How I Do It: Triaging Patients with Hepatocellular Carcinoma

Janette D. Durham, M.D.[1] Charles E. Ray, M.D., Ph.D., F.S.I.R.[1]

[1] Department of Radiology, University of Colorado Denver, Denver, Colorado

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Address for correspondence and reprint requests Charles E. Ray, Jr., M.D., Ph.D., F.S.I.R., Department of Radiology, University of Colorado Denver Anschutz Medical Campus, Mail Stop L954, 12401 E. 17th Avenue, Room 526, Aurora, CO 80045 (e-mail: Charles.ray@ucdenver.edu).

Hepatocellular carcinoma (HCC) is a malignancy that is increasing in incidence in the United States (4.9 per 100,000) with mortality rates that remain close to 50% at 1 year, despite improvement in programs aimed at the prevention of cirrhosis and early detection of liver cancer in high-risk patients. Liver cancer is now the third cause of cancer-related death. Diagnosis at an advanced stage excludes >85% of patients from curative surgical therapies. Medical therapy remains of limited benefit for nonsurgical patients. Sorafenib has shown the most promising results for palliative therapy in HCC patients, imparting a 10-week survival benefit in patients with advanced disease.

Liver-directed therapies provide alternatives to patients with HCC who are not considered surgical candidates. Radiofrequency ablation (RFA) has survival rates comparable with surgical resection in optimally selected patients with early disease; however, increasing size (>3 cm), multiple lesions (more than three), and central location limits application in patients with stage III disease and patients whose tumor location is adjacent to vascular structures or central bile ducts. Chemoembolization with single or multiple drugs mixed with ethiodized oil (cTACE) has the longest track record in the treatment of nonsurgical HCC patients and has been shown to improve survival in several randomized controlled trials compared with symptomatic treatment. Chemoembolization with drug-eluting beads (DEB) and selective internal radiation therapy (SIRT) with yttrium are newer therapies that appear to have similar efficacy and may be preferred in certain subpopulations. When to use them remains controversial because direct comparative evidence to guide choices is lacking.

This article presents several common scenarios of patients presenting with HCC to highlight the clinical and anatomical factors that lead to a treatment decision.

Case 1

A 56-year-old man with cirrhosis secondary to hepatitis C undergoing surveillance imaging has a new 1.8-cm lesion compatible with HCC. He continues to work and has no physical restrictions. His serum bilirubin is 1.8 mg/dL, serum creatinine 1.0 mg/dL, international normalized ratio (INR) 1.0, and serum albumin 3.5 g/dL. He has no encephalopathy or ascites. He is currently undergoing liver transplant evaluation but is not yet listed.

Case Evaluation

Three factors are important predictors of the survival of patients with HCC: overall physical condition, liver function, and tumor burden. There are many classifications that assess patients using these parameters. The Barcelona Clinic Liver Cancer (BCLC) classification combines these three prognostic factors using Eastern Cooperative Oncology Group (ECOG) performance status to evaluate physical condition, Child-Turcotte-Pugh (CTP) classification to evaluate liver function, and the modified TNM staging classification of malignant tumors to evaluate tumor burden. The BCLC classification is useful to stratify the complex population of patients undergoing treatment for HCC into groups with similar survival expectations. In addition, it prescribes treatment for each population segment based on the currently available evidence. Although individual and institutional biases, combined with rapidly evolving treatments, result in local variation from this prescription, organizing treatment strategies based on the BCLC categories permits the evaluation of therapeutic outcomes in identifiable patient populations.

This patient is classified as BCLC A (early disease) with an ECOG performance status of 0, CTP A (6) cirrhosis, and stage I tumor (<2 cm). If well encapsulated, this lesion may represent in situ carcinoma, and resection or ablation might be curative. It is not possible to make this determination until the lesion is inspected for microvascular invasion by histology.

Patients rarely present with small HCCs without underlying liver disease. These asymptomatic individuals who are lucky enough to be diagnosed at such an early stage are candidates for resection or ablation therapy that can be curative with 5-year survival rates approaching 90% for in situ tumors. Survival

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following resection in patients with more advanced cancer or liver disease approximates 50% at 5 years. Unfortunately, at 5 years, recurrence occurs in most patients.

Most patients with HCC, however, have underlying liver disease, with its separate mortality risk that will complicate all cancer treatment decisions. The presence of portal hypertension or bilirubin elevation has a negative impact on the otherwise favorable outcome following resection. Surveillance of patients at risk for HCC, including all patients with known cirrhosis, permits discovery of early cancers. Once HCC is identified, even when the patient does not meet criteria for liver transplant based on liver impairment alone, transplant evaluation is warranted. Liver transplant offers patients with liver disease and HCC the best opportunity for tumor-free survival, on the order of 70% at 4 years.

