Hepatocellular Carcinoma

15

Malcolm H. Squires III and David A. Kooby

Abbreviations

PST	Performance status (ECOG classification)
CLT	Cadaveric liver transplantation
LDLT	Living donor liver transplantation
RF	Radiofrequency ablation
PEI	Percutaneous ethanol injection
TACE	Transarterial chemoembolization
OS	Overall survival

Learning Objectives

After reading this chapter, you should be able to:

- Describe the diagnostic workup for a suspected hepatocellular carcinoma liver lesion
- Understand the multiple staging systems for patients with hepatocellular carcinoma
- Appreciate the treatment paradigm for hepatocellular carcinoma within the context of HCC stage and the severity of underlying liver disease
- Understand the indications for hepatic resection, transplantation, locoregional therapy, and systemic therapy for patients with hepatocellular carcinoma

M.H. Squires III, M.D. • D.A. Kooby, M.D. (✉)
Division of Surgical Oncology, Winship Cancer Institute, Emory University, 1365C Clifton Rd. NE, 2nd Floor, Atlanta 30322, GA, USA
e-mail: msquire@emory.edu; dkooby@emory.edu

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy worldwide and ranks as the fifth most common cancer diagnosis overall and the third leading cause of cancer mortality worldwide [1]. In Southeast Asia and sub-Saharan Africa, regions where hepatitis B is endemic and the incidence of HCC is highest, HCC is currently the leading cause of cancer mortality [1, 2]. In the United States, greater than 30,000 new cases of HCC are diagnosed each year, with over 21,000 deaths due to HCC estimated to occur. The annual incidence of both new diagnoses and deaths attributed to HCC continues to increase; in fact, the incidence of HCC in the United States tripled between 1975 and 2005, largely due to the increasing prevalence of hepatitis C-related cirrhosis [1, 3]. Most cases of HCC arise in the setting of chronic liver disease, regardless of the etiology, with viral hepatitis B and C, alcohol abuse, and nonalcoholic steatohepatitis (NASH) constituting the majority of cases. Patients with cirrhosis have a significant risk, estimated at 1–8 % per year and a greater than 30 % lifetime risk, of developing HCC within the cirrhotic liver [4]. Even more concerning are recent data suggesting that the risk of developing HCC may be accentuated in the setting of cirrhosis secondary to nonalcoholic fatty liver disease (NAFLD) or NASH [5].

Despite advances in nonsurgical interventional therapies, the best potential curative treatment

Q.D. Chu et al. (eds.), *Surgical Oncology: A Practical and Comprehensive Approach*,
DOI 10.1007/978-1-4939-1423-4_15, © Springer Science+Business Media New York 2015

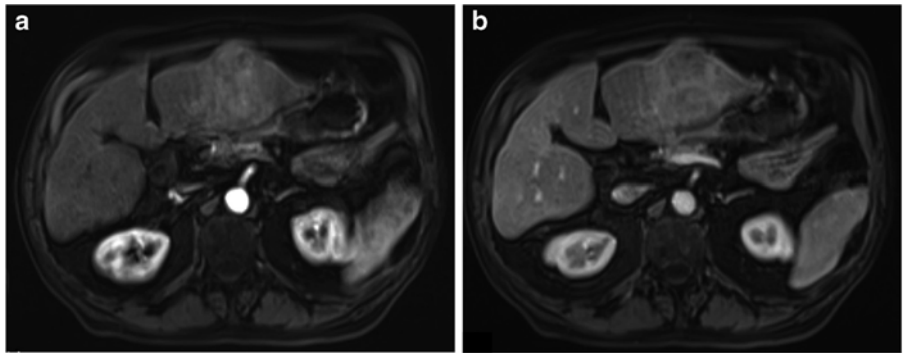

Fig. 15.1 MRI appearance of an HCC lesion in the left liver lobe demonstrating characteristic enhancement in the early arterial phase (**a**), with subsequent contrast washout in the delayed, portal venous phase (**b**)

option for HCC remains resection: either in the form of partial hepatectomy or liver transplantation [6–9]. Optimal surgical management of HCC patients remains a point of debate, due to variability in disease status and degree of liver fibrosis, with practices varying among institutions worldwide.

Diagnostic Workup and Staging

Cross-sectional imaging is a key component of the diagnostic algorithm for patients with suspected HCC. Ultrasound may be valuable in the context of surveillance screening patients at risk for HCC or as an initial imaging modality, but definitive radiologic diagnosis requires contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Clinical practice guidelines adopted by the American Association for the Study of Liver Diseases (AASLD) and by the European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer (EASL/EORTC) outline noninvasive diagnostic imaging criteria for HCC [10]. HCC nodules typically have characteristic features of intense arterial enhancement followed by contrast washout during delayed or portal venous phases, as a result of their hypervascularity and dependence on hepatic arterial circulation (Fig. 15.1).

For patients with cirrhosis, lesions greater than 1 cm in size that display these hallmark imaging characteristics are diagnostic of HCC and do not require a confirmatory tissue biopsy. For patients with liver nodules suspicious for HCC but lacking these imaging features on one imaging study, a second modality should be considered. If imaging remains inconclusive, or for patients with liver nodules arising in the absence of underlying cirrhosis, histologic confirmation by core needle biopsy is necessary for pathologic diagnosis. Improved imaging technology and adoption of the diagnostic criteria above have helped limit the need for invasive percutaneous biopsy, which carries risks of potential complications such as tumor rupture or biopsy track seeding, estimated at 0–5.1 % [11, 12]. Serum alpha-fetoprotein (AFP) may play a role as an adjunctive test in patients with suspicious liver lesions, with some degree of AFP elevation observed in the majority of patients, but elevated AFP levels are not a requisite component of the most recent iteration of diagnostic criteria [13]. An initially elevated AFP level, however, can be of benefit to gauge tumor response to therapy and monitor for future recurrence following treatment.

Cross-sectional imaging also provides information regarding morphologic features of the HCC, including tumor focality (uninodular vs. multinodular), macrovascular invasion, presence of main portal or hepatic venous thrombus, and involvement of the biliary tree, as well as potential lymph node involvement or extrahepatic spread of disease (Figs. 15.2 and 15.3). Chest imaging is also appropriate, as HCC commonly

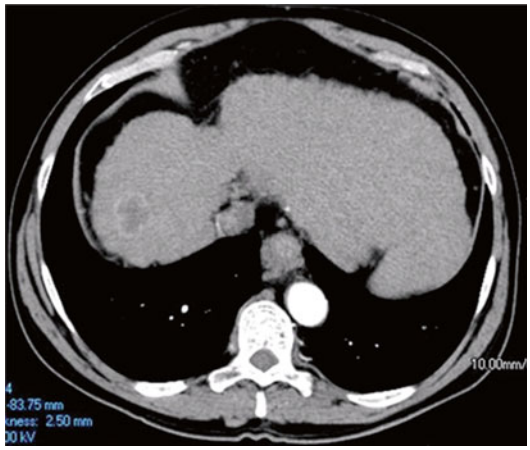

Fig. 15.2 Small HCC lesion arising in the background of a cirrhotic liver. In the absence of any evidence of vascular invasion or distant metastases, this lesion would meet Milan Criteria

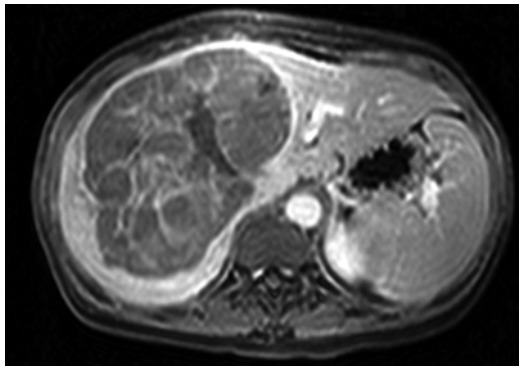

Fig. 15.3 A large HCC lesion arising in the setting of otherwise normal-appearing liver parenchyma

metastasizes to the lungs. Clinical management of patients with HCC requires an understanding of these tumor-specific features as well as the severity of their liver dysfunction and natural history of cirrhosis.

