Hepatocellular Carcinoma—How to Determine Therapeutic Options

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Deciding on specific treatment strategies involves not only tumor stage, performance status, and severity of underlying liver disease, but additional factors such as biomarkers, organ availability, and radiographic tumor response to treatment. In this review, we present hepatocellular carcinoma (HCC) cases to highlight how to determine therapeutic options for HCC in specific scenarios, including resection versus liver transplant, choice of initial local regional treatment, tumor downstaging, and systemic therapies for advanced HCC. (*Hepatology Communications* 2020;4:342-354).

Treatment options for hepatocellular carcinoma (HCC) are rapidly evolving. There are several HCC staging systems that currently exist to help stratify patients and guide initial treatment, with the Barcelona Clinic Liver Cancer (BCLC) classification[1] being one of the most used. This staging system stratifies patients with HCC from very early stage 0 (single tumor [<2 cm] and compensated liver disease) to stage C (vascular invasion and/or metastatic disease), with stage D encompassing patients with decompensated Child-Pugh C cirrhosis who are not HCC treatment candidates (but may be liver transplant candidates). Recent American Association for the Study of Liver Diseases (AASLD) guidelines[2] describe the level of evidence for tumor-directed therapies by BCLC stage, with the highest level of evidence assigned for resection for very early-stage 0 patients, and transarterial chemoembolization (TACE) for stage B patients who have multinodular HCC confined to the liver. However, deciding on specific treatment strategies involves not only factors common to these treatment algorithms such as tumor stage, performance status, and severity of underlying liver disease, but additional factors such as biomarkers, organ availability, and radiographic tumor response to treatment. In this review, we present HCC cases to highlight the approach to therapeutic options for HCC in specific scenarios including resection versus liver transplantation (LT), choice of initial local regional treatment (LRT), tumor downstaging, and systemic therapies for advanced HCC.

Case 1, Part A

Sixty-two-year-old man with chronic hepatitis C (HCV) presents to clinic for consideration of HCV treatment. Pertinent labs include HCV RNA 3 million IU/mL, alanine aminotransferase 50 U/L, alpha-fetoprotein (AFP) 16 ng/mL, and platelet count of 150,000 with normal international normalized ratio, albumin, and bilirubin. Transient elastography measurement suggests at least bridging fibrosis. Abdominal ultrasound shows an

echogenic liver with a 2-cm left lobe mass, which is followed by a contrast-enhanced MRI that shows a 2.7-cm segment 3 lesion with arterial enhancement, delayed washout, and capsular enhancement (Liver Reporting and Data System [LI-RADS] 5, as defined per AASLD guidelines and LI-RADS v.2018). What are his treatment options?

LI-RADS provides excellent discrimination of liver lesions, with LI-RADS-5 designation having a positive predictive value of over 95% for HCC, whereas 75% of LI-RADS-4 lesions (probable HCC) and 35%-40% of LI-RADS-3 lesions (intermediate) are eventually diagnosed as HCC.[3] This patient is classified as BCLC stage A, given well-compensated liver disease with normal performance status and single tumor (2-3 cm). Although very-early-stage BCLC 0 patients are advised to undergo resection, recent AASLD HCC treatment guidelines[2] indicate that resection and LT (and ablation) have the same level of evidence for BCLC stage A disease (level 2).

RESECTION VERSUS LT FOR EARLY-STAGE HCC

Surgical resection and LT are potentially curative therapies for early-stage HCC, offering 5-year survival rates of up to 60% for resection[4] and over 70% for LT.[5] Resection for early-stage HCC is increasingly performed due to the increased incidence of HCC as well as organ shortages, with only about 7% of HCC cases in the United States undergoing LT.[6] There are no randomized control trials that have evaluated resection versus LT, leading to the ongoing debate of which treatment strategy is more appropriate for patients with cirrhosis within the Milan criteria (1 lesion ≤5 cm or 2-3 lesions ≤3 cm)[5] with adequate liver function for resection.[7] LT is thought to be the better oncologic option, replaces the diseased liver, and thus restores normal hepatic function. Numerous studies have shown

