Chapter 13
The Management of Hepatocellular Carcinoma

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Epidemiology

Hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, is the fifth most common neoplasm and the second leading cause of cancer death worldwide, resulting in approximately 800,000 deaths per year [1, 2]. The case fatality ratio of HCC is 0.8, with the number of new cases nearly similar to the number of deaths each year, equivalent to pancreatic cancer [3]. The highest incidence areas worldwide are in East Asia and sub-Saharan Africa, with incidences of 24.2/100,000 and 35.5/100,000, respectively [4].

Unlike most common cancers, which have seen a reduction in death rates, the incidence and number of deaths due to HCC have increased in the United States. Between 2000 and 2012, the age-adjusted incidence of HCC in the United States increased from 4.4/100,000 to 6.7/100,000, more than four times the incidence of 1.6/100,000 in 1976 [5, 6]. In parallel to the rising incidence, there has been a two-fold increase in deaths due to HCC between 1999 and 2016 [7]. These trends are driven by the high rate of hepatitis C virus (HCV) in the "Baby Boomers" birth cohort from 1945 to 1964, where researchers estimate HCC cases due to HCV will peak in 2020 [8], as well as the epidemic of nonalcoholic fatty liver disease (NAFLD).

HCC is unique in that >90% of cases are associated with some form of underlying chronic liver disease and/or cirrhosis. Risk factors for developing HCC include chronic viral hepatitides (hepatitis B virus [HBV] and HCV), alcoholic liver disease, diabetes, NAFLD, and less common causes of cirrhosis such as hereditary hemochromatosis [8]. Worldwide, over 50% of cases of HCC are due to HBV, followed by

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HCV, which accounts for approximately 20% [9]. While chronic viral hepatitis is implicated as the etiologic factor in the development of the majority of HCC, these risks are now modifiable in light of both vaccination efforts and antiviral therapies. Efforts to reduce HBV rates with universal vaccination efforts have been effective in reducing HCC mortality in high incidence areas, such as Taiwan and East Asia [10]. Furthermore, the recognition that the risk of HCC in patients with HBV is higher in patients who have higher HBV DNA viral load [11] underscores the importance of aggressive HBV antiviral therapy, which results in a 50–60% risk reduction of HCC following successful treatment [12, 13]. However, inactive carriers with no viral load (HbcAb positive, HbsAb negative) remain at higher risk than patients without HBV, with an annual incidence of 0.06% versus 0.02% [14]. Regarding HCV, the risk of HCC in patients achieving a sustained virologic response (SVR), which is considered a virologic cure, is lower than patients who do not achieve SVR, whether SVR is achieved by interferon or directly acting antivirals (DAAs) [15–17]. Even after achieving SVR, patients with HCV who have cirrhosis will develop HCC with an incidence of approximately 1% per year [18, 19]. DAAs for HCV may lead to a reduction in HCC over the next 1–2 decades, with the degree of this impact depending on the availability of these medications [17].

NAFLD, an increasingly important etiologic factor in the development of HCC, warrants specific discussion. NAFLD has become the most common cause of chronic liver disease in the developed world, and it is a rising cause of HCC-related liver transplant in the United States [20]. The prevalence of NAFLD is higher among Latinos compared to other ethnic groups in the United States [21]. Diabetes mellitus is commonly found in patients with NAFLD and is itself associated with a two- to threefold increase in the risk of developing HCC [22]. Perhaps most alarmingly, HCC has been found to arise in NAFLD patients without established cirrhosis, complicating surveillance recommendations for this specific group of patients. Recently, Mittal and coworkers reviewed a national cohort of VA patients with HCC and found 13% of patients with HCC did not have cirrhosis, with NALFD accounting for approximately 1/3 of patients with noncirrhotic HCC [23]. Additional research is required to define high-risk subgroups with NAFLD to facilitate surveillance and early disease detection.

Pathophysiology

HCC most commonly forms in the setting of liver injury, whereby hepatocyte damage results in genomic instability and transformation into HCC. The great majority of HCC, approximately 80–90%, develops in the context of cirrhosis. Among patients with established cirrhosis, the annual incidence of HCC is 3–8% [24].

The common denominator for the development of HCC is thought to be the ongoing inflammation and cell turnover in patients with cirrhosis and can be due to viral hepatitis, alcoholic or nonalcoholic steatohepatitis (NASH), or other disease processes that lead to injury and repair. In this setting, patients develop precancer-

ous dysplastic nodules which may be low or high grade, based on degree of cellular atypia. The presence of stromal invasion differentiates HCC from dysplastic nodules [25]. In patients without cirrhosis, there are discrete alternate pathways for the development of HCC. The DNA virus HBV integrates its DNA randomly into the host hepatocyte genome and may directly contribute to the development of HCC via activation of oncogenes or inactivation of tumor suppressor genes. The viral regulatory protein HBx causes cell cycle dysregulation via chromatin remodeling and abnormal transcription activity, leading to cell proliferation [26]. Aflatoxins, carcinogens produced by Aspergillus molds, contaminate agricultural crops in developing nations and can lead to HCC. Aflatoxin directly binds to DNA, forming DNA adducts that cause DNA strand breakage and mutations in the *p53* tumor suppressor gene [27, 28]. Malignant transformation of hepatic adenomas into HCC has been associated with mutations *TERT* and *CTNNB1* genes [29].

More recently, there have been numerous studies detailing the genetic landscape of HCC using next-generation sequencing methodologies that have allowed for detailed genomic and transcriptomic molecular analyses of HCC. HCC lesions carry numerous somatic mutations, with an average of 40–60 alterations in protein-coding areas of the genome [29]. Study of recurrent mutations has shown common mutations in pathways for telomere maintenance, cell cycle signaling, WNT-β-catenin signaling, epigenetic chromatin modification, receptor kinases, and oxidative stress [29–32]. At present, a minority of HCC tumors harbor potentially targetable mutations with available agents [33]. As the molecular landscape of HCC becomes better defined, HCC treatment may become more individualized, with personalized treatments targeting patient-specific aberrations.

Diagnosis and Staging

Surveillance and Diagnosis

The majority of patients diagnosed with HCC present with advanced disease, with 60–70% presenting with disease not amenable to surgical resection (SR) or liver-directed therapies [34]. Because 80–90% of HCC develops in patients with underlying advanced liver disease, there is an opportunity to impact mortality with early detection. The very purpose of HCC surveillance is to reduce mortality by detecting disease at a treatable stage. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have promulgated guidelines for surveillance for HCC, which inform the discussion of surveillance in this chapter [35, 36] (Table 13.1).

A requirement for effective surveillance is first identifying high-risk patient groups who are appropriate for testing. Cost-effectiveness studies have defined an appropriate incidence for surveillance at 1.5%/year [37]. High-risk groups meeting these criteria include patients with established cirrhosis due to any underlying etiology. Other high-risk groups include noncirrhotic patients with HBV who have

Table 13.1 AASLD and EASL surveillance guidelines

	AASLD	EASL
Target patient groups	Cirrhotic patients[a]	Cirrhotic patients[a]
		Chronic HBV infection[b]
		Chronic HCV with bridging fibrosis
Surveillance testing	US +/− AFP, every 6 months	US every 6 months
Diagnostic testing	CT or MRI, using LI-RADS criteria, for cirrhotic patients	CT or MRI, using li-RADS criteria, for cirrhotic patients
	Biopsy for noncirrhotic patients or cirrhotic patients with nondiagnostic imaging	Biopsy for noncirrhotic patients or cirrhotic patients with nondiagnostic imaging

[a]Patients with decompensated cirrhosis who are ineligible for curative therapies are excluded from surveillance

[b]High-risk factors to consider for screening include PAGE-B score ≥10, active viral replication, geographic origin (e.g., Asia and Africa), increased age, and male gender

specific features. Noncirrhotic HBV patients from Asia or Africa and patients with higher levels of HBV replication or active hepatitis are appropriate for surveillance [38, 39]. The Platelet, Age, Gender, Hepatitis B (PAGE-B) system may help define which patients with HBV are intermediate or high risk and merit surveillance. PAGE-B scores are based on a decade of age, gender, and platelet count, and scores 10–17, and ≥18, correspond to intermediate and high risk [40]. Patients with chronic HCV and bridging fibrosis without cirrhosis have also been recommended for surveillance, due to the difficulty identifying progression from fibrosis to cirrhosis, as well as the possibility of understaging liver disease [41]. Lastly, patients with chronic HCV with advanced disease who have achieved SVR merit surveillance as they continue to be at risk for HCC. Because advanced liver failure prevents the use of many HCC therapies due to debility, surveillance is not recommended for patients with decompensated Child-Pugh B or C cirrhosis who cannot tolerate liver-directed or systemic therapies [35, 36].