Patients with HCC typically have some degree of underlying liver disease, the severity of which can be quantified on the basis of the Child-Turcotte-Pugh (CTP) score or the Model for End-Stage Liver Disease (MELD) score. The CTP score stratifies patients with underlying cirrhosis on a scale of 5–15 points and incorporates points assigned for quantitative serum values for bilirubin, albumin, and INR (international normalized ratio) as well as the more subjective variables of ascites and encephalopathy (Table 15.1) [14, 15]. Patients with CTP Class A cirrhosis (score of 5–6 points) have a 2-year mortality risk of 10 % versus 20–40 % for those with Class B cirrhosis (score of 7–9 points) or 50–80 % for those with Class C cirrhosis (score 10–15 points) [14].

Table 15.1 Child-Turcotte-Pugh (CTP) classification of hepatic function

Variable	1 Point	2 Points	3 Points
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	Absent	Slight	Moderate–severe
Encephalopathy (grade)	None	Mild (I–II)	Severe (III–IV)

CTP Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points. Abbreviations: *INR* international normalized ratio

The MELD score, calculated from the patient's serum creatinine, bilirubin, and INR values using a linear regression model, is more objective than the CTP score as it does not incorporate subjective variables such as degree of ascites or encephalopathy [16]. The MELD score ranges from 6 to 40 and has been demonstrated to have prognostic value for survival in patients with underlying chronic liver disease, regardless of the etiology. Importantly, neither of these scoring systems assess tumor involvement.

As compared with other solid tumor types, the TNM staging system is less commonly employed for HCC, as it does not account for liver dysfunction, a crucial variable when examining treatment options for individual patients. The 7th edition American Joint Committee on Cancer (AJCC) staging system defines the stages for HCC as follows (Table 15.2): Stage I as a solitary tumor, any size, without vascular invasion; Stage II as a solitary tumor with vascular invasion or multiple tumors but none >5 cm in size; Stage IIIA as multiple tumors with at least one >5 cm in size; Stage IIIB as one or more tumors of any size involving a major branch of the portal vein or hepatic veins; and Stage IIIC as tumor(s) with perforation of the visceral peritoneum or direct invasion of adjacent organs other than the gallbladder [18].

Table 15.2 American Joint Committee on Cancer (AJCC) TNM Staging for Hepatocellular Carcinoma (7th edition)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors, none > 5 cm
T3a	Multiple tumors, one or more > 5 cm
T3b	Tumor(s), any size, involving major branch of portal vein or hepatic veins
T4	Tumor(s) with perforation of visceral peritoneum or direct invasion of adjacent organs other than the gallbladder

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups			
Group	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Adapted from Compton et al. [17]. With permission from Springer Verlag

Any regional lymph node involvement or distant metastases is classified as Stage IV disease.

Several alternative staging systems have been proposed to better define the prognosis of patients with HCC and appropriately stratify patients for treatment. One of the more established clinical staging systems is the Barcelona Clinic Liver Cancer (BCLC) system [19]. The BCLC classification stratifies patients on the basis of hepatic function as represented by the CTP score, clinical Eastern Cooperative Oncology Group (ECOG) performance status, and tumor stage, which encompasses tumor size, number of lesions, presence of vascular invasion, and extrahepatic spread of disease. Subsequent updates to the BCLC classification scheme have incorporated additional evidence-based treatment recommendations [6, 20]. The widely adopted EASL/EORTC consensus guidelines for management of HCC follow the BCLC staging algorithm (Fig. 15.4).

Very early HCC (BCLC Stage 0) includes patients with an ECOG performance status 0; well-preserved liver function, defined as CTP Class A along with normal serum bilirubin and normal portal pressures; and a solitary HCC tumor, measuring less than 2 cm, with no evidence of vascular invasion. While few patients are typically diagnosed this early in their disease course, resection and transplantation both offer excellent 5-year survival rates of 80–90 % [21]. Early HCC (BCLC Stage A) includes patients with ECOG performance status 0, well-compensated CTP Class A liver disease, and solitary tumors >2 cm or up to three tumors, each <3 cm in diameter. For appropriately selected patients, 5-year survival approaches 50–70 % following hepatic resection or liver transplant [22].

Intermediate HCC (BCLC Stage B) includes patients with ECOG performance status 0, moderate liver dysfunction within CTP Class A or B, and large or multinodular tumors. As the majority of patients within BCLC Stage B are not surgical candidates for resection or transplant, locoregional therapy with chemoembolization generally offers the best chance for improved symptom control and survival within this cohort [19, 23].

Patients with advanced HCC (BCLC Stage C) include patients with diminished ECOG performance status, moderate liver disease within CTP Class A or B, and advanced tumors exhibiting macrovascular invasion and/or extrahepatic spread in the form of nodal disease or distant metastases. Stage C patients have a poor prognosis, and the multi-kinase inhibitor sorafenib (Onyx Pharmaceuticals, San Francisco, CA) is currently the only therapeutic option shown to have a survival benefit, demonstrating a 3-month improvement in overall survival as compared to placebo [24]. For patients without portal