significantly higher 5-year recurrence rates with resection (~40%-70%) compared with LT, with recurrence rates of approximately 10%-15%.[5,8] An intention-to-treat meta-analysis[9] showed that resection carried nearly 10-fold higher odds of recurrence than LT. A recent multicenter-matched case-control series found that the background liver was a large driver of this effect, with postresection recurrence occurring in over 70% of patients with cirrhosis compared with less than 40% of patients with histologically normal liver parenchyma.[10] However, decreased recurrence with LT must be balanced with the fact that HCC incidence has been rising due to the aging cohort with cirrhosis due to chronic hepatitis C as well as increasing rates of nonalcoholic fatty liver disease,[11] currently the fastest growing indication for LT in patients with HCC.[12] Consequently, the number of HCC wait-list registrations in the United States rose by nearly 2,000 from 2005-2009 to 2010-2014, which has resulted in an increase in wait times and wait-list dropout and a decrease in intention-to-treat survival in those listed for LT.[13]

In patients otherwise eligible for LT, studies have shown post-resection 5-year recurrence-free survival of 40%-50%[14,15] with similar 5-year overall survival for resection compared to LT in patients with a single small (<3 cm) HCC.[16,17] Poon et al.[18] studied the long-term survival of patients with Child-Pugh A cirrhosis with HCC within the Milan criteria undergoing resection (n = 204) compared with LT (n = 43) and showed that tumor size and number were prognostic of survival, whereas treatment type was not. More recently, a large multinational study[19] reported long-term outcomes of patients with HCC treated with either LT (n = 1218) or resection (n = 2068) to determine the likelihood of statistical cure. Resection patients were older (59 vs. 53 years) with lower median Model for End-Stage Liver Disease MELD (8 vs. 11) and more likely to have solitary tumor (77% vs. 41%) but had larger tumor

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size and so were less likely to be within the Milan criteria (61% vs. 81%). Overall survival at 10 years was 70% for LT and 32% for resection, although numbers are not directly comparable given the baseline differences between groups. In patients with single HCC (<3 cm) and MELD <11 (such as our patient in case 1), the authors found a nearly 40% cure rate (compared to 75% with LT) with respect to recurrence-free survival. Overall survival rates with resection dropped dramatically with increasing tumor burden, ranging from 60% with a single lesion smaller than 3 cm down to 10% for patients with either more than three tumors or a single tumor larger than 8 cm. Factors predicting improved performance of resection compared with LT included a wait-list dropout rate of 20% or more and presence of a single small tumor, especially smaller than 3 cm. Extrapolating these results to case 1, assuming at least a 10%-20% wait-list dropout rate, there likely would be no difference in intention-to-treat survival at least at 5 years when comparing resection to LT.

Another key aspect of case 1 is the location of tumor in the left lateral segment, which would require only a minor hepatectomy (i.e., fewer than three segments). European Association for the Study of the Liver clinical practice guidelines[20] note that the lowest risk for liver decompensation and liver-related mortality after resection is in patients with MELD ≤9 without clinically significant portal hypertension (e.g., platelet count >100,000) undergoing minor hepatectomy. Case 1 meets all criteria and therefore would have an estimated risk of liver decompensation of only 5% with liver-related mortality of 0.5% as opposed to more than 30% and 25%, respectively, in a higher-risk patient with portal hypertension who required major hepatectomy.

LT SURVIVAL BENEFIT

While 10-year outcomes overall appear superior for LT than resection, there remains the question of whether a patient with a single, small, resectable HCC should be offered LT. This question takes on greater importance after Berry and Ioannou[21] found that patients with HCC derive a significantly lower survival benefit from LT than patients without HCC. Using the MESIAH (Model to Estimate Survival in Ambulatory HCC Patients) score,[22] the patient in case 1 is predicted to have excellent 3-year intention-to-treat survival of >75% given favorable liver- and tumor-related characteristics. Multiple additional

studies further support that the patient in case 1 would have reduced LT survival benefit.[16,23-25] For example, Lai et al.[23] showed that MELD score ≤13 and tumor burden within Milan criteria decreased the survival benefit of LT, similar to the data from our institution,[26] which showed that patients with a single, small 2-3-cm tumor have a low risk of wait-list dropout. An analysis of the United Network for Organ Sharing (UNOS) database[27] also found that a combination of tumor characteristics (single lesion 2-3 cm and AFP ≤20 ng/mL) and favorable liver function (Child-Pugh A cirrhosis and MELD-Na <15) identifies a subgroup with a low risk of wait-list dropout. The patient in case 1 has compensated liver disease and relatively minimal tumor burden, and therefore a long wait-list life expectancy and low urgency for LT. As a result, this patient would not derive the same benefit from LT as other wait-list candidates.