Patients are ranked for transplant according to their mortality risk score in accordance with the Model for End-stage Liver Disease (MELD), based on bilirubin, INR, and creatinine. The MELD score has been prospectively analyzed to predict risk of death in patients with end-stage liver disease. Because cancer carries its own mortality risk, an automatic MELD exception is permitted for patients with HCC based on viable tumor burden. To qualify for an automatic upgrade, candidates must have stage II disease (one nodule 2.0 to 5.0 cm; two or three nodules, all $<$3.0 cm). Patients meeting this criteria without vascular invasion or extrahepatic disease are granted extra priority on the transplant list equivalent to the MELD score equivalent of 15% probability of death in 3 months (MELD score of 22 points). Subsequently, every 3 months, the candidate receives additional points. By granting exception points, these patients can move up the list faster than they would if MELD points were assigned by the severity of their liver disease alone. The hope is they will stay within criteria for transplant until they reach the top of the list and are transplanted and that transplant outcomes will approach those of a patient without cancer. Transplant evaluation prior to treatment is important so that automatic upgrade is not compromised.

Once listed for transplant, the primary goal of treatment is to keep the patient within criteria for transplant while waiting. There is little evidence to support the widely applied strategy of offering adjunctive therapy to patients on the waiting list; however, long delays between listing and transplant make this a practical solution to avoid drop-off due to tumor progression. About 20% of patients fall off the list due to tumor progression.

Treatment Options

This patient's elevated bilirubin suggests resection results may be diminished due to his liver disease. Depending on the location of this tumor, he may be a candidate for ablation therapy with favorable intermediate-term cancer survival, particularly if microvascular invasion has not occurred in this small lesion. But transplant will offer him the best hope of cancer-free survival. To obtain a MELD exception, the lesion must be watched until it reaches 2 cm.

When transplant evaluation is complete, even with the upgrade of points he receives for his HCC diagnosis, this patient will likely be on the transplant list for a long time. At our institution the average wait time for liver transplant is $>$6 months. Keeping the tumor within Milan criteria (stage II disease) with minimal impact on his physical condition becomes the goal of therapy.

At our institution we rarely perform RFA in liver transplant candidates and typically recommend TACE. This is because the very low tract seeding that accompanies RFA would preclude transplant. Other transplant centers use ablation therapy as their primary adjunctive strategy prior to transplant.

Data from the Precision V trial would suggest that cTACE and DEB with doxorubicin result in similar tumor response in patients with BCLC B (intermediate) disease. This study demonstrated an advantage to DEB in patients with more advanced CTP B disease and a reduction in therapy-related liver toxicity. Once introduced 3 years ago into our practice, we experienced a rapid preference for DEB over cTACE, for nearly all indicating. Although initially we hoped for a less symptomatic patient (perhaps even ready for same-day discharge), what we found anecdotally was the procedures went more quickly, the approach was more standardized between operators, the small bead size permitted aggressive selective embolization without more morbidity, and the postprocedure imaging was simplified by the elimination of ethiodized oil. Rarely are patients discharged the same day.

Recommendation

Complete transplant evaluation with MELD exception upgrade when lesion reaches 2 cm. Single-session DEB with selective embolization utilizing a vial of 100 to 300 micron beads loaded with 75 mg doxorubicin until near stasis is achieved. Three-month surveillance imaging until transplant. Repeat intervention if there is significant persistent tumor enhancement or recurrence after initial response.

Case 2

A 65-year-old asymptomatic woman with nonalcoholic steatohepatitis presents with three lesions consistent with HCC. The largest lesion is 4.0 cm in segment 7. Two 2-cm lesions are in segments 2 and 3. Her ECOG status is 0, CTP A (6), with a serum bilirubin of 1.8.

Case Evaluation

This patient has BCLC B (intermediate) disease, with a performance status of ECOG 0, preserved liver function but stage III tumor. She falls outside Milan criteria and therefore is not currently a transplant candidate due to tumor burden. Survival on average for patients with intermediate disease is 16 months. Conventional TACE is thought to improve survival by 4 to 6 months and would be the standard of care for this patient.

Mazzaferro initially proposed the Milan criteria to select patients with HCC for transplant who would have survival rates following transplant that were similar to patients without cancer. More recently, investigators have questioned whether the Milan criteria are too stringent. Rather than

using a single lesion of 5 cm or the presence of three lesions, the largest of which must be <3 cm, the University of California, San Francisco (UCSF) criteria propose a single lesion of 6.5 cm, three lesions with the largest ≤4.5 cm, or total tumor diameter ≤8 cm. This has introduced some variation in the decisions of regional transplant review boards, and adjustments for candidates just outside Milan have become more common. In addition, measurement of only enhancing tumor diameter (modified Response Evaluation Criteria in Solid Tumors [mRECIST]) after liver-directed therapy rather than enhancing and nonenhancing tumor diameter (RECIST) allows patients who were initially believed to be outside of Milan criteria to be reconsidered if downstaged to within Milan criteria.

Treatment Options

This patient is within UCSF criteria but just outside Milan criteria. At another center she might be listed for transplant and any therapy would be considered adjunctive. At our institution we would undertake liver-directed therapy with the goal to decrease the size of the tumor to the point that she can be downstaged to within Milan criteria. If that strategy fails she would have received optimum treatment to enhance survival.

