Several noninvasive approaches show promise for patients with hepatocellular carcinoma who are not optimal candidates for surgery.

Nonsurgical Options for Hepatocellular Carcinoma: Evolving Role of External Beam Radiotherapy

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Background: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and thus poses a global concern. Its incidence is expected to increase in North America secondary to the increasing incidence of patients who develop hepatitis C. Patients who ultimately develop cirrhosis have an increased risk of developing hepatocellular carcinoma.

Methods: The authors focus on nonsurgical therapies for this disease with an exploration of how external beam radiotherapy can be used alone or with other modalities. The development of partial liver strategies secondary to an explosion in radiation treatment planning and delivery advances is reviewed. Integration of advanced technology has evolved from three-dimensional conformal treatment to intensity-modulated radiation therapy and image-guided radiation therapy, along with stereotactic body radiation therapy, tomotherapy, and proton beam therapy.

Results: Current data show a promising future for treatment strategies incorporating radiation with high rates of infield tumor control and low rates of radiation-induced liver disease. Radiation can be delivered in conjunction with transarterial catheter embolization for advanced-stage patients. External beam radiotherapy also has a role in the setting of patients with macrovascular tumor thrombus.

Conclusions: Future directions include how to best synergize the effects of radiation strategies with novel agents, given the hypervascularity of HCC. Downstaging of larger lesions with these therapies to resectable or transplantable disease may lead to better outcomes for patients deemed inoperable at diagnosis, and definitive radiotherapy may offer cure to patients with smaller lesions.

Introduction
Primary hepatocellular carcinoma (HCC), which accounts for 90% of all malignant cancers developed in the liver, is a potentially fatal disease that disproportionately affects patients in developing countries and Asia. However, the incidence in North America is increasing given the rise of hepatitis C. In the United States in 2009, approximately 22,620 people were diagnosed with liver or intrahepatic bile duct cancer, and 18,160 deaths were caused by this disease. In Asia and Africa, hepatitis B viral infection is the most common risk factor, while hepatitis C viral infection is the most common in Europe, Japan, and North America. In the United States, current estimates note that 4 million individuals are chronically infected with the hepatitis C virus. Each year, 2% to 8% of patients with hepatitis C-related cirrhosis will develop HCC. In addition to
hepatitis C, hepatitis B infections are also a factor in the United States, with an incidence of approximately 1.5 million chronically infected individuals.7

In addition to viral infections, other risk factors for HCC include hereditary hemochromatosis, porphyria cutanea tarda, α1-antitrypsin deficiency, Wilson’s disease, autoimmune hepatitis, and primary biliary cirrhosis.8 Alcoholics as well as patients exposed to aflatoxin are at increased risk.6,8 Evidence is mounting that there is also an association between future development of HCC and nonalcoholic fatty liver disease in the setting of diabetes mellitus or metabolic syndrome.9 Because the majority of these risk factors are also risk factors for cirrhosis, studies estimate that 60% to 80% of patients with HCC also have cirrhosis.10

Surgical resection has been considered a preferred modality of treatment for long-term control of limited HCC. Although surgical resection gives the best chance for cure of HCC, only 10% to 30% of patients at diagnosis are eligible for surgical interventions.11 Retrospective series suggest that 5-year survival rates after resection range from 51% to 56%.12,14 with serious morbidity and mortality rates of approximately 5%. Recurrence rates at 5 years postresection are noted to exceed 70%.6,14 Liver transplantation is thus a potentially curative option with oncologic tumor removal as well as treatment of the underlying cirrhosis.

In 1989, the US Department of Health and Human Services identified HCC as a contraindication for liver transplant.15 However, studies showed that patients transplanted for end-stage liver diseases with small incidental HCC had low tumor recurrence rates, providing the rationale to transplant patients with early HCC and liver decompensation.16 In 1996 Mazzaferro et al17 reported 4-year overall and recurrence-free survival rates of 85% and 92%, respectively, for highly selected patients with early HCC and liver decompensation.16 In 1996 Mazzaferro et al reported 4-year overall and recurrence-free survival rates of 85% and 92%, respectively, for highly selected patients with early HCC. The selected patients had solitary HCC not exceeding 5 cm in diameter or no more than 3 tumor nodules ≤ 3 cm, conditions subsequently referred to as the Milan criteria.