An evolving area of particular concern is the appropriate recommendation for surveillance in patients without cirrhosis who have NAFLD. There is an increasing surge of NAFLD-related HCC cases occurring in patients without cirrhosis. However, due to the high prevalence of NAFLD and lack of specific high-risk NAFLD features, recommending universal surveillance is challenging [42]. Furthermore, ultrasound has lower sensitivity to detect tumor in patients with obesity, and routine surveillance using computed tomography (CT) or magnetic resonance imaging (MRI) would make health costs prohibitive [35]. At present, neither AASLD nor EASL recommends surveillance for noncirrhotic NAFLD. Research to define high-risk subgroups among patients with noncirrhotic NAFLD could make targeted surveillance more cost-efficient and effective.

Surveillance testing incorporates imaging and serologic studies. The most common imaging test for HCC surveillance is ultrasound (US). Studies investigating the effectiveness of US have found sensitivity ranging from 58% to 89% and specificity

higher than 90% [43]. The coarse echotexture of the cirrhotic liver presents a challenge to the ultrasonographer, and technician experience and quality of equipment impact US efficacy. Though more sensitive than US, CT and MRI are not recommended as surveillance due to their increased cost and a higher rates of false positive findings [44]. Both EASL and AALD recommend biannual US for high-risk groups. For lesions ≥1 cm discovered on ultrasound, further characterization with multiphase CT or MRI is recommended [36]. Lesions <1 cm are followed with ultrasound or other diagnostic imaging in 3-month intervals.

Serologic studies used to detect HCC include serum alpha-fetoprotein (AFP), the lectin-binding subfraction of AFP (AFP-L3), and des gamma carboxyl prothrombin (DCP), also known as protein induced by vitamin K absence/antagonist-II (PIVKA II). AFP is the most common serologic study used for surveillance, and some studies have shown an added sensitivity when AFP is used in addition to ultrasound [45, 46]. AASLD guidelines permit the inclusion of AFP in surveillance programs, but the guidelines do not go so far as to recommend universal AFP testing. AASLD guidelines recommend an AFP cut-off of 20 ng/mL for high-risk patients when it is used, which provides sensitivity of ~60% and specificity of ~90% [47]. EASL does not recommend inclusion of AFP in surveillance, citing studies that report a limited improvement in disease detection of only 6–8% of cases not already detected by US [48]. AFP-L3 and PIVKAII are novel biomarkers produced by HCC with promising predictive value. The Gender, Age, AFP-L3, AFP, and DCP (GALAD) model incorporates both AFP-L3 and PIVKAII, along with AFP to predict the risk of HCC development with a c-statistic of 0.88 [49]. These biomarkers are considered investigational until they are validated in larger study groups.

The diagnosis of HCC can be made with imaging studies or tissue biopsy. Imaging alone is sufficient to make the diagnosis of HCC in the vast majority of patients with underlying cirrhosis. The Liver Imaging Reporting and Data System (LI-RADS) has standardized the interpretation and reporting of liver lesions among patients with cirrhosis, providing a uniform method to diagnose HCC [50] (Table 13.2). For cirrhotic patients who undergo dynamic contrast-enhanced CT or MRI imaging, liver lesions meet the diagnostic criteria for HCC, a LI-RADS 5 lesion, if they exhibit nonrim-like arterial hyperenhancement and one of the following characteristics: nonperipheral "washout" in the venous phase of imaging, a ≥50% size increase in less than 6 months, and if the lesion size is ≥20 mm with an enhancing capsule [43]. The LI-RADS system is not validated to make the diagnosis of HCC in noncirrhotic patients. For noncirrhotic patients, EASL recommends tissue pathology to make the diagnosis of HCC. Biopsy is also an option to make a diagnosis in cirrhotic patients with nondiagnostic imaging. The risks of biopsy include bleeding and seeding of tumor along the biopsy needle tract. Historical rates of tumor seeding range from 0.6% to 5.1%. Due to these risks, AASLD guidelines recommend against routine biopsy of all indeterminate lesions. However, centers using new coaxial biopsy techniques have reported series with zero cases of tumor seeding after biopsy [51]. At present, biopsy represents a viable option for patients with lesions concerning for HCC, whose imaging remains nondiagnostic.

Table 13.2 LIi-RADS criteria (liver imaging reporting and data system)

Category	Significance	Examples	Enhancement criteria	Size criteria and presence of additional major criteria	Pathologic correlation	Natural history of lesions in 12 months
LR-1	Definitely benign	Cyst, hemangioma, hepatic fat deposition, confluent fibrosis or scar			0% are HCC or malignant	
LR-2	Probably benign	Cyst, hemangioma, hepatic fat deposition, confluent fibrosis or scar		<20 mm	8–22% are HCC or malignant	0–6% progress to LR-5
LR-3	Intermediate probability of malignancy	Hepatocellular adenoma	Nonrim arterial phase hyperenhancement	<20 mm	31–50% are HCC or malignant	3–11% progress to LR-5
			Arterial phase hypo- or isoenhancement	<20 mm with ≥1 additional major feature or >20 mm with no additional major features		
LR-4	High probability of HCC		Nonrim arterial phase hyperenhancement	<10 mm with ≥1 additional major feature; 10–19 mm with "capsule" as the only major feature; or ≥20 mm with no additional major features	67–95% are HCC or malignant	36–47% progress to LR-5
			Arterial phase hypo- or isoenhancement	<20 mm with ≥2 additional major features or ≥20 mm with ≥1 additional major feature		
LR-5	Definitely HCC		Nonrim arterial phase hyperenhancement	10–19 mm with nonperipheral "washout" or threshold growth or ≥20 mm with ≥1 additional major feature	92–99% are HCC or malignant	

Additional major features:

Nonperipheral "washout"—Temporal reduction in enhancement, relative to adjacent liver tissue, in venous phase of imaging

Enhancing "capsule"—Uniform, sharp border around most or all of lesions

Threshold growth—Size increase of ≥50% in ≤6 months or ≥100% in >6 months

Clinical Presentation and Staging

The clinical presentation of HCC can be quite variable, depending on a patient's degree of medical follow-up and the natural history of the disease at the time of diagnosis. Patients who undergo surveillance may be asymptomatic at the time of diagnosis, while patients with advanced HCC tumors may have local or systemic symptoms. Unfortunately, up to 60–70% of patients present with advanced disease [34]. Among patients with advanced disease, 75–90% have right upper quadrant abdominal pain, weight loss, and palpable mass [52]. Jaundice occurs in 19–44% of patients with HCC. The majority of cases with jaundice result from liver decompensation in the cirrhotic patient, and 1–12% are due to obstruction of the biliary system [53]. The most radical presentation of HCC is tumor rupture. Spontaneous rupture is life-threatening and accounts for 6–10% of patient deaths from HCC. The best treatment of rupture is transarterial embolization, as emergency hepatic surgery carries increased risk of mortality [54, 55].

Extrahepatic disease often occurs in cases of advanced HCC. The most common sites of extrahepatic disease are the lung (38–55%), abdominal lymph nodes (20–41%), and the bone (25–38%). Other less common sites of disease include the adrenal gland (8%) and the brain (1%) [56–59]. Large primary tumor size, vascular invasion by tumor (e.g., portal vein thrombus), and elevated serum AFP >1000 ng/dL have been associated with the presence of extrahepatic disease [60, 61]. Extrahepatic lesions may be detected by cross-sectional imaging during surveillance or by studies ordered for signs and symptoms such as bone pain, lymphadenopathy, and elevated AFP. Appropriate testing to detect extrahepatic disease include CT of the chest, nuclear medicine bone scintigraphy, and 18F-fluorodeoxyglucose positron emission tomography (PET scan) [62]. Metastatic disease is the direct cause of patient death in a minority of patients. In their series of 324 patients with extrahepatic disease, Uchino and colleagues found 23 (7.6%) patients expired as a direct result of extrahepatic disease, with the majority of patients succumbing due to their primary HCC (273 patients, 90.7%) or liver failure (13 patients, 4.3%). The median survival for patients with metastatic disease is 7–8 months [61].