Ablation of these lesions could be considered. The size of the dominant lesion and the presence of bilobar disease would necessitate multiple probes and multiple sessions. With current technology, it would be difficult to obtain an adequate margin surrounding the 4.5-cm lesion.

Because response is what is required to downstage this patient, DEB may be favored over cTACE if intra-arterial therapy is selected. A single institutional study suggests that SIRT may be more effective at downstaging than TACE. The data are, however, sparse at best and should be weighed against potential delays in providing the service and cost. Both therapies should be discussed with the patient.

Recommendation

Two-session DEB therapy in a segmental distribution. Selective embolization of the lesion in segment 7 initially with 100 to 300 micron beads. Consider partial embolization of the surrounding segment with larger beads because this disease is multifocal and the patient's liver function is relatively preserved. Repeat session for segments 2 and 3 in 4 to 6 weeks if no complications develop. Imaging 3 months after second treatment to evaluate response. Re-treat persistent enhancing tumor as needed. Consider RFA if tumor response is insufficient to downstage. Consider sorafenib once directed therapy is considered completed, if not listed for transplantation.

Case 3

A 60-year-old Asian woman with cirrhosis and hepatitis B presents with multifocal bilobar HCC including 15 lesions, all of which are <2 cm. She has nonenhancing intrahepatic segmental portal vein thrombosis (PVT). She is CTP A, ECOG 1, with a bilirubin of 1.3.

Case Evaluation

This patient is asymptomatic with relatively preserved liver function. Her tumor burden, however, is significant stage IV disease. If portal vein thrombus is due to tumor invasion, she would be classified as having BCLC C (advanced disease) with a mean untreated survival of 8 months. The current standard of care for patients with advanced HCC is sorafenib, supported by the Sorafenib HCC Assessment Randomized Protocol Trial (SHARP) trial that demonstrated a 10-week survival benefit for patients receiving the drug compared with control (10.7 months compared with 7.9 months). There was also an improvement in time to progression for patients in the sorafenib arm. Data to support more aggressive therapy are lacking in the setting of either vascular invasion or extrahepatic disease.

If portal vein thrombus is bland, her prognosis may be less severe. It is not always possible to distinguish between the two. At our institution, liver-directed therapy is offered to patients with extrahepatic PVT and well-developed collaterals (cavernous transformation) and to patients with limited intrahepatic PVT when tumor enhancement is not demonstrated. We inadvertently treat a few patients with tumor invasion with this approach. Complications related to hepatic ischemia and progression of portal vein thrombosis are more common.

Treatment Options

Lobar therapy is desirable in this patient to reduce treatment sessions. This approach is poorly tolerated in patients receiving TACE when liver disease is advanced, and it may result in progression of liver disease. TACE and SIRT have been used to treat CTP A patients in a lobar fashion with reasonable results. The complication profile and outpatient care following SIRT offers a significant advantage.

The safest approach for patients with nontumoral PVT is unclear. Regional therapies may not result in substantial prolonged survival. SIRT has been promoted for the treatment of patients with preserved liver function in this setting. An advantage in survival is yet to be established by prospective comparison of techniques.

Recommendation

SIRT performed in a lobar fashion after planning arteriography and MAA shunt study. Treatment of the lobe with the dominant tumor burden first; second lobe treatment in 4 to 6 weeks.

Case 4

A 70-year-old man with alcoholic cirrhosis, stable coronary artery disease, and diabetes mellitus has a solitary 4.5-cm lesion in segment 6. He is ECOG 1, CTP B (9) with a total serum bilirubin of 3.2 mg/dL, INR 1.7, and albumin of 2.9 g/dL.

Case Evaluation

This patient is within Milan criteria with stage II tumor but will likely be denied transplant because of his age and medical comorbidities. Elevation of bilirubin to >3 mg/dL increases significantly this patient's risk of liver failure with any form of liver-directed therapy. In addition, sorafenib is unlikely to be well tolerated. So options are limited, and no therapy may be indicated.

Treatment Options

We have favored RFA over TACE when liver function is marginal but rarely treat patients with bilirubin >3.5 mg/dL. RFA is more difficult in this patient because this lesion is large and outside the range for successful ablation therapy if a margin is to be accomplished. Although some operators ablate lesions >3 cm using multiple probes or treatment sessions, an alternative strategy combines RFA with TACE.

Combination therapy, typically performed as RFA followed by TACE within days or weeks of the ablation, may be possible if the initial treatment does not lead to progression of liver failure. A follow-up scan to determine the need for TACE can be performed as early as 1 day postablation.

Recommendation

If the lesion is in an optimal position for ablation, proceed to RFA. If significant residual tumor enhancement persists, consider selective TACE after a delay to monitor bilirubin.

Conclusions

Percutaneous ablation and intra-arterial therapies used in the treatment of HCC can provide a survival benefit, afford a bridge to transplant, or be used to downstage patients so they can undergo liver transplant. Although regional expertise plays a role in which technique is offered to any given patient, procedures should be tailored for each patient based on the goals of therapy, the degree of underlying liver disease, and the tumor burden. By balancing all of these factors, treatments can be maximized and overall outcomes improved in this otherwise challenging patient population.

Suggested Readings

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