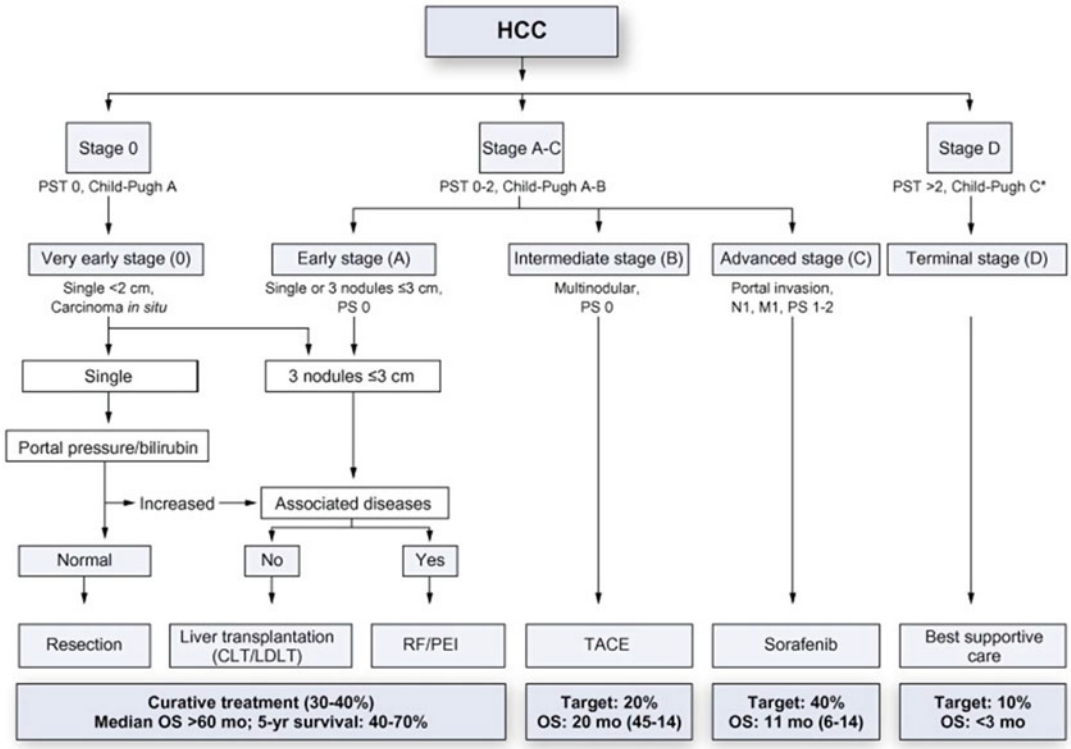

Fig. 15.4 BCLC (Barcelona Clinic Liver Cancer) staging system for management of HCC (Reprinted from European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56(4):908–43. With permission from Elsevier.)

invasion or metastatic disease, locoregional liver-directed therapy with chemoembolization or radioembolization in addition to sorafenib can be considered.

Patients within BCLC Stage D include patients with extremely poor performance status (ECOG 3–4), advanced liver disease within CTP Class C, and advanced HCC. These patients have a terminal prognosis, with median survival of 3–4 months, and are treated with best supportive care and palliation [19].

Hepatic Resection

For patients with normal or minimally diseased underlying liver parenchyma and HCC amenable to surgical resection, liver resection remains the treatment of choice. Most patients, however, develop HCC in the setting of some degree of underlying liver disease or dysfunction, making appropriate patient selection for resection essential. Most patients with well-compensated CTP Class A cirrhosis can typically tolerate hepatic resection, while patients with Class C cirrhosis and nearly all patients with Class B cirrhosis are not candidates for resection. The presence of significant portal hypertension, the sequelae of which are typically detectable on preoperative imaging in the form of parenchymal changes, splenomegaly, and/or varices, is a risk factor for postoperative liver failure following resection. Low preoperative platelet count, another hallmark of portal hypertension, has also been shown to be an important independent risk factor for increased complications, postoperative liver insufficiency, and mortality following hepatic resection for HCC [25]. Pathologically, the

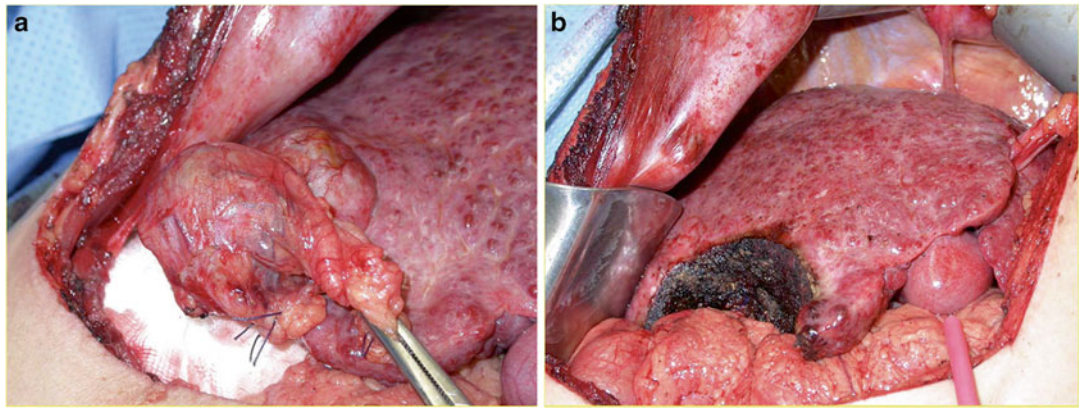

Fig. 15.5 (**a**) Hepatocellular carcinoma arising within a cirrhotic liver (note the fibrotic, nodular appearance of the uninvolved liver). (**b**) Liver remnant following limited hepatic resection of HCC lesion, again demonstrating the characteristic nodular appearance of cirrhosis

degree of hepatic fibrosis can be quantified by the METAVIR scoring system, which assigns a score on a five-point scale from 0 to 4, ranging from no liver scarring to cirrhosis or advanced scarring [26]. This score in turn is predictive of liver's ability to regenerate following hepatic resection.

A key consideration is the extent of the indicated hepatic resection, which must be balanced against the need to preserve an adequate functional liver remnant (FLR) with hepatic portal and arterial inflow, venous outflow, and biliary drainage [27]. The volume of the FLR (ideally >30 % of the total liver volume for patients with normal liver parenchyma or >40 % for well-compensated patients with cirrhotic liver parenchyma) must be taken into account, particularly in the setting of underlying liver disease [27]. Hepatic resection in the setting of fibrosis or cirrhosis carries increased risk of hepatic insufficiency and perioperative complications; this risk increases with the extent of resection (Fig. 15.5a, b). Portal vein embolization is a potential option to induce hypertrophy and increase the size of the FLR in cases where preoperative volumetric calculations suggest an inadequate FLR will remain following partial hepatectomy.

Ideal candidates for resection are patients with minimal or well-compensated liver dysfunction and unifocal, small lesions < 5 cm [7]. While multifocality and larger tumor size are not absolute contraindications for surgical resection, both features are surrogate markers for microscopic vascular invasion and more aggressive tumor histology [28]. Other tumor features associated with increased recurrence and worse survival include vascular invasion, infiltrative growth pattern, positive margin status, and lymph node involvement [29, 30]. In the absence of other adverse features, however, solitary tumors larger than 5 cm can be considered for resection if they involve < 50 % of the liver, as resection may offer 5-year survival rates of 20–25 % (Fig. 15.6a, b) [29, 30]. Resection margins of ≥2 cm are advocated when possible, as long as the adequacy of the FLR size is not compromised, as they are associated with improved recurrence-free and overall survival outcomes versus resection margins of 1 cm [31]. Techniques of resection are beyond the scope of this review, and we refer our readers to the following excellent sources:

- Poon RT. Current techniques of liver transection. HPB. 2007; 9(3): 166–73.
- Cunningham SC, Schulick RD. Management of Primary Malignant Liver Tumors. In: Cameron JL, Cameron AM (eds). Current Surgical Therapy, 10th edition. Philadelphia, PA: Elsevier Saunders; 2010.
- Sicklick JK, D'Angelica M, Fong Y. The Liver. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL (eds). Sabiston Textbook of Surgery, 19th edition. Philadelphia, PA: Elsevier Saunders; 2012.