RESECTION VERSUS ABLATION FOR SINGLE SMALL HCC

Tumor ablation, including radiofrequency ablation (RFA), microwave ablation (MVA), and cryoablation, has traditionally been reserved for nonsurgical candidates. However, ablation is gaining acceptance as an alternative first-line treatment to resection for small solitary tumor (especially <3 cm), given that ablation has lower morbidity and similar long-term outcomes when compared with resection.[28,29] In very early-stage HCC with a single lesion of 2 cm or smaller, ablation has been proposed as the treatment of choice. In a multicenter study[30] of 218 patients with a single lesion of 2 cm or larger undergoing RFA, sustained complete response was achieved in 97% after either one (86%) or two (12%) sessions. Additionally, 5-year survival was 55% with no peri-operative mortality, and low risk of major complications of less than 2%.

In both resection and ablation, the cumulative risk of HCC recurrence or development of new HCC exceeds 50% at 5 years.[28,29] A recent Cochrane systematic review[31] found four prospective randomized control trials that directly compared surgical resection versus RFA for patients with early-stage HCC.[32-35] Overall, the systematic review found no difference in overall survival, but cancer-related mortality was lower in the surgery than the RFA group. The quality of the evidence, however, was low or very low for all outcomes, and only two of the four

trials specifically analyzed outcomes for those with a single HCC smaller than 3 cm, such as the patient in case 1. Chen et al.[32] found no significant differences in overall and disease-free survival between groups for those with a single HCC smaller than 3 cm (n = 79), whereas Huang et al.[33] found that 5-year overall survival was superior with resection (n = 45; 82%) compared with RFA (n = 57; 61%).

Given the relatively small numbers studied in these trials, conflicting results, and largely RFA-focused interventions (with limited to no data on MVA or cryoablation), surgical resection cannot be conclusively proposed as superior to ablation for a patient with a single HCC smaller than 3 cm. However, both present excellent alternatives to LT in this specific scenario, given worldwide organ shortages and that many patients with compensated disease are unlikely to have liver disease progression (such as due to effective antiviral treatment or alcohol abstinence), and therefore no other indication for LT. In terms of optimal timing to treat HCV infection, a recent systematic review and meta-analysis found a pooled sustained virological response rate of 73% with direct-acting antiviral therapy for patients with active HCC compared to 93% for patients with inactive HCC or no HCC.[36] Thus, HCV treatment should be deferred until after HCC treatment (resection or ablation with curative intent), in line with the current practice of most providers.[37]

Case 1, Part B

The patient underwent laparoscopic left lateral segmentectomy with an uneventful postoperative course. Pathology showed a 2.9-cm, well-differentiated HCC without vascular invasion. Background liver showed bridging fibrosis. His HCV was cured with direct-acting antiviral therapy initiated 6 months after resection. Sixteen months after resection, surveillance computed tomography of the abdomen showed a new 2.1-cm LI-RADS-5 lesion near the cut edge. His AFP is normal at 4.7 ng/mL. Is LT now an option?

SALVAGE LT

A key concept with respect to LT versus resection for early-stage HCC is salvage liver transplantation (SLT), or performing LT after postresection recurrence within conventional transplant criteria. A recent analysis[38]

showed intention-to-treat survival of 83% at 10 years in patients who either did not recur after resection or who were able to undergo LT after recurrence. Importantly, having early-stage HCC at resection predicted success with this SLT strategy. Similarly, Lee et al.[39] found that initial disease within Milan, single tumor, and lack of lymphovascular invasion predicted decreased likelihood of postresection recurrence beyond Milan criteria. Therefore, the patient in case 1 with a single HCC smaller than 3 cm is expected to have a 10%-30% chance of recurrence beyond Milan and would likely be a candidate for SLT in the case of recurrence. Interestingly, a recent systematic review and meta-analysis[40] suggested improved 5-year post-LT survival after SLT compared with primary LT for HCC. Therefore, the patient in case 1 with recurrence within stage T2 criteria would likely be a good candidate for SLT.

Case 2, Part A

A 56-year-old man with chronic hepatitis B, well suppressed on antiviral therapy, has two LI-RADS-5 tumors in the liver right lobe measuring 5 cm and 3 cm. He has excellent performance status, works full time as a mechanic, and has no substance abuse or significant medical history. His AFP is 149 ng/mL, his bilirubin is 0.9, and his platelet count is 84,000 with mild splenomegaly on imaging. What is his expected post–LT survival?