Compared to other GI malignancies, treatment recommendations for HCC are particularly nuanced because the patient's underlying liver function weighs heavily in determining the most appropriate treatment. Numerous clinical staging systems have focused on assigning a treatment algorithm based on incorporation of both the extent of tumor involvement and measures of underlying liver function such as Child-Pugh status, performance status, and laboratory evaluations, with two of the more popular algorithms being the Okuda and Barcelona Clinic Liver Cancer (BCLC) staging systems.

The Okuda staging system was proposed in 1984, as the first staging system to incorporate tumor extent and liver function [63]. The Okuda system includes tumor size (≤50% or >50% of the entire liver), the presence or absence of ascites, albumin level ≤3 or >3 g/dL, and serum bilirubin level ≤3 or >3 mg/dL. Depending on how

many factors are present, clinicians categorize patients by Okuda stage: Stage I: not advanced; Stage II: moderately advanced; and Stage III: very advanced. The Okuda stages accurately discriminated survival in a validation cohort, with median survival of Stage I patients at 11.5 months, Stage II patients at 3 months, and Stage III patients at 0.9 months. Hepatic failure and gastrointestinal bleeding accounted for the majority of deaths in the series, rather than direct complications of malignancy.

The BCLC system is the most commonly used treatment algorithm-based staging system. BCLC was proposed in 1999, and it takes into account extent of tumor, liver function, physical status, and cancer-related symptoms [64] (Fig. 13.1). BCLC stages patients into five categories— very early stage (0), early stage (A), intermediate stage (B), advanced stage (C), and terminal stage (D). Unique among staging systems, BCLC offers treatment recommendations by stage. EASL guidelines endorse BCLC as the preferred staging system because it has been externally validated in different clinical settings and it has been shown to be adaptable with the addition of new clinical data [65, 66]. Since its original iteration, BCLC researchers have added Stage 0 (very early HCC) and new additional treatment modalities with transarterial chemoembolization (TACE) for intermediate HCC and sorafenib for advanced disease [67]. Current areas of further refinement for the BCLC include efforts to improve the discrimination and stratification of patients with BCLC-B and BCLC-C diseases, as the current categories include a wide range of patients with different liver function and tumor burden.

For HCC patients eligible for surgical resection or liver transplantation, pathologic staging is performed using the American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) staging system. The AJCC published the most recent iteration of the TNM staging system in 2017 (eighth edition), which featured changes to the primary tumor (T) classification [68] (Table 13.3). In their multi-institutional, retrospective study of 1109 patients, Shindoh and coworkers found tumors ≤2 cm with MVI did not have worse survival than tumors ≤2 cm without MVI ($p = 0.8$), although MVI was associated with worse survival in larger tumors [69]. As a result, The AJCC eighth edition of the HCC TNM staging system subdivides T1 and T2 staging to account for these data. The TNM staging system is the only staging system validated to predict outcome after resection and transplantation [69–71].

Locoregional Therapy

Locoregional therapy (LRT) refers to nonsurgical treatment of HCC that aims to destroy tumors and includes ablative and transarterial therapies, as well as external beam radiation therapy. The indications for LRT include definitive curative-intent therapy for very small HCC, “bridging” therapy for patients wait-listed for liver transplantation (LT) to mitigate tumor progression and wait-list dropout, “down-staging” therapy for patients whose extent of disease is outside of criteria for surgical resection or LT, and destination therapy to prolong survival in patients with

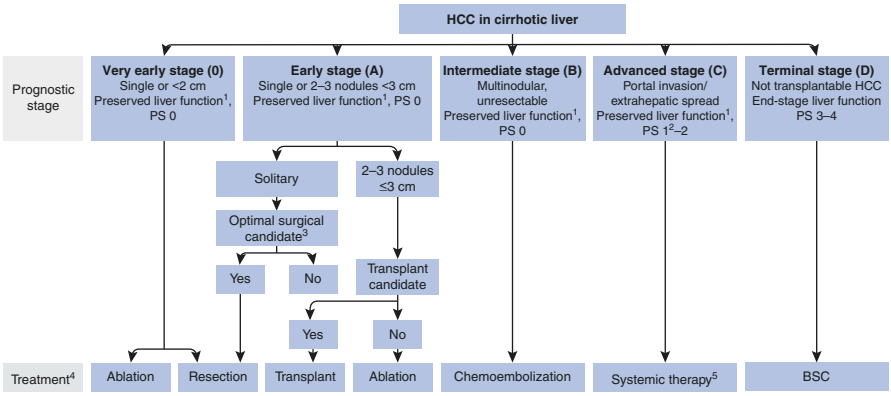


Fig. 13.1 BCLC Staging Systems. (From Galle et al. [35])

locally advanced disease who are not candidates for surgical resection or LT. Patient selection for LRT is guided by the extent of disease and the patient's hepatic reserve. General contraindications to LRT include decompensated cirrhosis (e.g., ascites, encephalopathy, or other symptoms of portal hypertension), MELD>20, and elevated total bilirubin >3 mg/dL [72–74]. Tumor location and the presence of portal vein thrombosis (PVT) affect treatment decisions regarding treatment modality.

Ablative Therapies

Methods of ablative therapy include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave ablation (MWA). Ablative techniques require the placement of an electrode or applicator, which is performed percutaneously or intraoperatively. Laparoscopic ablation may be employed for tumors in difficult locations, such as for subcapsular tumors. For accurate percutaneous placement of the ablation device, operators may use US or CT, according to personal experience and preference.

PEI was the first established ablative technique. It causes coagulative necrosis in the tumor, with outcomes of complete necrosis in 90% of tumors <2 cm [75, 76]. Disadvantages of PEI include unequal distribution of ethanol within the tumor and poor tissue diffusion of ethanol in the cirrhotic liver, limiting the zone of necrosis. Meta-analyses of randomized controlled trials (RCTs) have compared PEI to RFA, and RFA has been shown to be superior to PEI for overall survival (OS), disease-free survival, and recurrence [77, 78]. In one representative study, Germani and coauthors found the hazard ratio (HR) of death was 0.53 for RFA versus PEI, with the odds ratio for local recurrence strongly favoring RFA (0.27 for RFA compared to PEI) [79].

Table 13.3 AJCC staging system (eighth ed.)

		Stage	T	N	M
T category	*N category*	IA	T1a	N0	M0
T1a—Single tumor ≤2 cm	N0—No lymph node metastasis	IB	T1b	N0	M0
T1b—Single tumor >2 cm without vascular invasion	N1—Any lymph node metastasis	II	T2	N0	M0
T2—Single tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm	*M category*	IIIA	T3	N0	M0
T3—Multiple tumors, at least one of which is >5 cm	M0—No distant metastasis	IIIB	T4	N0	M0
T4—Tumor involving major branch of PV or HV or direct invasion of adjacent organs	M1—Distant metastasis	IVA	Any T	N1	M0
		IVB	Any T	N0	M1

RFA achieves coagulative necrosis and tumor death by generating frictional heat through high-frequency alternating current. A zone of necrosis forms around the tumors, which may explain the lower rate of local recurrence for RFA over PEI. RFA has been used as definitive therapy for early stage HCC (BCLC 0 and BCLC A), with 5-year overall survival (OS) and recurrence-free survival of 67.9% and 25.9%, respectively [80]. There have been meta-analyses comparing RFA to surgery for solitary, small HCC. A recent Cochrane review showed no difference in overall mortality between surgery and RFA (HR 0.80, CI 0.60–1.08) but improved cancer-related mortality at maximal follow-up for patients who had surgery (or 0.35, CI 0.19–0.65) [81]. At present, EASL guidelines state RFA offers "competitive results" with respect to surgery for HCC lesions ≤2 cm [35]. Furthermore, EASL guidelines state surgery is acceptable for any size lesion, and AASLD guidelines recommend surgery over RFA for patients who are resectable (*see* section "Surgical Resection") [35, 36]. The risk of tumor progression after RFA increases with increasing tumor size, with an increased risk of local tumor recurrence/progression for tumors >2 cm compared to those which are ≤2 cm (3-year rate 17.6% vs. 5.1%, $p < 0.001$) [76, 82, 83]. These larger tumors present a challenge to RFA. LRT treatment strategies for tumors that are 3–5 cm have been developed to address this, including multi-polar RFA and combination of RFA with transarterial chemoembolization (TACE; *see* section "Transarterial therapies") [84–86]. Meta-analyses of combination RFA and TACE show improved OS compared to RFA alone, with a statistically significantly higher or of survival at 1, 2, and 3 years of 2.96, 3.72, and 2.65, respectively [86].