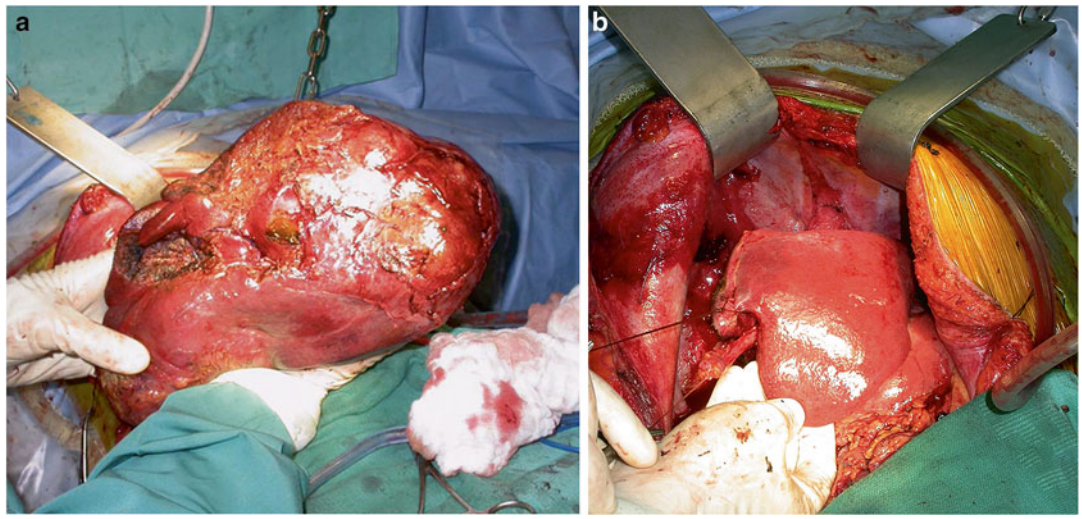

Fig. 15.6 (**a**) Intraoperative photograph of a large HCC lesion. (**b**) Liver remnant after resection of a large HCC lesion

- Fan ST. Major Hepatic Resection for Primary and Metastatic Tumors. In: Fischer JE (ed). Mastery of Surgery, 6th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
- Maithel SK, Jarnagin WR, Belghiti J. Hepatic Resection for Benign Disease and for Liver and Biliary Tumors. Jarnagin WR (eds). Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas, 5th edition. Philadelphia, PA: Elsevier Saunders; 2012.

Patients with hepatitis B as the etiology of their cirrhosis and HCC often have comparatively well-preserved hepatic function versus patients with underlying hepatitis C, making resection a potentially more viable treatment for these patients. In Asia and Africa, where hepatitis B is endemic and where cadaveric organs are severely limited, resection is commonly employed for most patients with HCC amenable to surgical treatment. HCC arising secondary to NASH presents a new disease paradigm, and results to date suggest that these patients have a greater tendency to develop HCC within non-cirrhotic liver parenchyma. These patients may possess a theoretical lower risk of HCC recurrence in the liver remnant as compared with patients with underlying hepatitis B or C, and the benefit of resection may be greater in this patient population [32, 33].

One significant advantage of resection is the potential for immediate treatment, as opposed to the risk of disease progression while on the transplant wait list [34]. A trade-off for more expedited surgical therapy, however, is the significant risk of disease recurrence following partial hepatectomy. Recurrence rates following resection for HCC, whether from true recurrence or de novo tumor development in the cirrhotic liver remnant, have remained extremely high, reaching 50–75 % at 5 years in some series (Table 15.3) [35–47, 48]. Some groups have advocated a strategy of initial resection in patients with HCC within Milan Criteria and with relatively well-preserved liver function, followed by "salvage transplantation" or "secondary transplantation" for those who subsequently develop recurrent disease [49–52]. While primary resection of patients with early HCC and Child-Pugh Class A cirrhosis may be feasible, a significant portion of patients with recurrent disease following resection will not be candidates for transplantation, due to age, comorbidities, or recurrence outside of Milan Criteria [49, 51].

Table 15.3 Representative series of resected hepatocellular carcinoma from Western and Eastern series

						Recurrence-free survival			Overall survival		
Author	Year	Study period	N	% Cirrhosis	Miscellaneous	1 year	3 years	5 years	1 year	3 years	5 years
Llovet [35]	1999	1989–1997	77	100 %	Mean size 3.3 cm	73 %	39 %	25 %	85 %	62 %	51 %
Poon [36]	2001	1989–1994	136	50 %	72 % major resections	42 %	23 %	16 %	68 %	47 %	36 %
		1994–1999	241	43 %	63 % major resections	60 %	38 %	25 %	82 %	62 %	49 %
Belghiti [37]	2002	1990–1999	328	50 %	42 % major resections	NR	NR	NR	61 %	57 %	37 %
Ercolani [38]	2003	1983–1999	224	100 %	Median size 4.1 cm	70 %	43 %	27 %	83 %	63 %	43 %
Cha [39]	2003	1990–2001	164	40 %	85 % major resections	NR	NR	25 %	79 %	51 %	40 %
Ikai [40]	2007	1992–2003	27,062	43 %	27 % multinodular	NR	NR	NR	88 %	69 %	53 %
Shah [41]	2007	1992–2004	193	95 %	Median size 4.5 cm	72 %	48 %	39 %	85 %	68 %	53 %
Park [42]	2009	1994–2007	213	100 %	All within MC	79 %	57 %	44 %	92 %	78 %	69 %
Dahiya [43]	2010	1983–2002	373	100 %	69 % major resections	70 %	43 %	32 %	82 %	63 %	44 %
					31 % minor resections (all tumors < 5 cm)	67 %	43 %	32 %	86 %	65 %	51 %
Lee [44]	2010	1997–2007	130	100 %	63 % within MC	68 %	54 %	50 %	80 %	65 %	52 %
Huang [45]	2011	2000–2005	648	100 %	Mean size 3.6 cm	80 %	57 %	43 %	94 %	83 %	76 %
Arnaoutakis [46]	2013	1992–2011	334	0 %	Median size 6.5 cm	71 %	NR	35 %	87 %	NR	55 %
Sapisochin [47]	2013	1991–2007	95	100 %	All <5 cm in size	81 %	NR	33 %	85 %	NR	62 % (4 years)

Abbreviations: *NR* not reported, *MC* Milan criteria
Adapted from [48]. With permission from Elsevier

Transplantation

Liver transplant offers arguably the most effective cure for HCC, as it removes both the malignancy and the underlying diseased liver parenchyma in which HCC typically arises. Transplantation is limited, however, by access to donor organs and must be balanced against the need for lifelong immunosuppression. Across the globe, the most widely accepted transplant selection criteria are referred to as the Milan Criteria. First reported in 1996 by Mazzaferro et al [53], the Milan Criteria defined transplant criteria for patients as a single HCC lesion < 5 cm in maximum diameter or ≤ 3 lesions each < 3 cm in size, with no evidence of macrovascular invasion or extrahepatic disease on imaging. Numerous studies worldwide, many included in a comprehensive 2011 meta-analysis by the Milan group, have confirmed the favorable outcomes that can be achieved with transplantation for patients meeting these criteria [54]. Others have advocated broader transplantation guidelines, such as the expanded University of California, San Francisco (UCSF) criteria, which include patients with a single lesion < 6.5 cm or up to three tumors, each measuring less than 4.5 cm and a total tumor diameter < 8 cm [55, 56].