POSTTRANSPLANT SURVIVAL BASED ON TUMOR BURDEN AND BIOMARKERS

A recognized challenge in LT has been expanding LT indications for HCC to meet the growing demand while ensuring acceptable post-LT outcomes. Although the Milan criteria[5] remain the gold standard for candidate selection in the United States, there is now a plethora of evidence indicating that tumor size and number alone do not solely determine a patient's expected post-LT outcome.[41] Several additional selection criteria have been developed further in the pretransplant setting to more accurately predict an individual's expected post-LT survival.[42,43] Most models incorporate serum biomarkers in addition to various tumor size and number cutoffs, although other criteria incorporate either ^{18}F-FDG PET scan[44] or tumor differentiation[45] for patients beyond Milan criteria.

In terms of biomarkers, AFP is the most studied, with worsening post-LT survival with AFP cutoffs of 20 ng/mL or higher.[46,47] Because post-LT outcomes worsen as AFP rises, various thresholds have been used for excluding patients from LT, including over 400 ng/ML[48] and over 1,000 ng/mL in the United States.[49,50] Additional serum markers associated with worse post-LT outcome include AFP-L3 greater than 35% and des-γ carboxyprothrombin greater than 7.5 ng/mL.[51-53] A neutrophil-to-lymphocyte ratio over 5[54] may also portend worse post-LT outcome, but this requires further study.

Particularly relevant to case 2 is the AFP model proposed by Duvoux et al.[55] and the Metroticket 2.0 model,[56] both of which combine tumor size and number with AFP to estimate post-LT survival. Using the validated AFP model,[55] the patient in case 2 would receive 1 point for the largest tumor diameter of 3-6 cm, 0 points for having two tumors, and 2 points for an AFP between 100 and 1000 ng/mL. An AFP model score of 3 places this patient in the high post-LT recurrence risk category, with expected 5-year recurrence and survival rates of 40%-50%. Similarly, Mazzaferro et al.[56] performed a large multicenter study, which demonstrated that combining AFP with tumor burden discriminates post-LT prognosis (C statistic 0.78) far better than using tumor burden alone. For the patient in case 2, the validated Metroticket 2.0 model[56] would predict an HCC-specific survival of only 60% at 5 years following LT. This patient is therefore not likely to do well with immediate LT and is instead advised to pursue tumor down-staging with LRT.

Case 2, Part B

What Are LRT Options for Tumor Down-staging?

TUMOR DOWN-STAGING

Down-staging of HCC is defined as a reduction in the size of tumor(s) using LRT to meet acceptable LT criteria (i.e., Milan criteria) with tumor response based on the radiographic measurement of viable tumors. The rationale is to select suitable LT candidates with initial tumors exceeding Milan criteria who have favorable tumor biology based on their response to LRT, and thus presumably are likely to do well after LT.[57,58] If the patient in case 2 with 5-cm and 3-cm tumors undergoes LRT with complete response (i.e., no enhancing tumor identified on post-LRT imaging), his tumor biology and post-LT outcome is anticipated to be more favorable than if several new tumors were identified with stable disease in the targeted lesions after LRT. In 2017, UNOS/Organ Procurement and Transplantation Network adopted the region 5 down-staging protocol (UNOS down-staging [DS]; Table 1) with automatic MELD exception awarded to patients who achieve successful down-staging to within Milan criteria, becoming eligible after the mandatory 6 months waiting period.[59] This policy was largely based on data[60,61] showing a low likelihood of unfavorable explant features and excellent 5-year post-LT survival of 80% with recurrence rate of less than 15% in patients meeting these inclusion criteria who were successfully down-staged before LT. Down-staging from UNOS-DS criteria also appears to be achievable in approximately 80% of patients.[61]

TABLE 1. UNOS-DS PROTOCOL

Inclusion Criteria

HCC exceeding UNOS T2 criteria but meeting one of the following:
1. Single lesion 5.1-8 cm
2. 2-3 lesions each ≤5 cm with the sum of the maximal tumor diameters ≤8 cm
3. 4-5 lesions each ≤3 cm with the sum of the maximal tumor diameters ≤8 cm

Plus the absence of vascular invasion or extrahepatic disease based on cross-sectional imaging

