Bryant Furlow

Incidence and mortality of hepatocellular carcinoma (HCC) are increasing rapidly, and HCC is now the third leading cause of cancer death. While localized, HCC is potentially curable with surgery, liver transplantation, or radiofrequency ablation. Tragically, HCC represents a unique paradox in clinical practice, notes Theodore S. Hong, MD, of Harvard Medical School and Massachusetts General Hospital, in Boston, Massachusetts. Although HCC is localized within the liver at diagnosis, few patients (less than 30%) are candidates for potentially curable treatment strategies. The reason for this is largely because in most cases localized HCC is diagnosed only after tumors have become multifocal, large (greater than 10 cm), and invade the vasculature, which is often associated with tumor thrombus. Frequently, comorbidities (and risk factors for HCC) such as hepatitis B or C infection, alcohol abuse, and liver cirrhosis also compromise liver function and limit treatment options (Table 1). Liver cirrhosis eventually develops into HCC in 5% of patients with the condition; however, up to 80% of patients with HCC have underlying liver cirrhosis. Cirrhosis-associated HCC is usually multifocal.

Transarterial chemoembolization (TACE) can improve survival times for patients with HCC who are not candidates for surgery and whose tumors have not led to major vascular thrombosis. Among those patients with HCC who are not candidates for TACE, sorafenib (Nexavar) may improve 1-year survival by 15%. However, neither TACE nor sorafenib is curative; tumor progression is nearly universal despite these interventions.

RADIOTHERAPY OPTIONS

Until recently, the risk of radiation-induced liver disease (RILD) precluded external-beam radiotherapy as a treatment option for most patients with HCC. Historically, two-dimensional (2D) radiography treatment planning involved large treatment volumes and precluded the determination of volumetric dose-toxicity relationships in the liver. Delivery of potentially curative doses of ionizing radiation to tumor tissues required irradiation of relatively large volumes of nontarget liver tissue, increasing the likelihood of RILD.

But with 3D computed tomography (CT)-based treatment planning and improvements in the conformally targeted delivery of radiation doses to tumor tissue contours, radiotherapy has emerged as a more promising solution to the HCC treatment conundrum, and is becoming a more commonly used modality for HCC. In conjunction with 3D planning tools, clinical trials and evidence-based planning to reduce the risk of RILD were also developed. Stereotactic body radiotherapy (SBRT) allows HCC radiotherapy delivery in fewer than six dose fractions.

A new report of results from phase 1 and phase 2 nonrandomized clinical trials provide additional support for cautious optimism that SBRT is a viable option for patients who are not candidates for surgery or other curative-intent treatments. Among those patients who are not candidates for surgery, TACE, or radiofrequency ablation, SBRT can yield improved survival rates with low risk of serious toxicity, according to Alexis Bujold, MD, of the Princess Margaret Hospital, University of Toronto, Canada, and colleagues. Their trials enrolled 101 patients with localized HCC, more than 50% of whom had tumor vascular thrombus and a Cancer

TABLE 1. Risk Factors for hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>α-fetoprotein (AFP) &gt;50 ng/mL</td>
<td>Age &gt;40 years</td>
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<tr>
<td>Alcohol use</td>
<td>Asian ethnicity (for patients with underlying liver disease)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Liver cirrhosis</td>
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<tr>
<td>Male sex</td>
<td>Tobacco use</td>
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Liver Italian Program (CLIP) score of 2–4, and the median diameter of their largest tumors was 7.2 cm.\(^1\)

CLIP is one of several staging systems that, unlike traditional TNM staging, account for liver function status as well as tumor morphology and extent; the inclusion of functional criteria is believed to improve prognostic utility.\(^7\,8\)

CLIP combines Child-Turcotte-Pugh (CTP) functional cirrhosis assessment scores (Table 2) with assessment of portal vein tumor invasion, number of tumors (imaged nodules), degree of liver involvement, and \(\alpha\)-fetoprotein levels, assigning each of these factors a value of 0, 1, or 2 as follows.\(^8\)

- **CTP score** Stage A, 0 points; stage B, 1 point; stage C, 2 points.
- **Tumor morphology** One nodule, 0 points; multinodular, 1 point; massive tumors or extension greater than 50%, 2 points.
- **\(\alpha\)-fetoprotein level** Less than 400 ng/mL, 0 points; 400 ng/mL or higher, 1 point.
- **Portal vein tumor thrombosis** No, 0 points; yes, 1 point.

The values are added together to yield an overall CLIP score. Lower CLIP scores are associated with better patient prognosis.\(^8\)

In spite of the high-risk status of the study populations, Bujold’s team reported achieving a 1-year local tumor control rate of 87% with SBRT.\(^1\) Grade 3+ adverse events occurred in 30% of the trial participants (grade 3, 26.5%; grade 4, 2.9%), with seven deaths possibly related to treatment.\(^1\) A total of 11 patients experienced serum AST/ALT abnormalities (all grade 3), nine patients experienced grade 3 platelet abnormalities, and five patients experienced grade 3 or 4 bilirubin abnormalities.\(^1\) Other grade 3+ toxicities were rare, affecting two or fewer patients.\(^1\) Median overall survival was 17 months (10.4 to 21.3 months).\(^1\) Although promising, the authors noted that the results should be confirmed in a randomized clinical trial.

**CONCLUSION**

The findings contribute to a growing body of evidence that durable local control of liver tumors can be achieved with radiation.\(^2\) Liver transplantation and partial hepatectomy clearly remain the gold standards for curative-intent treatment of HCC, Hong wrote; however, in light of the new study, SBRT appears to be an additional alternative treatment for patients who are not candidates for curative-intent interventions, and results in outcomes comparable to treatment with sorafenib in patients who are not candidates for surgery.\(^3\) SBRT might therefore become a common treatment for these patients. Phase 2 local control outcomes with SBRT in patients previously treated with incomplete transarterial chemoembolization are also promising.\(^10\) Importantly, tumor vascular thrombus appears to be treatable (recanalized) with radiotherapy, presumably restoring vascular function to some degree.\(^1,3\)

The results of this trial add to the evidence base only for SBRT, and not other radiotherapy modalities such as intensity-modulated radiotherapy (IMRT). Radiotherapy planning and performance, modalities and equipment, and fractionation vary from facility to facility, cautions Hong, and these factors might affect patient outcomes.\(^2\)

Hong emphasized that although the study by Bujold and colleagues clearly shows that radiation is an effective local modality for treating high-risk HCC, that radiation therapy will ultimately

**REFERENCES**


improve survival is not a foregone conclusion.2 “Even if radiation can ablate a tumor and tumor thrombus, the competing risks of distant disease progression and underlying liver disease remain significant,” reported Hong.2

Bryant Furlow is a medical journalist based in Albuquerque, New Mexico.

REFERENCES