MWA has emerged as a new ablative technique to treat HCC. MWA uses electromagnetic energy to heat tissue and destroy tissue. Compared to RFA, MWA is less affected by the "heat sink" effect of adjacent vasculature. Studies have compared MWA to RFA, though no RCTs exist at this point. All studies to date have found no statistically significant difference in OS between the two modalities [87, 88].

Transarterial Therapies

Transarterial therapies for LRT include bland transarterial embolization (TAE), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) with yttrium-90 (Y90) microspheres. General indications for transarterial therapy include BCLC-B patients or patients with multifocal or large tumors >2 cm. Contraindications to transarterial therapy are similar to those listed above for ablative therapy. An additional consideration arises in patients with PVT. Because the liver relies on dual blood supply from the portal vein and hepatic artery, patients with HCC who have PVT are contraindicated to undergo TACE and TAE to prevent damaging liver ischemia. In contrast, TARE with Y90 uses smaller particles for embolization and causes less arterial ischemia. TARE with Y90 has been shown to be safe when used in patients with PVT. [89]

TACE is the EASL recommended therapy for patients with BCLC-B stage HCC [35]. TACE takes advantage of the neo-angiogenesis of HCC tumor development by allowing targeted intra-arterial administration of chemotherapy, followed by embolization of arterial vessels feeding the tumor, causing a cytotoxic and ischemic injury to the tumor. The most common chemotherapeutic drugs used in TACE are doxorubicin and cisplatin. A newer modification of TACE uses drug-eluting beads (DEB), which may reduce systemic exposure to chemotherapy. The survival benefit of TACE compared to best supportive care has been shown in two RCTs [90, 91]. Patients with unresectable HCC who received TACE achieved a 2-year survival that ranged from 31% to 63%, compared to 11–27% among the control group. Modern series have achieved a median survival of 40–50 months using more stringent selection of patients with asymptomatic Child Class A or B cirrhosis, uni- or paucinodular disease, and no vascular invasion or metastases [92–94]. Complications of TACE include postembolization syndrome (PES; affecting 60–80%), liver failure (7.5%), hepatic abscess (2%), gastroduodenal ulceration (3–5%), renal dysfunction (2%), and rare complications such as pulmonary and cerebral embolization, interstitial pneumonia, and access-related complications [73, 95, 96]. PES, the most common complication, occurs due to a complex pathogenesis involving the direct effects of chemotherapy, tumor necrosis, and effects of hypoxia on normal liver parenchyma. Manifestations of PES include liver enzyme abnormalities, fever, hematological/bone marrow toxicity, pain, and vomiting, which may persist for 7–10 days but are otherwise self-limiting.

TARE employs techniques similar to TACE but uses microspheres containing radioactive substances like Y90 to emit high-energy radiation directly to HCC tumors. The TARE therapy requires coordination with interventional radiologists, nuclear medicine specialists, radiopharmacists, and physicists. In its current iteration, TARE requires a pretreatment session of angiography with the injection of 99Tc macroaggregated albumin to calculate the dose to the HCC tumor and the amount of affected adjacent liver tissue and degree of hepatopulmonary shunting. Severe pulmonary shunting may contraindicate TARE in some patients. Studies of

long-term outcomes have shown median survival times for patients with intermediate-stage disease of 16–17 months and 10–12 months for patients with advanced disease [74, 97, 98]. At present, RCTs comparing TARE and TACE do not exist; however, retrospective studies comparing TARE and TACE have shown longer time to tumor progression (26 vs. 6 months) and improved quality of life with TARE [99–101].

External Beam Radiation Therapy

Historically, external beam radiation therapy (XRT) has not played a major role in the treatment of HCC. However, with technological advances allowing focal administration of ablative doses of radiation, termed stereotactic body radiation therapy (SBRT), radiation therapy has become an effective LRT modality for HCC.

Early use of XRT for liver cancer required large fields, which resulted in rates of radiation-induced liver disease (RILD), a progressive veno-occlusive disorder often resulting in mortality or serious morbidity, of >40% [102]. The development of three-dimensional conformal radiation therapy has allowed high doses of radiation to smaller fields with resultant lower rates of RILD. Several phase I/II trials have shown 1- and 2-year local control rates of 82–99% for HCC cases treated with SBRT, with low rates of RILD [103–106]. Clinicians have also studied SBRT in the neoadjuvant setting before LT. Mannina et al. reported results of 38 patients treated with SBRT who went on to LT with 1-, 3-, and 5-year survival of 92%, 77%, and 73%, respectively. Explant pathology showed a complete response in 45% of lesions and a partial response in 23% [107]. Furthermore, particle-based radiation therapy in the form of proton beam and carbon-based therapy has been used for HCC. In a prospective phase II study at Loma Linda University, clinicians treated 76 patients with proton beam therapy, of whom 47% had Child Class B cirrhosis, with a mean tumor size of 5.5 cm. Progression-free survival at 3 years was 60%, and local control was 80% [108]. At present, no RCTs exist comparing radiation-based therapy to other forms of LRT; however, retrospective studies have shown SBRT to have comparable efficacy to RFA and TACE, with some studies showing superior local control with the use of SBRT [109, 110].

LRT for Bridging and Downstaging Before Liver Transplantation

LRT is commonly used for "bridging" patients who are waiting for LT or to "downstage" patients who are outside criteria for LT so that they may have tumor reduction and become eligible for LT. AASLD and EASL guidelines recommend the use of LRT before LT for both bridging and downstaging [35, 36]. Several meta-analyses have demonstrated reduced dropout risk in patients who have a response to bridging

therapy [111, 112]. Mehta and coworkers studied 398 patients with HCC awaiting LT and found that a complete response to LRT, along with single tumor 2–3 cm, and AFP level <20 ng/mL was associated with a 1- and 2-year dropout risk of 1.3% and 1.6%, respectively, compared to 21.6% and 26.5% for all other patients [111]. Patient responses to pre-LT downstaging have been shown to predict post-LT tumor recurrence [113–116]. In their most recent published guidelines, neither society gives specific recommendations regarding the specific type of LRT to use for pre-LT treatment, and such decisions should be based on individual patient and tumor characteristics.

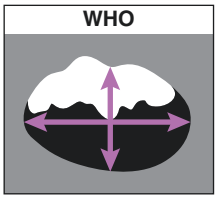
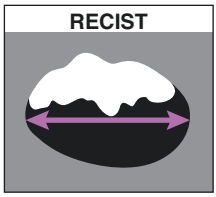
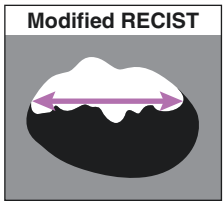
Assessing Response to Treatment

Patients treated with LRT undergo assessments with imaging and serologic tests to determine their response to treatment. Typically, patients have CT or MRI imaging at 4–6 weeks post-LRT and then every 3–6 months. Patients with elevated AFP before treatment may also undergo serial serologic testing to assess for an appropriate reduction in the serum AFP level.

Criteria to assess imaging response after treatment have been developed for HCC. The World Health Organization (WHO), Response Evaluation Criteria In Solid Tumors (RECIST) 1.0, and RECIST 1.1 report tumor size as the longest dimension of the tumor, and they are commonly used for solid tumors [117, 118]. Each system measures the change in tumor size after LRT and grades treatment response as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). (*See* Table 13.4 *for specific criteria*.) However, the treatment effect of LRT causes tumor necrosis with a resulting absence of arterial flow within the lesion. The imaging finding after treatment will therefore show a smaller area of arterial enhancement within the lesion, while the nonviable tumor remains in situ without necessarily a reduction in its overall size. Neither WHO nor RECIST 1.1 criteria limit the area of measurement to the part of the tumor with arterial enhancement or the viable portion of the tumor. To account for this, the modified RECIST (mRECIST) criteria has been developed to specifically evaluate the amount of viable tumor. These criteria measure the single longest dimension of the part of the tumor with arterial enhancement [119]. The mRECIST system also grades the response of tumor to treatment, similarly to the systems listed above. EASL and AASLD guidelines recommend mRECIST as the preferred method for assessing treatment response for HCC to LRT. Exceptions which are not eligible for the mRECIST system include infiltrative HCC lesions and other lesions with atypical enhancement.