Criteria for Successful Down-staging

1. Residual tumor size and diameter within Milan criteria (1 lesion ≤5 cm, 2-3 lesions ≤3 cm)
   a Only viable tumor(s) are considered; tumor diameter measurements should not include the area of necrosis from tumor-directed therapy
   b If there is more than one area of residual tumor enhancement, then the diameter of the entire lesion should be counted toward the overall tumor burden

Criteria for Down-staging Failure and Exclusion from LT

1. Progression of tumor(s) to beyond inclusion/eligibility criteria for down-staging (as defined above)
2. Tumor invasion of a major hepatic vessel based on cross-sectional imaging
3. Lymph node involvement by tumor or extrahepatic spread of tumor
4. Infiltrative tumor growth pattern
5. Per current UNOS policy, if AFP ≥1,000 ng/mL, then LT cannot be undertaken unless AFP level decreases to <500 ng/mL with LRT

Additional Guidelines

Per current UNOS policy, patient must remain within Milan criteria for 6 months after successful down-staging before receiving MELD exception points

Incorporating tumor down-staging into LT selection criteria is an important step forward in the efforts to expand access to LT. However, upper limits in tumor burden probably exist beyond which attempted tumor down-staging is unlikely to be successful. In a single-center analysis of the "all-comers" criteria (defined as any number of tumors with total tumor diameter larger than 8 cm but without extrahepatic disease or macrovascular invasion), the probability of tumor down-staging into Milan decreased with increasing tumor burden, and only 15% of those patients ultimately received LT.[62] Additionally, intention-to-treat survival at 5 years from the initial down-staging procedure was much worse in the "all-comers" cohort at 20% compared with nearly 60% of patients meeting UNOS-DS criteria.[62] In the UNOS database, 3-year post-LT survival was similar for Milan and UNOS-DS patients (83% and 79%, respectively), but only 71% in the "all-comers" patients who had been down-staged into Milan.[63] The patient in case 2 meets the UNOS-DS criteria (two lesions, largest 5 cm, total tumor diameter 8 cm), and thus is likely to have a favorable post-LT outcome if successfully down-staged.

CHOOSING AMONG LRT OPTIONS

Although tumor ablation (including radiofrequency, microwave, and cryoablation) works well for small tumors, efficacy is much lower with larger lesions. Treatment response rates for smaller lesions up to 3 cm ranges from 75% to 95%, compared with only about 50% for lesions larger than 3 cm.[64-67] Additionally, for lesions larger than 3 cm, the overall 5-year survival is only 30%-35%, with a 5-year recurrence rate up to 80%.[64-67] As the patient in case 2 has more significant tumor burden, the most commonly used LRT options are performed transarterially, namely, Yttrium-90 (Y-90) radio-embolization, and chemo-embolization (TACE). A side by side comparison of these two treatments is presented in Table 2. Y-90 uses glass or resin microspheres, whereas TACE can be delivered with cytotoxic agent(s) mixed with lipiodol and gelfoam particles (conventional or cTACE)

TABLE 2. TYPICAL FEATURES OF TACE COMPARED WITH Y-90 RADIO-EMBOLIZATION

	TACE	Y-90 Radio-embolization
Tumor therapy	Conventional TACE (chemotherapeutic drugs mixed with lipiodol and gelfoam particles) OR	Glass (TheraSphere*) OR
	DEB-TACE (doxorubicin drug-eluting beads)	Resin (SIR-Spheres[†]) Y-90 microspheres ranging from 20-60 μm in size
Mechanism	Combination of ischemic/embolic and cytotoxic (drug release for conventional: rapid vs. drug release for DEB-TACE: slow)	Radiation effect with little ischemic damage
Survival benefit	Yes[68] (compared with best supportive care)	Survival similar to sorafenib for locally advanced HCC (BCLC B + C patients)[86,87]
Typical bilirubin cutoff	<4 mg/dL	<2-3 mg/dL
Preparation before treatment	None	Planning angiogram to define vascular anatomy and Tc-99m MAA scintigraphy to estimate lung shunt fraction
Specific tumor burden scenarios	Y-90 is typically preferred over TACE for (1) large intrahepatic tumor burden, 2) segmental/lobar macrovascular invasion, or (3) inducing contralateral hypertrophy if resection is being considered	
Cost	A Monte Carlo simulation estimated that each unilobar Y-90 treatment costs about 2 times the cost of each TACE treatment[106]; however, larger lesions often require multiple TACE procedures	
Length of stay	Typically hospitalized overnight	Outpatient procedure
Time to maximum treatment effect	Days to weeks	Up to 3+ months
Most common adverse events	Postembolization syndrome (fever, abdominal pain, leukocytosis); infection (abscess, cholecystitis); hepatic decompensation	Post-radioembolization syndrome (fatigue, nausea/vomiting, abdominal pain); radioembolization-induced liver disease; radiation damage (e.g., gastrointestinal ulcer)