As a result of limited organ availability, the drawbacks of transplantation include the risk for disease progression and resulting patient dropout, while patients are on the transplant wait list. Particularly in parts of Asia where HCC is more prevalent, the number of patients with HCC on transplant wait lists far exceeds the supply of deceased donor livers available. In the United States, the UNOS (United Network for Organ Sharing) criteria dictate that patients with HCC meeting Milan Criteria radiographically receive a MELD "exception points" score of 22 when placed on the wait list. If patients remain on the wait list after 3 months, they typically receive an additional three exception points. Within this allocation scheme, wait times vary considerably across UNOS regions and globally, with median times to transplant of 6–12 months in many regions increasing patient dropout and affecting intention-to-treat outcomes [34, 57, 58]. As a result, many centers, particularly those with longer wait times, now offer locoregional neoadjuvant or "bridging" therapy to patients on the transplant wait list to attempt to minimize tumor progression while awaiting a donor organ [59]. Several non-randomized studies to date have reported decreased dropout rates, but none have demonstrated a correlation between pre-transplant bridging therapy with ablation or transarterial chemoembolization and improved posttransplant survival [60–64]. A cost-effective analysis of pre-transplantation bridging ablation therapy, however, demonstrated benefit if projected wait time to transplant exceeded 6 months [65].

Downstaging

No randomized controlled trials have evaluated the utility of locoregional therapy for downstaging patients initially outside of Milan Criteria, although several small series have demonstrated comparable 5-year outcomes for such patients successfully treated with radiofrequency ablation or chemoembolization followed by transplantation versus patients who meet Milan Criteria a priori [66–68]. In light of limited donor organ availability, studies are ongoing to better define which patients beyond Milan Criteria are most likely to benefit from downstaging followed by transplantation.

Living Donor Liver Transplantation

Living donor liver transplantation (LDLT) is also an option for patients and avoids the potential limitations of wait times for allocation of deceased donor livers and the restrictions of the Milan Criteria, although LDLT has been slow to be adopted. Some concerns were raised by early studies suggesting patients undergoing LDLT for treatment of HCC had higher rates of recurrence than seen with deceased donor transplantation [69, 70], although overall survival outcomes appear comparable [71, 72]. Because wait times are minimized, patients with more aggressive

tumors that would progress and render them ineligible for deceased donor transplant may be undergoing LDLT; thus, an observation period of 2–3 months has been proposed to assess the natural history of a patient's tumor [69, 73]. Markov cost-effectiveness modeling suggests that LDLT is most cost-effective in scenarios where wait list times are projected to exceed 7 months [74].

Locoregional Therapy

Ablation

Local ablation is the treatment of choice for patients with early-stage HCC not amenable to surgical therapies. Modalities include radiofrequency, chemical, and microwave ablation.

Radiofrequency ablation (RFA) involves the delivery of electrical energy to cause coagulative necrosis of tumor tissue and can be performed percutaneously, laparoscopically, or as an adjunct procedure from an open surgical approach. One recent study of early HCC lesions < 2 cm demonstrated sustained complete response in 95 % of patients following ablation, with a local recurrence rate of < 1 % [75]. For tumors >3 cm, the efficacy of ablation diminishes significantly [76]. Only two randomized, controlled comparisons of ablation versus resection for early HCC have been performed to date, with one study demonstrating equivalent recurrence and survival rates for the two treatment modalities and the other study suggesting resection was associated with lower recurrence rates and improved survival compared to RFA [77, 78]. Thus the use of RFA as a first-line definitive therapy in patients with resectable disease is not widely practiced. For patients who are not candidates for resection, however, ablation offers an excellent treatment option for smaller tumors. RFA also can be employed as a bridging therapy for HCC in patients awaiting liver transplantation [79].

Chemical ablation with percutaneous ethanol injection (PEI) was among the earliest ablative therapies tested and also induces coagulative necrosis of the HCC lesion. Effective necrosis rates of nearly 90 % for small tumors <2 cm in size have been demonstrated [80], but local recurrence rates are significant [81]. PEI is currently most often reserved for cases in which RFA is not technically feasible due to tumor location.

Microwave ablation is a newer alternative thermal treatment modality that may be more efficacious than RFA for treatment of lesions in close proximity to large vessels, which can serve as a heat sink for RFA and compromise complete necrosis of tumors. Early results with microwave ablation have been comparable to those with RFA [82, 83], although no prospective controlled head-to-head comparisons have been conducted.

Embolization

Embolization therapies take advantage of the dual blood supply of the liver and the fact that HCC tumors are predominantly supplied by the hepatic artery, whereas the uninvolved liver parenchyma is predominantly supplied by the portal venous circulation, allowing therapeutic agents to be delivered via minimally invasive arterial catheters under image guidance directly to the tumor. Intra-arterial therapeutic options include bland embolization, transarterial chemoembolization (TACE), drug-eluting bead (DEB) chemoembolization, and radioembolization.

Bland embolization, or transarterial embolization (TAE), involves injection of microparticles into the terminal hepatic arterial vessels feeding the tumor, causing occlusion of the vessel and inducing ischemic necrosis of the tumor. Multiple lesions can be treated during the same procedure by super-selective targeting of terminal arterial branches. This procedure can be serially repeated in patients with progressive disease or additional lesions with acceptable safety [84], and multiple studies have demonstrated a survival benefit compared to supportive care [23, 85].

TACE, or conventional chemoembolization, involves injection of hydrophilic cytotoxic chemotherapeutic agents, most commonly doxorubicin, into the arterial branches supplying the tumor(s), followed by occlusion of the feeding vessel with injected embolic particles to prevent washout [86]. This combined cytotoxic and ischemic effect is theorized to induce greater tumor

necrosis. Meta-analyses of multiple randomized, controlled trials evaluating TACE have demonstrated minimal procedure-related mortality and significantly improved survival compared to best supportive care, although bland TAE and PEI were also associated with similarly improved survival outcomes [87–90].

Drug-eluting bead chemoembolization (DEB-TACE) takes advantage of embolic microbeads impregnated with doxorubicin and engineered to release the chemotherapeutic agent in a slow, controlled rate over days to weeks within the tumor after being directly injected into the tumor-supplying vessels. This treatment strategy allows for increased, sustained chemotherapy concentrations locally within the tumor without increasing systemic levels [91, 92]. Significantly decreased rates of liver toxicity and systemic side effects compared to conventional TACE and comparable objective response rates of >50 % have been reported, and DEB-TACE has begun replacing TACE at many centers [93, 94].

Arterial catheter-based embolic therapies are recommended for patients with unresectable HCC lesions larger than 4 cm and thus not amenable to RFA or patients with multifocal disease. Per EASL/EORTC guidelines, TACE is the treatment of choice for patients with intermediate, BCLC Stage B, asymptomatic, multifocal HCC in the setting of well-compensated liver dysfunction [10, 95]. The presence of macroscopic vascular invasion or extrahepatic disease is an absolute contraindication to chemoembolization [23, 96]. Chemoembolization is typically limited to patients with Child-Pugh Class A or B cirrhosis, due to the increased risk of liver failure following TACE in patients with more advanced liver disease [97–99]. Other contraindications outlined by Raoul et al [100] include refractory ascites, encephalopathy, extensive bilobar tumor involvement, and renal insufficiency.