Additionally, the LI-RADS system has put forth criteria to grade treatment response, the LR-TR Response Algorithm. In this treatment assessment paradigm, treatment response is graded as LR-TR Nonviable, LR-TR Equivocal, and LR-TR Viable. Tumors with treatment responses graded as Nonviable show no enhancement within the lesion or only a treatment-specific, expected enhancement pattern. Viable lesions show nodular, mass-like, or irregular tissue along the treated tumor with enhancement similar to the pretreatment state, arterial phase hyperenhance-

Table 13.4 Assessment of treatment response: Comparison of WHO, RECIST 1.1, and mRECIST

	WHO	RECIST 1.1	mRECIST
Measured dimension(s)	Product of longest dimension and greatest perpendicular diameter	Sum of the longest unidirectional diameter of all lesions	Sum of the longest unidirectional diameter of all arterially enhancing, viable lesions
Area measured			
Complete response (CR)	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all intratumoral arterial enhancement
Partial response (PR)	≥50% decrease in the sum of the area of all lesions	≥30% decrease in the sum of diameters of all lesions	≥30% decrease in the sum of diameters of all arterial enhancing, viable lesions
Stable disease (SD)	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
Progressive disease (PD)	≥25% increase in the sum of the area of all lesions	≥20% increase in the sum of diameters of all lesions	≥20% increase in the sum of diameters of all arterially enhancing, viable lesions

Figures from Fig. 13.1: Imaging response criteria used in evaluation of HCC after treatment, Graphic 99,552 Version 1.0, from "Assessment of tumor response in patients receiving systemic and nonsurgical locoregional treatment of hepatocellular carcinoma
Authors: Iqbal and Stuart, UpToDate 2019

ment, or venous phase washout. Equivocal lesions have enhancement that is atypical for the expected treatment effect or enhancement that does not definitely meet criteria to be graded as viable.

Surgical Resection

Surgical resection (SR) is the gold-standard curative-intent therapy for well-compensated cirrhotic patients with HCC. EASL and AASLD guidelines recommend SR when HCC is deemed resectable and the patient's liver function permits the intervention. However, there is no consensus or universally accepted criteria for resectability, with further challenges posed by the myriad of factors a surgeon must consider when evaluating a patient's liver function for surgery. EASL and AASLD guidelines both include morphometric tumor characteristics when defining resectability [35, 36]. EASL guidelines allow surgery for single HCC lesions of any size and for multiple HCC lesions that lie within Milan criteria, if the amount of liver remaining after surgery is of sufficient size. AASLD guidelines define resectability

as T1 or T2 HCC (one to three unilobar lesions, less than 5 cm for single lesions and 3 cm for multiple lesions). Additional considerations include the presence of macrovascular tumor involvement, typically of the portal or hepatic veins. Any macrovascular involvement with tumor has traditionally been considered a contraindication to surgery; however, some centers in the East have reported success with resection for highly selected patients with HCC involving segmental branches of the portal vein. The Liver Cancer Study Group of Japan reported a median survival of 2.87 years for patients with portal vein invasion who had SR versus 1.10 for patients in the non-SR group [120]. The same group reported superior outcomes for patients with hepatic vein invasion who had SR, with median survival of 4.47 years versus 1.58 years for patients in the non-SR group [120].

A patient's liver function, as determined by the degree of portal hypertension and the amount of functional liver remaining after surgery, determines whether a patient will tolerate resection. SR is contraindicated for decompensated patients with clinically significant portal hypertension or advanced liver disease, as signified by Child Class B or C patients with jaundice, encephalopathy, ascites, or varices. In otherwise well-compensated Child A cirrhotic patients, an assessment of the degree of underlying portal hypertension is critical. Signs of significant portal hypertension include platelet count <100,000 platelets/μL and the presence of splenomegaly and varices on imaging. Clinically relevant portal hypertension can also be defined by a hepatic vein pressure gradient >10 mm Hg [121]. Furthermore, liver function can be assessed by measuring indocyanine green retention at 15 minutes (ICG_{15}) after administration. Patients with poor liver function retain a greater amount of ICG. Various groups have set ICG_{15} parameters for liver resection, with most advocating an ICG_{15} retention of <15–20% for patients to undergo hepatic resections safely [122, 123].

The functional liver remnant (FLR), defined as the volume of the liver remnant divided by the entire liver volume, will provide the hepatic reserve for the patient after surgery. FLR may be calculated before surgery using CT or MRI volumetrics, and the planned resection must provide a FLR of >30–40%, to reduce the risk of post-resection liver failure. For patients with inadequate FLR, clinicians may employ portal vein embolization (PVE) to increase the size of the FLR. Patients typically undergo PVE and then surgery 4–6 weeks afterwards, allowing for FLR hypertrophy in the intervening time period. The rate of growth of the liver remnant after PVE itself provides prognostic information. In a large single-center series, no patients with growth rate >2.66%/week after PVE developed liver failure after hepatectomy [124].

The technical conduct of SR has been shown to affect patient outcomes. To reduce bleeding from hepatic veins, surgeons employ low central venous pressure (CVP) during surgery. Components of low CVP surgery include the selective use of central venous catheters to guide resuscitation and limit the volume of intravenous infusions during surgery to prevent hepatic congestion and back-bleeding from transected hepatic veins. A minimally invasive approach to SR using laparoscopic or robotic surgery may be considered for small lesions, as well as lesions which are superficial or located on the periphery of the liver. Studies of minimally invasive

hepatectomies have reported equivalent overall and disease-free survival between open and minimally invasive surgery, with one large study showing statistically significantly less blood loss (158 g vs. 400 g, $p < 0.001$), shorter hospital length of stay (13 days vs. 16 days, $p < 0.001$), and a lower complication rate (6.7% vs. 13.0%, $p = 0.003$) in the laparoscopic resection group [125, 126]. However, it is important to note that since such studies are not prospectively randomized, inherent selection bias may be present that makes it difficult to draw definitive conclusions regarding the superiority of either technique.

The extent of surgical resection and surgical margins have also been studied. Historically, preference has been given to anatomic resections for lesions >2 cm. However, recent literature has reported equivalent outcomes for nonanatomic resection [127]. Similarly, the importance of wide tumor-free margins >1 cm has been studied with differing outcomes reported. An early Japanese series reported improved 3-year survival (77% vs. 21%) for patients with >1 cm margins, while more recent reports have shown no difference in outcomes for patients with tumor-free margins <1 cm [128, 129].

Contemporary outcomes following SR for HCC have improved dramatically, largely due to better patient selection, improved surgical techniques, and better anesthetic and perioperative management that have significantly reduced postoperative mortality and complications. EASL guidelines propose a benchmark perioperative mortality rate of <3%, as a standard for cirrhotic patients undergoing resection for HCC [35]. The most common cause of death after SR is posthepatectomy liver failure (PHLF), which is often progressive, occurring outside a traditional 30-day postoperative period. The International Study Group of Liver Surgery (ISGLS) offered a consensus definition of PHLF in 2013, as an increased INR (≥1.5 for Grades A and B and ≥2.0 for Grade C PHLF) and hyperbilirubinemia after postoperative day 5 [130]. Clinicians grade the severity of PHLF from Grade A to Grade C (most severe). For Grade A PHLF, there is no required change in clinical management. For Grade B PHLF, patients require a deviation from normal postoperative management in the form of intermediate or ICU level of care, plasma transfusion, albumin infusion, diuretics, and other noninvasive interventions. Lastly, for Grade C PHLF, patients require interventions in the form of intubation, hemodialysis, transplantation, and other invasive treatments. The ISGLS definition was validated in a test group of 835 patients undergoing liver resection, of which 65 (11%) developed PHLF. The ISGLS PHLF definition discriminated postoperative mortality accurately, with mortality rates of 0%, 12%, and 54% for patients with Grade A, B, and C PHLF, respectively [131]. Fukushima and coworkers assessed the ISGLS PHLF definition in their study of 210 HCC patients undergoing curative hepatectomy. They found major hepatectomy (>1 segment), blood loss >1000 mL, and liver fibrosis stage ≥3, were independently associated with PHLF [132].