*Boston Scientific, Marlborough, MA.
†Sirtex Medical, Woburn, MA.
Abbreviation: MAA, macroaggregated albumin.

or with doxorubicin drug-eluting beads (DEB)-TACE. An older meta-analysis showed that chemoembolization was significantly more effective than best supportive care and resulted in a median survival of 20 months.[68] The PRECISION V study[69] was a randomized control trial comparing cTACE versus DEB-TACE in over 200 patients from 14 European centers. The authors observed a trend for better efficacy with DEB-TACE (52% objective response vs. 44%, P = 0.11), and the incidence of liver toxicity and systemic effects, primarily alopecia, was significantly lower in the group receiving DEB-TACE.

As opposed to TACE, Y-90 results in profound radiation effect but appears to cause little ischemic damage.[70] A large, prospective study[71] demonstrated high antitumor effects from Y-90. Several large series from Europe have shown similar results with objective tumor response rates of 40%-60% in mostly BCLC B/C patients.[72-74] The recently published PREMIERE trial[75] was a single-center phase 2 randomized study that compared conventional TACE with Y-90. Nonresection candidates were included if they were Child-Pugh class A or B and BCLC stage A or B with a total bilirubin less than 2 mg/dL and no evidence of macrovascular invasion. The primary endpoint was median time to progression, which was significantly longer with Y-90 at more than 26 months compared to 7 months with TACE, but there was no significant difference in radiographic response rate or median survival (19 months for Y-90 and 18 months for TACE). Based on their experience with Y-90 in over 1,000 patients with HCC,[76] the Northwestern group has instituted Y-90 as their first-line transarterial therapy for all patients with HCC.

Stereotactic body radiation therapy (SBRT) is a relatively new HCC treatment, which has been used increasingly for HCC, with local control rates approaching 90% at experienced centers with favorable toxicity profiles and quality-of-life outcomes.[77-81] Wahl et al.[82] found improved tumor control rates with SBRT compared with RFA for tumors 2 cm or larger, and similar tumor control rates for very small tumors. In a national cohort of patients with early-stage HCC, treatment with RFA versus SBRT had similar survival, 90-day hospitalization, and cost.[83] In terms of SBRT versus TACE, a relatively large single-center analysis found SBRT to be a safe alternative to TACE for 1-2 tumors and provided superior local control rates (91% vs. 23% at 2 years)

with similar survival.[84] A randomized control trial comparing these two modalities as primary tumor treatment is currently underway in the Netherlands (NCT02470533).

With respect to bridging LRT prior to LT, Sapisochin et al.[85] retrospectively evaluated 379 patients listed for LT who received LRT. RFA was the most common LRT (n = 244; 60% of cohort), followed by TACE in 99 patients (24%) and SBRT in 36 patients (9%). Most patients in the SBRT group were not eligible for TACE or failed TACE and were generally sicker at baseline, resulting in a higher rate of postprocedure liver dysfunction with SBRT. However, there were no significant differences observed in waitlist dropout, intention-to-treat survival, or post-LT survival among these three types of LRT.

The patient in case 2 is BCLC B and requires tumor down-staging to meet conventional LT criteria. At this time, the choice between Y-90 and TACE as initial LRT would likely vary from center to center, at least until a multicenter randomized trial comparing these two modalities in early to intermediate stage HCC is performed. Additionally, SBRT appears to be a viable treatment option for HCC, especially at LT centers with significant experience in performing SBRT, typically in those who have failed or are too decompensated for other LRTs. Finally, if the initial decision in this patient is to pursue TACE, there is emerging evidence from several Asian centers that combination therapy with TACE followed by RFA in BCLC A and B patients with HCC larger than 3 cm is generally safe and leads to superior overall and progression-free survival compared with TACE alone.[86-92] Chu et al.[91] showed improved outcomes in patients undergoing combination TACE-RFA for a single 3.1-5 cm HCC compared with either modality alone. In a recent single-center retrospective analysis of 128 patients undergoing TACE-RFA compared with 271 receiving TACE alone, Ren et al.[87] found improved overall and progression-free survival at 5 years, not only for patients with tumor diameter of 3.1-5 cm, but also for those with tumors larger than 5 cm as well.