Radioembolization

Radioembolization refers to the transarterial catheter-based injection of microspheres loaded with the radioactive isotope yttrium-90 (Y-90). As with chemoembolization, the Y-90 microbeads are selectively injected into the terminal arterial branches supplying the HCC lesion, where they then lodge and deliver a high dose of radiation directly to the tumor, with little penetrance to the surrounding liver parenchyma [101, 102]. Pre-procedure arteriogram mapping of the vasculature and liver-lung shunt studies are required to minimize the risk of radioembolization to the gastrointestinal tract or lungs. The smaller diameter Y-90 microspheres have less embolic effect; therefore portal vein thrombosis is not a contraindication to radioembolization [103]. Trials to date have demonstrated radioembolization is safe and efficacious, with similar objective response rates and overall survival to that seen with chemoembolization [104, 105]. Radioembolization and chemoembolization have yet to be directly compared in a randomized, controlled prospective fashion. Existing retrospective comparisons of these modalities fail to show a survival advantage of one over the other [106, 107].

Among the catheter-based therapies described above, no single therapy has demonstrated a definitive superior survival benefit in a randomized, controlled fashion when compared to the other embolization treatment options. As a result, there is significant heterogeneity among centers as to which liver-directed locoregional therapy is employed.

SBRT

External beam radiation therapy has little role for treatment of HCC due to the risk of radiating the liver in the setting of cirrhosis [108]. Stereotactic body radiation therapy (SBRT) offers a more precise modality for targeting liver lesions with a smaller number of higher doses of radiation, thereby sparing more of the uninvolved liver parenchyma [109, 110]. For unresectable patients with single HCC tumors ≤6 cm in diameter or up to three lesions with a sum diameter ≤6 cm, local control rates of 90 % and overall survival of 60 % at 2 years have been demonstrated with SBRT [111, 112].

Systemic Therapy

Until 2007, no systemic therapeutic agent was approved for the treatment of HCC, and conventional chemotherapy such as doxorubicin, the standard agent for unresectable or metastatic HCC prior to sorafenib, is largely ineffective. Sorafenib, an oral multi-tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and other molecular targets, demonstrated a tolerable side effect profile and a nearly 3-month median overall survival improvement in patients with advanced (BCLC Stage C) metastatic HCC versus the placebo arm in phase II and III studies [24, 113, 114]. In a multicenter, phase III trial of 602 patients with HCC who were not eligible for or had disease progression after surgical resection or locoregional therapies, patients who received sorafenib 400 mg twice daily had a median survival of 10.7 months versus 7.9 months in the placebo group [24]. The patients in this study had an ECOG performance status ≤ 2 and CTP Class A liver dysfunction. Based on these trials, sorafenib is currently recommended as standard of care systemic therapy for patients with advanced, BCLC Stage C disease, or disease progression while undergoing locoregional therapies [10]. Treatment guidelines recommend dose maintenance until evidence of disease progression or intolerable side effects [10].

Numerous phase I through III trials are underway to examine the efficacy of additional molecular targeted agents for the treatment of advanced HCC, either alone or in combination with sorafenib.

Conclusion

Management of patients with hepatocellular carcinoma remains a challenge due to the typical combination of malignant disease and organ dysfunction. Resection remains the treatment of choice for patients with early solitary HCC and normal or well-compensated liver dysfunction. Transplantation should be offered to patients with HCC meeting Milan Criteria (a single lesion <5 cm or up to three lesions each <3 cm), although donor organ availability and long wait times pose limitations. For patients with early HCC not amenable to surgical management, radiofrequency ablation is typically indicated for solitary lesions up to 3 cm in size. Patients with multiple HCC lesions and without evidence of macrovascular invasion or extrahepatic disease are candidates for locoregional therapy, typically with TACE, DEB-TACE, or radioembolization. For patients with advanced HCC, sorafenib is currently the only approved therapeutic agent.

Salient Points

- Hepatocellular carcinoma (HCC) most commonly arises in the setting of cirrhosis or chronic liver disease, for which the most common etiologies worldwide include viral hepatitis B and C, alcohol abuse, and nonalcoholic steatohepatitis (NASH).
- HCC lesions characteristically demonstrate intense arterial enhancement followed by delayed contrast washout on portal venous phases of CT or MRI.
- For lesions >1 cm arising in the background of known cirrhosis and displaying these hallmark imaging characteristics diagnostic of HCC, a tissue biopsy is not necessary, particularly if the patient may be considered for transplant.
- Resection remains the treatment of choice for patients with early solitary HCC and normal or well-compensated liver dysfunction (i.e., CTP Class A).
- Recurrence rates following resection of HCC remain as high as 50–75 % at 5 years in most studies.
- The Milan Criteria define transplant criteria for patients with HCC as a single HCC lesion <5 cm in size, or ≤ 3 lesions each <3 cm in size, with no evidence of macrovascular invasion or extrahepatic disease.
- Liver transplantation should be offered to patients with HCC meeting Milan Criteria, although donor organ availability and long wait times pose limitations in many countries and some UNOS regions within the United States.

- For patients with early-stage, small HCC lesions not amenable to surgical therapies, local ablation is the treatment of choice. Modalities include radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and microwave ablation.
- Patients with multiple HCC lesions and without evidence of macrovascular invasion or extrahepatic disease are candidates for locoregional therapy, typically with transarterial chemoembolization (TACE), drug-eluting bead (DEB)-TACE, or radioembolization.
- The only systemic therapeutic agent approved for advanced or metastatic HCC is sorafenib, an oral multi-kinase inhibitor.

Questions

1. Based on the Milan Criteria, in which of the following scenarios would a patient with HCC NOT be eligible for consideration for transplantation based on these guidelines:
   A. A single 2.5 cm lesion
   B. Three lesions measuring 2.0 cm, 2.5 cm, and 3.0 cm respectively
   C. A single 3.5 cm lesion with evidence of portal vein invasion
   D. Two 2.0 cm lesions involving both the right and left hepatic lobes
2. The characteristic feature of an HCC lesion on cross-sectional imaging with CT or MRI is:
   A. Intense, homogenous contrast enhancement on arterial phase images, with a distinct hypointense central scar
   B. Initial peripheral nodular contrast enhancement with peripheral-to-central progressive infilling of the lesion on delayed phases
   C. Lesion enhancement on arterial phase imaging with contrast washout on delayed phases
   D. Low-attenuation, delayed arterial enhancement
3. The only FDA-approved systemic therapy for a patient with metastatic, Stage IV HCC is:
   A. Everolimus
   B. Sorafenib
   C. Imatinib
   D Herceptin
4. A patient with a serum bilirubin of 2.5, normal serum albumin and INR levels, and no evidence of ascites or encephalopathy would be described as what Child-Turcotte-Pugh (CTP) Class?
   A. CTP Class A
   B. CTP Class B
   C. CTP Class C
   D. CTP Class 3
5. Given a patient with a 7 cm HCC lesion in the setting of cirrhosis and ascites, the most appropriate therapy recommended by BCLC guidelines would be:
   A. Resection
   B. Transplantation
   C. Radiofrequency ablation (RFA)
   D. Transarterial chemoembolization (TACE)
6. Which of the following lab values does NOT factor into the calculation of a patient's MELD (Model for End-Stage Liver Disease) score?
   A. Bilirubin
   B. Albumin
   C. Creatinine
   D. INR
7. In a patient with known cirrhosis and chronic hepatitis C and a large liver lesion suspicious for HCC found on routine surveillance ultrasound, initial workup and staging includes all of the following except:
   A. CT or MRI of abdomen and pelvis
   B. Serum AFP
   C. Percutaneous needle biopsy
   D. Chest imaging
8. All of the following are associated with increased risk of morbidity and mortality following hepatic resection for HCC except:
   A. Splenomegaly
   B. Esophageal varices
   C. Female gender
   D. Low preoperative platelet count
9. All of the following are benefits of transplantation over hepatic resection for the treatment of HCC except:
   A. Clear resection margins
   B. Reduced risk of HCC recurrence
   C. Treatment of the underlying liver disease
   D. Decreased time to surgery