Common complications following hepatic resection include hemorrhage, bile leak, pleural effusion, and infection. To standardize the reporting of postoperative complications, ISGLS has offered definitions of posthepatectomy hemorrhage (PHH) and bile leak [133]. The criteria for ISGLS PHH are met by a drop in hemoglobin >3 g/dL (compared to preoperative levels) and/or the need to trans-

fuse PRBCs and/or the need for invasive intervention to stop bleeding. PHH is further categorized as Grades A to C, with C being the most severe. Grade A PHH includes transfusion up to 2 units of PRBCs; Grade B PHH indicates a transfusion >2 units of PRBCs, without the need for invasive intervention; and Grade C PHH requires intervention (e.g., embolization or laparotomy). In a validation group, postoperative mortality corresponded to PHH grade, with mortality rates of 0%, 17%, and 50%, for patients with Grade A, B, and C PHH, respectively. The ISGLS has also defined posthepatectomy biliary leak as a bilirubin concentration in surgical drain fluid exceeding three times the serum bilirubin, on or after postoperative day 3 [134]. Similar to other ISGLS definitions, biliary leaks are graded from A to C, with C being the most severe. Grade A biliary leaks persist ≤1 week and have little or no impact on a patient's clinical management. Grade B leaks require a change in patient management and include leaks persisting ≥1 week, leaks causing infection and needing antibiotic therapy, and leaks requiring percutaneous drain placement, endoscopic therapy (e.g., ERCP and sphincterotomy), or transhepatic biliary drain placement and stenting. Severe Grade C biliary leaks often require reoperation to control the complication, many times with reconstruction of a bilioenteric anastomosis. Altogether, postoperative complications occur in as many as 47% of patients undergoing SR. Therefore, an evaluation of a patient's fitness for surgery includes an assessment of their ability to tolerate postoperative morbidity [131].

The efficacy of SR has been demonstrated with 5-year overall survival ranging from 60% to 80%. However, recurrence of HCC following SR remains a significant issue, in part because the diseased liver left behind after resection is prone to de novo lesions. Clinicians distinguish early recurrences, which occur within 2 years of SR, versus late recurrence, arising more than 2 years after SR, because late recurrence often represent new lesions instead of true local recurrences from the primary lesion [135]. Risk factors of early recurrence have included nonanatomic resection, the presence of microscopic vascular invasion, and elevated AFP; whereas risk factors of late recurrence include higher hepatitis activity and the presence of multiple tumors [136]. The overall 5-year recurrence rate after SR is about 70%. In their large series of 661 patients undergoing SR, Tabrizian and coworkers reported 1- and 5-year recurrence rates of 35% and 70% [137]. Of the patients who had recurrences, the authors reported the different strategies used to treat each recurrence and their efficacy. Sixty-eight patients (19%) were eligible for re-resection and underwent repeat surgery with a median survival after treatment of 56 months. Additionally, 56 patients (16%) were listed for transplant and 35 patients underwent transplant, with median survival of 47 months; and 145 patients (40%) underwent ablation or embolization with median survival of 27 and 19 months, respectively. The remaining patients not eligible for treatment with curative intent were mostly treated with sorafenib or best supportive care and had median survival of <8 months. Thus, in this representative study, many patients undergoing SR remain eligible for treatment with curative intent after tumor recurrence.

Given that recurrence following SR is a significant concern, a unique option that has been espoused for patients with post-resection recurrent HCC is the

so-called salvage LT (SLT). In this setting, patients undergo surgery and then are listed for LT if they recur. The advantages of this approach for individual patients include immediate treatment without waiting for organ allocation and the avoidance of a more intensive intervention (i.e., LT), immunosuppression, and the attendant risks of the immunosuppressed state. Potential societal advantages of SLT include a more efficient allocation of organs and possible cost savings.

In practice, the main challenges to the SLT strategy have been identifying patients at high-risk for recurrence outside of transplant criteria who may have lost their opportunity for cure and the development of post-resection liver failure requiring urgent LT. One of the earliest studies looking at SLT was reported by Belghiti et al. in 2003, where they showed that HCC patients undergoing SLT who had similar characteristics to SR patients had equivalent perioperative complications and similar survival [138]. More recently, De Haas and colleagues reported their outcomes of SLT using an intention to treat analysis in 110 patients who underwent SR. [139] In their group, 63 patients (57%) recurred with 47 patients (42.7%) listed for LT and 30 patients (27.2%) undergoing SLT. The intention-to-treat overall and disease-free survival was 69% and 60%, respectively. The patients who had a successful outcome with this strategy, defined by SR patients who either did not develop recurrence or developed recurrence and underwent LT, had an 83% disease-free survival at 5 years, while not surprisingly, patients failing the strategy and developing untransplantable disease following resection had a dismal 7% survival. Overall, the ITT SLT strategy was successful in 55% of the patients. In a different study, a head-to-head comparison of an intention-to-treat SLT strategy to primary LT was reported by Bhangui et al. [140] While the overall (73% vs. 58% at 5 years) and recurrence-free (69% vs. 27% at 5 years) survival of primary transplant patients was superior to patients enrolled in a SLT strategy, the best outcomes at 5 years were observed in resection patients who went on to undergo salvage liver transplantation (87% disease-free at 5 years), highlighting that the most important factor is to identify patients who are best suited for salvage LT.

In order to define which patients might benefit from the SLT strategy, researchers have sought to identify risk factors for unsalvageable recurrence after SR, for example, tumor recurrence beyond criteria for transplant. Lee et al. studied 320 patients undergoing SR for HCC, of which 183 patients (62.5%) had recurrence within 5 years [141]. Factors associated with unsalvageable recurrence were preoperative disease beyond Milan criteria, the presence of microsatellite lesions or multiple tumors, and lymphovascular invasion. An international collaborative subsequently analyzed 1023 patients and validated these findings. Features associated with recurrence beyond criteria for LT included preoperative disease beyond Milan criteria (HR 1.95), the presence of multiple nodules or satellite lesions (HR 1.51), and microvascular invasion (HR 2.12) [142]. Despite its challenges, SLT remains a viable option for patients with HCC, and improvements in patient selection for SR versus up-front LT will further refine its implementation in the future.

Liver Transplantation

History and Organ Allocation

Liver transplantation is unequivocally the gold-standard treatment for cirrhotic patients with surgically unresectable HCC meeting specified criteria. However, the early experiences with liver transplant for HCC were met with dismal results, with recurrence rates as high as 80% within 1 year and >70% mortality within 2 years, largely due to a lack selection criteria based on tumor burden [143–145]. In 1996, Mazzafero and colleagues published outcomes of liver transplant for HCC which is now widely known as the Milan criteria. Their group transplanted 48 patients diagnosed with either a single tumor of ≤5 cm or up to three tumors each ≤3 cm. Overall actuarial 4-year survival was 75 percent, and 4-year recurrence-free survival was 83 percent [146]. The Milan criteria have subsequently been validated in numerous other studies and have become ubiquitously accepted as the gold-standard size and number criteria for the selection of HCC patients for LT [147, 148].

Given the successful outcomes when utilizing the Milan criteria, LT for HCC has increased dramatically over the last two decades, and HCC has now become a leading indication for LT in the United States, accounting for nearly 25% of all transplants performed on a yearly basis [149]. This increase has largely been driven by a Model for End-Stage Liver Disease (MELD) exception policy that allows allocation of organs to HCC recipients who typically have lower physiologic MELD scores. Since HCC patients often do not have physiologically decompensated liver disease, clinicians intended the MELD exception points to balance the risk of wait-list dropout due to tumor progression and allow access to LT. The first iteration of the MELD exception policy was instituted in 2002. Patients with T1 tumors (1 lesion <2 cm) were assigned a MELD of 24, and patients with T2 tumors (one tumor >2 cm but <5 cm or three tumors each <3 cm) were designated a MELD of 29. One additional point was awarded for each 3 months the patients remained on the list without progression beyond Milan [150]. However, it soon became evident that patients with HCC were being overprioritized, receiving transplants at a higher rate than non-HCC patients. Consequently, there have since been numerous iterations of the HCC MELD exception policy to better balance this risk of wait-list dropout between HCC and non-HCC listed patients. In 2003, MELD exception prioritization decreased to 20 points for T1 lesions and 24 for T2 lesions, with another revision in 2004 not granting MELD exception points for the T1 lesions. In 2005, MELD exception points were once again reduced to 22 points for T2 lesions. In 2019, ongoing discussions are being considered to potentially change the priority of MELD exception points in patients with HCC once again; however no definitive guidelines have yet to be set.