Case 2, Part C

The patient has had two Y-90 treatments, and 3 months after the last treatment develops progressive disease

involving increased size of dominant right lobe lesion along with new right portal vein tumor thrombus, with three new LI-RADS-5 right-lobe lesions measuring 2-3 cm each. AFP has risen to 745 ng/mL. His liver function remains well-compensated. What are his current treatment options?

For patients with HCC with BCLC Stage C disease due to extrahepatic disease or main portal vein tumor thrombus, nearly all staging classifications and society guidelines recommend pursuing systemic therapy. In patients with HCC with relatively small tumor burden and tumor thrombus confined to the same hepatic lobe, resection to remove both the main tumor and the tumor thrombus in carefully selected patients is increasingly being performed, especially at highly specialized Asian centers, with reported median overall survival ranging from about 14 to 25 months.[93-95] In this patient with locally advanced HCC, defined as progressive disease despite LRT or portal vein invasion without extrahepatic disease, the decision on whether to transition from LRT to systemic therapy can be challenging. Two randomized, open-label phase 3 studies have compared Y-90 and sorafenib for locally advanced, unresectable Child-Pugh A/B7. The large multicenter international SARAH trial,[96] which included over 450 patients, showed no difference between Y-90 and sorafenib in terms of overall and progression-free survival, although those treated with Y-90 had better quality-of-life assessments. A multicenter international trial from Asia (SIRvenib) showed very similar findings.[97] Therefore, the choice between Y-90 and sorafenib in locally advanced HCC should be determined on a case-by-case basis.

Regarding combination therapy, the phase 2 prospective, randomized trial SORAMIC[98] compared Y-90 and sorafenib versus sorafenib alone for locally advanced HCC and showed similar median overall survival between groups (12.1 vs. 11.4 months, respectively). As the patient in case 2 has progressive disease with rising AFP despite two Y-90 treatments, transition to systemic therapy is most appropriate at this time.

In terms of specific systemic therapies, sorafenib, a multikinase and angiogenesis inhibitor, was the first systemic therapy to be approved by the US Food and Drug Administration for advanced unresectable HCC based on results of the SHARP trial[99] and Asia Pacific study.[100] In the SHARP trial,[99] 602 patients with advanced HCC (including 50% with vascular invasion or metastases) were randomized to oral sorafenib versus placebo with sorafenib, showing a significant survival benefit (median benefit of 3 months). Several other tyrosine kinase inhibitors[101-106] have been evaluated further in phase 2 and 3 clinical trials but have either significant toxicity or failed to achieve the primary endpoints of survival or tumor-free survival.

Since 2018 there has been a marked rise in other approved therapies for advanced HCC. The open-label phase 3 study REFLECT[107] compared first-line lenvatinib (an inhibitor of all three vascular endothelial growth factor [VEGF] receptors) with sorafenib in patients with advanced HCC without macrovascular invasion. Lenvatinib was found to be noninferior to sorafenib, with a median overall survival of 13.6 versus 12.3 months, respectively. There were also improvements in secondary endpoints, including improved progression-free survival, time to progression, and overall response rate. Lenvatinib was therefore approved as first-line therapy for advanced HCC in 2018 in the United States, Europe, and Japan. Which agent to choose is generally guided by tolerability and potential adverse events. Sorafenib has higher rates of hand-foot syndrome; therefore, in our patient who works as a mechanic, many oncologists would choose lenvatinib as the initial systemic therapy. Of note, most clinical trials of these first-line drugs have been limited to Child-Pugh A patients. Prospective registry data for sorafenib suggest that the safety profile is similar for Child-Pugh A and B patients, although overall survival was only 5 months in the latter group.[108] Both agents can be used with caution in Child-Pugh B patients, although they are contraindicated in Child-Pugh C patients.

Case 2, Part D

The patient is started on lenvatinib and has stable disease for 6 months before having further tumor progression, now with pulmonary metastases. His liver disease remains well-compensated. What are his treatment options?

