-arterial injection and can lead to cell death. A randomized, controlled trial of 43 patients following curative HCC resection found that the actuarial disease free survival was 52.4% in the lipiodol group compared to 31.8% in the control group [Lau *et al.* 2008].

Interferon alpha may decrease HCC recurrence in patients with hepatitis C associated HCC. A single, randomized trial treated patients with HCV associated, or HCV and HBV associated, HCC with interferon- α 2b administered subcutaneously three times per week for 48 weeks. Investigators found a decreased rate of late recurrence (>2 years) in patients with HCV associated HCC who were treated with interferon [Mazzaferro *et al.* 2006]. A similar result was obtained with interferon alpha following second or third HCC recurrence treated with percutaneous ethanol injection (PEI) [Shiratori *et al.* 2003].

Locoregional therapies

If neither LT nor primary resection is possible, locoregional therapies should be considered. Locoregional therapies include PEI, RFA, trans-arterial embolization (TAE), and TACE. PEI is performed by introducing 1-4 ml of 95% ethanol directly into the tumor resulting in cell necrosis. RFA uses an electrode to deliver alternating high frequency which generates heat within the tumor leading to cell necrosis. RFA is an effective treatment for patients with Childs A or B cirrhosis when the tumor is not amenable to resection or patients are not candidates for LT [Lencioni *et al.* 2005]. When compared with PEI, RFA achieves better local tumor control and requires fewer treatments (4.8 *versus* 1.2) [Ikeda *et al.* 2001; Livraghi *et al.* 1999]. In a randomized, controlled trial of 102 patients with a single lesion less than 5 cm or three lesions less than 3 cm, RFA had a significantly greater survival advantage over PEI at 2 years (77% *versus* 43%) [Lencioni *et al.* 2003]. A second randomized controlled trial detected no overall survival advantage of RFA over PEI but did note a significantly higher rate of complete response at one year (65.7% *versus* 36.2%) in patients receiving

RFA [Brunello *et al.* 2008]. Both PEI and RFA carry a small risk of tumor seeding along the needle track. The tumor seeding in RFA occurs in approximately 1% of patients and 0.6–1.4% of patients undergoing PEI [Latteri *et al.* 2008; Livraghi *et al.* 2005; Di Stasi *et al.* 1997].

TAE is an intra-arterial therapy whose effectiveness relies on successfully compromising the blood supply of HCCs. Early in development, HCCs are supplied predominantly from the portal vein. However, as they grow to greater than 2 cm, the hepatic artery plays an increasingly important role in the tumor blood supply. This change is exploited in intra-arterial therapies by inducing selective tumor necrosis via hepatic artery embolization [Bruix *et al.* 2004]. TAE has utilized several different media to embolize the hepatic artery including Gelfoam cubes, the most commonly used media currently, along with metallic coils, Gelfoam powder, polyvinyl alcohol or starch microspheres [Bruix *et al.* 2004].

TACE combines embolization with directed chemotherapeutic agents including doxorubicin, mitomycin and cisplatin. Techniques used include injecting the chemotherapeutic agent into the hepatic artery alone or followed by the injection of a second substance such as a coil or gelfoam to create an arterial occlusion. Alternative techniques include suspending the chemotherapeutic agent in lipiodol, an oily contrast agent which can be used to embolize the artery, or using chemotherapy eluting beads as emboli.

TAE prevents tumor progression compared to untreated controls [Bruix *et al.* 1998; Bruix and Sherman, 1995] A meta-analysis of patients with unresectable HCC demonstrated a 2-year survival benefit in the patients receiving TAE when compared with controls. A sensitivity analysis demonstrated that the benefit was driven by those subjects receiving chemoembolization with doxorubicin or cisplatin and no benefit was seen with TAE alone [Llovet *et al.* 2003]. TACE has demonstrated benefit in patients with unresectable HCC [Huang *et al.* 2005; Bruix *et al.* 2004; Lo *et al.* 2002]. TACE delays tumor progression, vascular invasion and induces a partial response in many subjects. Both TAE and TACE can produce considerable cell necrosis and hepatic decompensation in patients with advanced liver disease.

Several factors guide the decision making when one is deciding between RFA and TACE for HCC including tumor size, proximity to vessels and abdominal viscera, and the presence of portal vein thrombosis. RFA is the treatment of choice for tumors less than 3 cm in size while TACE is used for tumors that exceed for 3 cm [Camma *et al.* 2005; Livraghi *et al.* 2000]. In addition, vessels can serve as a heat sink diminishing the effects of RFA, while proximity to other viscera can lead to extra-hepatic thermal injury [Livraghi *et al.* 2003; Lu *et al.* 2002] TACE is preferred in these cases. TACE cannot be performed in the presence of pre-existing portal vein thrombosis as it risks severely compromising the sole remaining hepatic blood supply, the hepatic artery.

Systemic therapies

Systemic chemotherapies have proved disappointing for the treatment of HCC. However, newer targeted therapies have provided a new avenue for systemic treatment and some optimism for the future. Sorafenib is a multikinase inhibitor with activity against tyrosine kinases, platelet-derived growth factor receptors (PDGFR) and vascular endothelial growth factor receptors (VEGFR), c-kit receptors, serine/threonine kinases, B-Raf and Raf-1. Blockage of PDGFR and VEGFR inhibits angiogenesis and blockage of B-Raf via its actions on RAS/MAPK, inhibits cell proliferation.

A phase II trial examined the effects sorafenib 150 mg given orally daily to 38 patients with advanced HCC. Thirty-two percent of patients were progression free at 6 months, disease control was seen in 59% and median survival time was 13 months [Philip *et al.* 2005]. These results provided the data for a randomized controlled trial in which patients with advanced HCC received sorafenib or placebo. Patients assigned to sorafenib had increased survival time from 7.9 to 10.7 months [Llovet *et al.* 2008].

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody that binds to epidermal growth factor receptors and may prevent the growth of EGFR-positive tumor cells [Asnacios *et al.* 2008; Zhu *et al.* 2007]. HCC cells demonstrate increased expression of EGFR and may be a target for cetuximab. In a pilot clinical trial, Zhu and colleagues treated 30 patients with metastatic or unresectable HCC with cetuximab. All of the patients were Childs A or B. No patients

achieved even a partial response and 80% had progression while on therapy and received only one cycle of treatment [Zhu *et al.* 2007].

A second trial evaluated the use of cetuximab in combination with oxaliplatin and gemcitabine (GEMOX) in 45 patients with Childs A or B cirrhosis and advanced HCC [Asnacios *et al.* 2008]. The objective response rate was 20% with nine patients achieving a partial response which lasted from 2 to 14 months. Stable disease was noted in 40% of patients with a disease control rate of 60%. The mean progression free survival time was 4.7 months. A randomized trial comparing gemcitabine and oxaliplatin alone to GEMOX plus cetuximab is underway.

Conclusions

Treatment of HCC remains a challenge and requires a multidisciplinary team to individualize therapy for each patient. Liver transplantation and primary resection remain the only curative therapies but advances in locoregional therapies and targeted systemic therapy provide hope for the future.

Conflict of interest statement

None declared.

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