Despite these refinements in the allocation of MELD exception points in 2005, LT for HCC continued to increase over the subsequent decade, and HCC patients continued to remain overprioritized with lower rates of wait-list dropout and higher transplant rates despite inferior survival [151–153]. During this time period, it also became apparent that patients expedited to transplant in regions with “short waiting

times" had greater post-LT recurrence and inferior post-LT outcomes compared to HCC-listed patients from "long wait time" regions [154, 155]. Subsequently, MELD exception policy was once again revised in 2015, with institution of a 6-month delay for patients with T2 lesions prior to being granted 28 exception points and with capping of the MELD at 34—which is the current policy in the United States [156].

Pretransplant Models to Expand Eligibility Criteria to Beyond Milan

While the tumor size and number paradigm of the Milan criteria remain the gold standard for the selection of HCC candidates for LT, there have been concerns they may be too restrictive, excluding some patients beyond criteria with an otherwise acceptable posttransplant recurrence risk. Over the past two decades since the establishment of the Milan criteria, there have been numerous expanded criteria proposed that allow for recipients with tumors beyond Milan to receive LT. In 2001, Yao and colleagues defined the UCSF criteria, which allowed inclusion of patients with a single tumor ≤6.5 cm and up to three lesions ≤4.5 cm, with total tumor diameter ≤8 cm. Patients who met these UCSF criteria and underwent LT had survival rates of 90% and 75.2% at 1 and 5 years, respectively [157]. These results were validated by Yao and colleagues in 2007 in a series of 168 patients with disease exceeding Milan but meeting UCSF criteria, with 1- and 5-year survival without recurrence of 92.1% and 80.7%, respectively [158].

In addition to the UCSF criteria, numerous other expanded criteria have been proposed and externally validated to result in outcomes similar to Milan criteria. These include the Up-to-7 criteria (i.e., criteria using 7 as the sum of the size (cm) of the largest tumor and the number of tumor nodules; total tumor volume (TTV) criteria and alpha-fetoprotein (AFP) (i.e., TTV <115cm^3 and AFP <400 ng/ml)); and the AFP-French model (i.e., points system using tumor size, number of tumors, and an AFP cut-off at 100 ng/ml and 1000 ng/ml) [159–161]. Selected pretransplant models based on morphometric and serum biomarkers are summarized in Table 13.5.

Wait-List Management: Surveillance and Bridging Therapy

Patients with HCC listed for liver transplant undergo baseline imaging and lab testing at the time of diagnosis, commonly with dynamic CT or MRI of the abdomen, CT of the chest, and serologic AFP testing. Additional metastatic workup may include nuclear medicine bone scanning and MRI of the brain to rule out distant disease. After placement on the LT waiting list, patients require quarterly CT or MRI to continue to receive MELD exception points in the United States [162].

While remaining on the transplant wait list, patients with HCC are at risk for tumor progression. To ameliorate this risk, AASLD and EASL guidelines recommend "bridging" treatment with LRT, especially if patients are expected to remain

Table 13.5 Pretransplant models defining HCC eligibility criteria

Lead author	Morphometric criteria	Biomarker criteria	Donor type	Year	Patient outcomes
Mazzaferro (Milan) [146]	One lesion ≤5 cm or ≤3 lesions ≤3 cm each		Cadaveric	1996	4-year OS, 85%; 4-year RFS, 92%
Yao (UCSF) [157]	One lesion ≤6.5 cm or 2–3 lesions ≤4.5 cm each. Total tumor diameter ≤8 cm		Cadaveric	2001	5-year OS, 72.4%
Herrero [194]	One lesion ≤6 cm or 2–3 lesions ≤5 cm each		Cadaveric	2001	5-year OS, 79%
Roayaie [195]	Any number of lesions 5–7 cm each		Cadaveric	2002	5-year RFS, 55%
Keneteman [196]	One lesion <7.5 cm or multiple lesions <5 cm each		Cadaveric	2004	4-year OS, 82.9%; 4-year RFS, 76.8%
Onaca (Baylor criteria) [197]	One lesion ≤6 cm or 2–4 lesions ≤5 cm each		Cadaveric	2007	5-year RFS, 63.9–64.6%
Soejima [198]	Any number of lesions ≤5 cm each		Living	2007	3-year OS, 68.6%
Jonas [199]	Any number of lesions ≤6 cm each. Total tumor diameter ≤15 cm		Living	2007	3–year OS, 53%
Sugawara (5–5 rule) [200]	≤5 lesions ≤5 cm each		Living	2007	3-year RFS, 94%
Kwon [201]	Any number of lesions ≤5 cm each	AFP ≤400 ng/mL	Living	2007	5-year OS, 79.9%
Takada [202]	≤10 lesions ≤5 cm each	PIVKA-II 400 mAU/mL	Living	2007	5-year OS, 87%
Silva [203]	≤3 lesions ≤5 cm each. Total tumor diameter ≤10 cm		Cadaveric	2008	5-year OS, 67%
Zheng (Hangzhou criteria) [204]	Total tumor diameter ≤8 cm or <8 cm if grade I or II	AFP ≤400 ng/mL if tumor diameter >8 cm	Living	2008	5-year OS, 70.7%; 5-year RFS, 62.4%
Mazzaferro (up-to-7) [159]	The sum of the number of lesions and the size of the lesions (in cm) ≤7		Both	2009	5-year OS, 71.2%
Fujiki [205]	≤10 lesions ≤5 cm each	DCP ≤400 mAU/mL	Living	2009	5-year OS, 89%
Lai [206]	Total tumor diameter 8 cm	AFP ≤400 ng/mL	Cadaveric	2012	5-year RFS, 74.4%
Grat [207]	UCSF or up-to-7 criteria	AFP <100 ng/mL	Cadaveric	2014	5-year OS, 100%
Toso [160]	Total tumor volume ≤115 cm^3	AFP ≤400 ng/mL if tumor diameter >8 cm	Cadaveric	2015	4-year OS, 74.6%
Lee [208]	Total tumor diameter ≤10 cm	PET negative uptake	Living	2015	5-year OS, 73.4%; 5-year RFS, 80.4%

on the waiting list for more than 6 months [35, 36]. Neither society prescribes the exact type of LRT to be used, and these decisions are made based on individual patient factors. Several studies have supported reduced dropout risk with the use of LRT and response to treatment [111, 112]. Mehta and colleagues reviewed the experience of 398 patients listed for LT for HCC, and they found the risk of wait-list dropout correlated with degree of response to LRT as assessed by mRECIST, with risk of dropout of 9.3% for patients with complete response, 19.2% for partial response, 39.5% for stable disease, and 85% for progressive disease [111].

Living Donor LT for HCC

Clinicians have used living donor liver transplant (LDLT) for HCC in areas where cadaveric organs are less available (e.g., East Asia) and as a way to bring HCC patients to transplant earlier, reducing the risk of disease progression. In an intention to treat analysis comparing LDLT and deceased donor liver transplant (DDLT), Bhangui and colleagues found a shorter mean waiting time for LDLT than DDLT (2.6 vs. 7.9 months) and similar recurrence rates for the two groups (12.9% and 12.7%). [163] Other studies have compared LDLT to DDLT using decision analysis and cost-effectiveness analysis, with findings that showed an improved life expectancy with LDLT (4.5 years longer compared to DDLT) and decreased health costs if patients spent greater than 7 months on the wait list [164, 165].