Second-line therapy for advanced HCC includes regorafenib, a multikinase inhibitor, which can be used in Child-Pugh A patients with good performance status who tolerated sorafenib. The phase 3 RESOURCE trial[109] showed a median overall survival of 11 months for regorafenib compared with 8 months for placebo among patients who progressed on sorafenib. Regorafenib also conferred longer time

TABLE 3. ONGOING PHASE 3 RANDOMIZED CONTROL TRIALS FOR FIRST-LINE SYSTEMIC THERAPY FOR HCC

Study	Phase 3 Drug	Comparator Arm	Target Enrollment	NCT No.
CheckMate 459	Nivolumab	Sorafenib	1,723*	NCT02576509
HIMALAYA	Durvalumab with or without tremelimumab	Sorafenib	1,310	NCT03298451
COSMIC-312	Cabozantinib + atezolizumab	Sorafenib	740	NCT03755791
LEAP-002	Lenvatinib + pembrolizumab	Lenvatinib	750	NCT03713593
PHOCUS	Sorafenib + pexastimogene devacirepvec (Pexa-Vec)	Sorafenib	600	NCT02562755
RATIONALE 301	BGB-A317	Sorafenib	660	NCT03412773
IMbrave150	Atezolizumab + bevacizumab	Sorafenib	480	NCT03434379

*Actual enrollment.

to progression and improved disease control and objective response rate. Notably, sequential sorafenib followed by regorafenib leads to a median overall survival of more than 2 years.[110] Cabozantinib is another option, which in the phase 3 CELESTIAL trial[111] achieved the primary endpoint of improved overall survival (median 10.2 vs. 8.0 months) and progression-free survival (median 5.2 vs. 1.9 months) compared with placebo in patients who failed prior systemic therapy. The anti-VEGF inhibitor ramucirumab is also now approved as second-line therapy for patients with advanced HCC with AFP greater than 400 based on the phase 3 REACH-2 trial[112] in patients who progressed, or were intolerant to sorafenib.

Immune checkpoint blockade is a burgeoning area in HCC. Tumor cells express interferon-gamma-induced PD-L1 or PD-L2, which binds to the PD-1 receptor and attenuates the antitumor response from activated T cells. With immunotherapy, a monoclonal antibody blocks the PD-1 receptor on activated T cells from binding to PD-L1 or PD-L2, thus restoring the ability of T cells to attack the tumor cells. Nivolumab is a PD-1 inhibitor that has been approved by the FDA as second-line treatment for advanced HCC based on the phase 1/2 CheckMate 040 study.[113] This study demonstrated manageable safety profile and acceptable tolerability, and the adverse events were not dose-related. The authors found an objective response rate of 15%-20%, and the response appeared durable. Similar objective response rates were seen for pembrolizumab in the phase 2 Keynote-224 study,[114] leading to recent accelerated FDA approval as second-line therapy.

Numerous phase 3 trials are also underway to evaluate additional first-line systemic therapies for advanced HCC (Table 3). Preliminary results of the CheckMate 459 phase 3 randomized multicenter trial (NCT02576509) comparing nivolumab to sorafenib for advanced HCC did not meet its primary endpoint of improved overall survival with nivolumab (hazard ratio [HR] 0.85; $P = 0.075$).[115] However, initial results from the phase 3 IMbrave 150 study showed that combination therapy with atezolizumab (PD-L1 inhibitor) and bevacizumab (VEGF inhibitor) significantly improved overall survival (HR 0.58; $P < 0.001$) and progression-free survival compared with sorafenib (NCT0434379), although the median reported follow-up was relatively short at less than 9 months.[116]

SUMMARY

There have been tremendous advances in the management of patients with HCC over the past decade. For patients with compensated liver disease and a single, small HCC, resection and ablation are viable options, with LT often reserved for tumor recurrence or hepatic decompensation. Markers of tumor biology, including response to LRT, serum biomarkers and positron emission tomography scan, are progressively being combined with tumor size and number to refine transplant selection criteria, increasing access to LT without unduly affecting post-LT outcomes. The role of LRT continues to expand, with newer therapies such as Y-90 successfully treating large tumors and lobar/segmental portal vein tumor thrombus. SBRT also serves as a reasonable therapeutic option in patients who are too sick to receive other treatment modalities. For advanced HCC, median survival now surpasses 2 years with the recent approval of multiple systemic therapies. The results of several ongoing phase 3 trials are eagerly awaited for potential new

first-line systemic treatments. While more progress is needed to further improve patient survival, the prognosis and available treatment options for HCC are only anticipated to improve.

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