10. Given a patient with CTP Class B cirrhosis, evidence of portal hypertension, and two HCC nodules, each < 3 cm in size, which of the following is the least appropriate therapy by BCLC guidelines?
    A. Transplantation
    B. Radiofrequency ablation (RFA)
    C. Transarterial chemoembolization (TACE)
    D. Hepatic resection

Answers

1. C
2. C
3. B
4. A
5. D
6. B
7. C
8. C
9. D
10. D

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2. Center MM, Jemal A. International trends in liver cancer incidence rates. Cancer Epidemiol Biomarkers Prev. 2011;20:2362–8.
3. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116:544–73.
4. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
5. Siegel AB, Zhu AX. Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. Cancer. 2009;115:5651–61.
6. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362:1907–17.
7. Jarnagin WR. Management of small hepatocellular carcinoma: a review of transplantation, resection, and ablation. Ann Surg Oncol. 2010;17:1226–33.
8. Rahbari NN, Mehrabi A, Mollberg NM, Muller SA, Koch M, Buchler MW, et al. Hepatocellular carcinoma: current management and perspectives for the future. Ann Surg. 2011;253:453–69.
9. Kooby DA, Egnatashvili V, Graiser M, Delman KA, Kauh J, Wood WC, et al. Changing management and outcome of hepatocellular carcinoma: evaluation of 501 patients treated at a single comprehensive center. J Surg Oncol. 2008;98:81–8.
10. European Association For The Study Of The L, European Organisation For R, Treatment Of C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56:908–43.
11. Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev. 2007;33:437–47.
12. Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut. 2008;57:1592–6.
13. Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol. 2001;34:570–5.
14. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44:217–31.
15. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–9.
16. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70.
17. Compton CC, Byrd DR, Garcia-Aguilar J. Liver. In: Compton CC, Byrd DR, Garcia-Aguilar J, editors. AJCC cancer staging atlas. New York: Springer; 2012. p. 241–9.
18. Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer, 2010, pp 191–9.
19. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
20. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100:698–711.
21. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, et al. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology. 1998;28:1241–6.
22. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol. 2008;48 Suppl 1:S20–37.
23. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoem-

bolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359:1734–9.
24. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90.
25. Maithel SK, Kneuertz PJ, Kooby DA, Scoggins CR, Weber SM, Martin 2nd RC, et al. Importance of low preoperative platelet count in selecting patients for resection of hepatocellular carcinoma: a multi-institutional analysis. J Am Coll Surg. 2011;212:638–48. discussion 648–50.
26. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349:825–32.
27. Melstrom LG, Fong Y. "The management of malignant liver tumors." In: Cameron JL, Cameron AM, eds. Current surgical therapy. 11th ed. Elsevier 2014. p. 328–332.
28. Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, et al. Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl. 2005;11:1086–92.
29. Schiffman SC, Woodall CE, Kooby DA, Martin RC, Staley CA, Egnatashvili V, et al. Factors associated with recurrence and survival following hepatectomy for large hepatocellular carcinoma: a multicenter analysis. J Surg Oncol. 2010;101:105–10.
30. Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg. 2005;140:450–7. discussion 457–8.
31. Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245:36–43.
32. Reddy SK, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J, et al. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Hepatology. 2012;55:1809–19.
33. Takuma Y, Nouso K. Nonalcoholic steatohepatitis-associated hepatocellular carcinoma: our case series and literature review. World J Gastroenterol. 2010;16:1436–41.
34. Freeman RB, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. Am J Transplant. 2006;6:1416–21.
35. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology. 1999;30:1434–40.
36. Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg. 2001;234:63–70.
37. Belghiti J, Regimbeau JM, Durand F, Kianmanesh AR, Dondero F, Terris B, et al. Resection of hepatocellular carcinoma: a European experience on 328 cases. Hepatogastroenterology. 2002;49:41–6.
38. Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg. 2003;237:536–43.
39. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg. 2003;197:753–8.
40. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res. 2007;37:676–91.
41. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery. 2007;141:330–9.
42. Park YK, Kim BW, Wang HJ, Kim MW. Hepatic resection for hepatocellular carcinoma meeting Milan criteria in Child-Turcotte-Pugh class a patients with cirrhosis. Transplant Proc. 2009;41:1691–7.
43. Dahiya D, Wu TJ, Lee CF, Chan KM, Lee WC, Chen MF. Minor versus major hepatic resection for small hepatocellular carcinoma (HCC) in cirrhotic patients: a 20-year experience. Surgery. 2010;147:676–85.
44. Lee KK, Kim DG, Moon IS, Lee MD, Park JH. Liver transplantation versus liver resection for the treatment of hepatocellular carcinoma. J Surg Oncol. 2010;101:47–53.
45. Huang J, Hernandez-Alejandro R, Croome KP, Yan L, Wu H, Chen Z, et al. Radiofrequency ablation versus surgical resection for hepatocellular carcinoma in Childs A cirrhotics-a retrospective study of 1,061 cases. J Gastrointest Surg. 2011;15:311–20.
46. Arnaoutakis DJ, Mavros MN, Shen F, Alexandrescu S, Firoozmand A, Popescu I, et al. Recurrence patterns and prognostic factors in patients with hepatocellular carcinoma in noncirrhotic liver: a multi-institutional analysis. Ann Surg Oncol. 2014;21(1):147–54.
47. Sapisochin G, Castells L, Dopazo C, Bilbao I, Minguez B, Lazaro JL, et al. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol. 2013;20:1194–202.
48. Earl TM, Chapman WC. Conventional surgical treatment of hepatocellular carcinoma. Clin Liver Dis. 2011;15:353–70,vii-x.
49. Cherqui D, Laurent A, Mocellin N, Tayar C, Luciani A, Van Nhieu JT, et al. Liver resection for transplantable hepatocellular carcinoma: long-term survival and role of secondary liver transplantation. Ann Surg. 2009;250:738–46.
50. Cucchetti A, Vitale A, Gaudio MD, Ravaioli M, Ercolani G, Cescon M, et al. Harm and benefits of primary liver resection and salvage transplantation