Notably, some centers have offered LDLT for patients outside of Milan criteria. Hong and colleagues from the Seoul National University reported their experience with LDLT for HCC, including >30% of patients receiving LDLT beyond Milan. They reported excellent outcomes for low-risk patients (AFP <200 ng/mL with no FDG avidity on PET) who were inside and outside Milan criteria, with 5-year disease-free survival of 88.4% and 80.3%, respectively [166]. However, the Adult to Adult Living Donor Transplantation Cohort Study (A2ALL) has reported an increased risk of disease recurrence for patients receiving LDLT, compared to DDLT (HR = 2.34; $p = 0.04$). The authors have attributed this difference to a foreshortened wait time as well as greater tumor burden and serum AFP in the group undergoing LDLT [167]. Undoubtedly, LDLT will remain a treatment option for patients with HCC. Because the living donor recipient does not remove a cadaveric organ from the limited donor pool, there will likely remain a tendency for these transplants to "push the envelope" beyond traditional criteria.

HCC Recurrence After Liver Transplantation

Modern series of post-LT outcomes report recurrence rates ranging from 8% to 21%, with median times to post-LT recurrence of 13–15 months [168–172]. Researchers have sought to identify prognostic factors to predict which patients will

have recurrence to improve post-LT surveillance and inform organ allocation criteria. In the largest reported single-center experience of LT for HCC, Agopian and coauthors analyzed the UCLA experience with 865 patients undergoing LT for HCC, 117 (13.5%) of whom suffered recurrence. A novel clinicopathologic nomogram was developed to allow for the individualized prediction of post-LT HCC recurrence, with independent factors including tumor grade, the presence of macrovascular or microvascular invasion, tumors outside Milan criteria, radiological maximum tumor diameter >5 cm, and increased pretransplant AFP and neutrophil-to-lymphocyte ratio [170]. Additional predictive models include the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score, which uses explant pathologic features such as the size of viable tumor and presence of microvascular invasion, as well as serum AFP levels, to calculate a risk of recurrence at 1 and 5 years [171], and the Model of Recurrence After Liver Transplantation (MoRAL) score includes neutrophil-lymphocyte ratio and histologic grade to calculate a risk of tumor recurrence [172]. As newer therapies become available that have efficacy in the adjuvant setting, models that allow for individualized prediction of post-LT HCC recurrence will become all the more valuable.

Unfortunately, recurrence of HCC following LT has a far worse prognosis compared to recurrence following SR, where numerous treatment options including salvage LT exist. In a large series examining outcomes of HCC recurrence following LT, Bodzin and colleagues reported a median post-recurrence survival of only 10.6 months, which is in line with a median survival of only 13 months reported in a systematic review of 61 studies examining 1021 LT patients with post-LT recurrence [173, 174]. However, several studies have now established that a subset of patients with HCC recurrence following LT may have improved survival, with median survivals ranging from 28 to 32 months for select patients whose recurrences were amenable to surgical resection or curative-intent ablation [173, 175]. Optimizing the identification of such patients who stand to benefit from more aggressive treatment of their recurrence is necessary.

Systemic Therapy

Systemic therapy is an option for locally advanced or metastatic HCC patients who have adequate liver function but who are not candidates for resection, LT, or LRT due to their tumor burden. Traditional cytotoxic systemic therapy has been ineffective in HCC, largely due to inherent chemotherapy resistance of HCC, as well as the concomitant underlying hepatic dysfunction in patients with HCC, limiting the applicability of drug therapy. After years of failed trials of cytotoxic chemotherapy, sorafenib, a tyrosine kinase inhibitor (TKI) which targets multiple kinases, was the first agent discovered to provide a survival benefit in a prospective randomized controlled trial in 2007 [176]. This initial positive trial with sorafenib was followed by a drought of 10 years, during which time no additional targeted therapies were found to be efficacious. During this time, multiple, large, prospective randomized

controlled trials investigating the kinase inhibitors sunitinib, brivanib, linifanib, and erlotinib each failed to show an improvement in survival for patients with HCC compared to sorafenib [177–180]. However, since 2017, there have been numerous new drug approvals for HCC in both the first and second lines, including the targeted therapies lenvatinib, regorafenib, and cabozantinib and the checkpoint inhibitors nivolumab and pembrolizumab.

In 2007, sorafenib was established as the gold-standard treatment for advanced HCC on the basis of the SHARP trial, a prospective RCT. Patients receiving sorafenib had a median overall survival of 10.7 months compared to 7.9 months in the placebo group [176]. Sorafenib is a small molecule that inhibits Raf-1 and B-Raf, vascular endothelial growth factor receptors (VEGFR 1, 2, and 3), and platelet-derived growth factor receptor-β (PDGFR-β). These pathways play an important role in the pathogenesis of HCC [181, 182]. Additional analyses have suggested sorafenib provides a greater survival for patients with HCC due to HCV, compared to HCC due to HBV or alcohol. Although sorafenib is FDA-approved for all stages of cirrhosis, data consistently shows worse outcomes for treated patients with greater than Child A cirrhosis [183–185]. Side effects of sorafenib include diarrhea and hand-foot skin reaction. Combination treatment with sorafenib and doxorubicin has been attempted, but the only randomized phase III trial was terminated by the data monitoring safety board due to futility at planned interim analysis [186]. Sorafenib in the neoadjuvant and adjuvant setting for LT is being investigated, and results from trials are pending. The largest trial to date of sorafenib in the adjuvant setting after SR is the STORM trial. This RCT tested sorafenib versus placebo in patients who underwent successful SR; however, the authors found an improvement in recurrence-free survival for the sorafenib group [187].

Lenvatinib is a small molecule that inhibits VEGFR, PDGFR, RET, KIT, and fibroblast growth factor receptors (FGFR). Lenvatinib was compared to sorafenib in patients with unresectable HCC and Child A cirrhosis in a non-inferiority trial. The authors reported a median survival of 13.6 months for lenvatinib and 12.3 months for sorafenib, and they concluded lenvatinib was non-inferior [188]. Lenvatinib has since been FDA approved in August 2018, and it is being used as frontline systemic treatment, in addition to sorafenib.

Clinicians offer second-line therapy to patients who have progression of disease while on first-line therapy and can tolerate additional systemic treatment. Progression of disease manifests as radiographic progression and an increase in serum AFP. Since 2017, numerous new drugs have been approved for HCC in the second line, including the tyrosine kinase inhibitors regorafenib and cabozantinib, as well as the immune checkpoint inhibitors nivolumab and pembrolizumab.

Regorafenib is a small molecule inhibitor of VEGFR and tyrosine kinase inhibitor (TKI). It is similar in structure and function to sorafenib. The RESORCE trial studied patients who progressed on first-line treatment with sorafenib and were treated with regorafenib. Patients who were randomized to regorafenib had significantly increased median survival (10.6 vs. 7.8 months) and higher rates of disease control (65% vs. 36%) compared to placebo [189]. Cabozantinib is another small molecular kinase inhibitor, which has been studied in patients previously treated

with sorafenib. The phase III CELESTIAL trial included patients who received cabozantinib versus placebo as second- or third-line treatment after receiving sorafenib. Results showed increased median survival for patients treated with cabozantinib (10.2 months) versus the placebo group (8.0 months), resulting in its approval by the FDA in 2019 [190].

Nivolumab is a human monoclonal antibody to programmed cell death 1 receptor (PD-1), which functions to restore T cell activity against tumor cells. The CheckMate 040 trial studied nivolumab as a second-line treatment for patients with HCC and Child A or B cirrhosis who had disease progression on sorafenib. In the study and follow-up reports, patients had an overall response rate of 18%, significantly greater than the 2% historically reported for sorafenib. Most notably, the patients who did respond demonstrated durable responses to treatment with some reports of complete tumor response [191, 192]. Pembrolizumab is also a monoclonal antibody and PD-1 inhibitor. The Keynote-224 trial supports the efficacy of pembrolizumab as second-line treatment following sorafenib failure with similar rate of objective responses and stable disease (17 and 44 percent, respectively) compared to nivolumab [193]. Pembrolizumab was FDA approved in November 2018 for patients with HCC who were previously treated with sorafenib. Currently, there are numerous ongoing prospective, randomized controlled trials evaluating both single-agent and combination therapies in HCC in both frontline and second line. Further development and validation of radiologic, serologic, and molecular biomarkers will greatly improve the ability to allow for personalized treatment decisions for advanced HCC.

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