for hepatocellular carcinoma. Am J Transplant. 2010;10:619–27.
51. Fuks D, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. Hepatology. 2012;55:132–40.
52. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg. 2002;235:373–82.
53. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334: 693–9.
54. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl. 2011;17 Suppl 2:S44–57.
55. Yao FY, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl. 2002;8: 765–74.
56. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg. 2007;246:502–9. discussion 509–11.
57. Facciuto ME, Rochon C, Pandey M, Rodriguez-Davalos M, Samaniego S, Wolf DC, et al. Surgical dilemma: liver resection or liver transplantation for hepatocellular carcinoma and cirrhosis. Intention-to-treat analysis in patients within and outwith Milan criteria. HPB (Oxford). 2009;11:398–404.
58. Pelletier SJ, Fu S, Thyagarajan V, Romero-Marrero C, Batheja MJ, Punch JD, et al. An intention-to-treat analysis of liver transplantation for hepatocellular carcinoma using organ procurement transplant network data. Liver Transpl. 2009;15:859–68.
59. Schwartz M, Roayaie S, Uva P. Treatment of HCC in patients awaiting liver transplantation. Am J Transplant. 2007;7:1875–81.
60. Porrett PM, Peterman H, Rosen M, Sonnad S, Soulen M, Markmann JF, et al. Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. Liver Transpl. 2006;12:665–73.
61. Heckman JT, Devera MB, Marsh JW, Fontes P, Amesur NB, Holloway SE, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. Ann Surg Oncol. 2008;15: 3169–77.
62. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, et al. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. Liver Transpl. 2005; 11:767–75.
63. Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg. 2004;240:900–9.
64. Lu DS, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. Hepatology. 2005;41:1130–7.
65. Llovet JM, Mas X, Aponte JJ, Fuster J, Navasa M, Christensen E, et al. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. Gut. 2002;50: 123–8.
66. Yao FY, Kerlan Jr RK, Hirose R, Davern 3rd TJ, Bass NM, Feng S, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology. 2008;48:819–27.
67. Hanje AJ, Yao FY. Current approach to down-staging of hepatocellular carcinoma prior to liver transplantation. Curr Opin Organ Transplant. 2008;13:234–40.
68. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant. 2008;8:2547–57.
69. Fisher RA, Kulik LM, Freise CE, Lok AS, Shearon TH, Brown Jr RS, et al. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant. 2007;7:1601–8.
70. Lo CM, Fan ST, Liu CL, Chan SC, Ng IO, Wong J. Living donor versus deceased donor liver transplantation for early irresectable hepatocellular carcinoma. Br J Surg. 2007;94:78–86.
71. Gondolesi GE, Roayaie S, Munoz L, Kim-Schluger L, Schiano T, Fishbein TM, et al. Adult living donor liver transplantation for patients with hepatocellular carcinoma: extending UNOS priority criteria. Ann Surg. 2004;239:142–9.
72. Todo S, Furukawa H, Japanese Study Group on Organ T. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg. 2004;240:451–9. discussion 459–61.
73. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology. 2004;127:S277–82.
74. Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocellular carcinoma: a life-expectancy and cost-effectiveness perspective. Hepatology. 2001;33:1073–9.
75. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is

resection still the treatment of choice? Hepatology. 2008;47:82–9.
76. Yan K, Chen MH, Yang W, Wang YB, Gao W, Hao CY, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term outcome and prognostic factors. Eur J Radiol. 2008;67:336–47.
77. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243:321–8.
78. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252:903–12.
79. Martin AP, Goldstein RM, Dempster J, Netto GJ, Katabi N, Derrick HC, et al. Radiofrequency thermal ablation of hepatocellular carcinoma before liver transplantation–a clinical and histological examination. Clin Transplant. 2006;20:695–705.
80. Sala M, Llovet JM, Vilana R, Bianchi L, Sole M, Ayuso C, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology. 2004;40:1352–60.
81. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology. 1995;197:101–8.
82. Iannitti DA, Martin RC, Simon CJ, Hope WW, Newcomb WL, McMasters KM, et al. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. HPB (Oxford). 2007;9:120–4.
83. Swan RZ, Sindram D, Martinie JB, Iannitti DA. Operative microwave ablation for hepatocellular carcinoma: complications, recurrence, and long-term outcomes. J Gastrointest Surg. 2013;17:719–29.
84. Erinjeri JP, Salhab HM, Covey AM, Getrajdman GI, Brown KT. Arterial patency after repeated hepatic artery bland particle embolization. J Vasc Interv Radiol. 2010;21:522–6.
85. Maluccio MA, Covey AM, Porat LB, Schubert J, Brody LA, Sofocleous CT, et al. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol. 2008;19:862–9.
86. Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA Cancer J Clin. 2012;62:394–9.
87. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003;37:429–42.
88. Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002;224:47–54.
89. Befeler AS. Chemoembolization and bland embolization: a critical appraisal. Clin Liver Dis. 2005;9:287–300, vii.
90. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. 2006;131:461–9.
91. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81.
92. Poon RT, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol. 2007;5:1100–8.
93. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol. 2012;56:1330–5.
94. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52.
95. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020–2.
96. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology. 2004;127:S179–88.
97. Chan AO, Yuen MF, Hui CK, Tso WK, Lai CL. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. Cancer. 2002;94:1747–52.
98. Shah SR, Riordan SM, Karani J, Williams R. Tumour ablation and hepatic decompensation rates in multiagent chemoembolization of hepatocellular carcinoma. QJM. 1998;91:821–8.
99. Hwang JI, Chow WK, Hung SW, Li TC, Cheng YP, Ho YJ, et al. Development of a safety index of transarterial chemoembolization for hepatocellular carcinoma to prevent acute liver damage. Anticancer Res. 2005;25:2551–4.
100. Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev. 2011;37:212–20.
101. Sangro B, Bilbao JI, Inarrairaegui M, Rodriguez M, Garrastachu P, Martinez-Cuesta A. Treatment of hepatocellular carcinoma by radioembolization using 90Y microspheres. Dig Dis. 2009;27:164–9.
102. Ibrahim SM, Lewandowski RJ, Sato KT, Gates VL, Kulik L, Mulcahy MF, et al. Radioembolization for the treatment of unresectable hepatocellular carci-

noma: a clinical review. World J Gastroenterol. 2008;14:1664–9.
103. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47:71–81.
104. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2011; 140:497–507 e2.
105. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138:52–64.
106. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010;116: 1305–14.
107. Kooby DA, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol. 2010;21:224–30.
108. Cheng JC, Wu JK, Huang CM, Liu HS, Huang DY, Cheng SH, et al. Radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: dosimetric analysis and implication. Int J Radiat Oncol Biol Phys. 2002;54:156–62.
109. Lo SS, Fakiris AJ, Chang EL, Mayr NA, Wang JZ, Papiez L, et al. Stereotactic body radiation therapy: a novel treatment modality. Nat Rev Clin Oncol. 2010;7:44–54.
110. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008;26:657–64.
111. Price TR, Perkins SM, Sandrasegaran K, Henderson MA, Maluccio MA, Zook JE, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. Cancer. 2012;118:3191–8.
112. Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2011;81:e447–53.
113. Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2006;24:4293–300.
114. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10:25–34.