Those who suggest that the Milan criteria are too stringent note that with criteria from the University of California San Francisco (ie, solitary HCC up to 6.5 cm or up to 3 tumor nodules with the largest ≤ 4.5 cm and total tumor diameter < 8 cm), survival rates of 90% and 75.2% at 1 and 5 years, respectively, have been reported.18 However, surgical patients must be medically fit and have adequate liver function; optimal United Network for Organ Sharing (UNOS) transplant criteria consist of a single lesion ≤ 5 cm or up to 3 lesions ≤ 3 cm.19 In addition, prolonged wait times for donor organs are associated with tumor progression, with some patients becoming unsuitable for transplantation and subsequently dying while they are on the wait list. Vitale et al20 reported a study from 2000–2007 evaluating dropout rates with the criteria of macroscopic vascular invasion, metastases, or a poorly differentiated tumor, comparing patients with HCC vs benign chronic liver disease. In their analysis, 28% of the HCC patients showed tumor progression beyond Milan criteria before liver transplant.

The majority of patients are not ideal surgical candidates. Resection may not be possible due to poor liver function or macrovascular tumor invasion. Patients may present with large bulky tumors often measuring 5 cm to 10 cm and with multifocal disease. They may have major vascular invasion or portal venous thrombosis. Their hepatic function as measured by the Child-Pugh classification may be limited. The Child-Pugh score evaluates laboratory as well as clinical parameters to place patients into one of three classes. Class A patients have compensated cirrhosis, while class B and C patients have decompensated cirrhosis.21,22 This classification system differs from the Model for End-Stage Liver Disease (MELD) system in that the MELD score ranges from 6 to 40 (seriously ill) and evaluates only serum bilirubin, creatinine, and international normalized ratio (INR) for prothrombin time.23

### Staging Systems for HCC

At least 12 staging systems have been developed to differentiate patients with HCC.24,25 The Okuda classification,26 a system based on tumor size, ascites, jaundice, and serum albumin, was reported in 1985 to predict survival in patients with relatively advanced HCC. Since that time, advances in imaging have allowed diagnosis of HCC in earlier stages. The Barcelona Clinic Liver Cancer (BCLC) staging system and the Cancer of the Liver Italian Programme (CLIP) score are two such more recent clinical staging systems that integrate the Child-Pugh score.25 In the BCLC staging system, variables related to tumor stage, liver function, physical status, and cancer-related symptoms form the basis of four distinct stage groupings that correlate with specific treatment algorithms.27 For example, patients with BCLC stage A disease have early HCC and are candidates for resection, transplantation, or percutaneous therapies, while stage C patients have advanced disease and are candidates for new agents. The CLIP staging system reported in 1998 devised a six-category prognostic index that incorporated Child-Pugh grading, tumor morphology and extent, α-fetoprotein (AFP) levels, and the presence of portal vein thrombosis (PVT).28 Two pathological staging systems have been proposed as well: the American Joint Committee on Cancer, 6th edition (AJCC) and the Japanese Integrated Staging (JIS) score. The AJCC tumor-node-metastasis (TNM) staging system evaluates criteria based on characteristics of the patient’s tumor burden. Kudo et al29 reported the JIS score, which includes TNM stage according to criteria set by the liver cancer study group of Japan as well as Child-Pugh grade and increases predictive efficacy compared with the CLIP system.
Like the JIS system, the Chinese University Prognostic Index (CUPI) system incorporates the TNM stage but adds the following factors: total bilirubin, ascites, alkaline phosphatase, α-fetoprotein, and asymptomatic disease on presentation.\(^3^0\)

Although multiple staging systems have been proposed, controversy remains as to which system is most predictive of outcomes. Leung et al\(^3^0\) have reported that the CUPI system was more discriminant than the TNM, Okuda, or the CLIP score in patients with hepatitis B-associated HCC in terms of classifying patients into different risk groups and predicting survival in a population of 926 ethnic Chinese patients. In a study evaluating 305 patients undergoing radiotherapy (RT), Seong et al\(^3^1\) reported that among the TNM, Okuda, CLIP, and JIS systems, the TNM approach appeared to be the best predictor of prognosis. Still other investigators have concluded that MELD-based systems are superior to the Child-Pugh-based systems as prognostic indexes for HCC.\(^2^5\)

Since the majority of patients with HCC are not candidates for surgery, many interventional radiology approaches have been investigated, including radio-frequency ablation (RFA), transhepatic arterial chemoembolization (TACE), percutaneous ethanol injection (PEIT), cryotherapy, and high-intensity focused ultrasound, but the optimal treatment approach remains controversial. Given the noninvasive, painless approach associated with external beam radiation therapy (EBRT) options, this modality is being used in early disease with curative intent, in locally advanced disease to improve survival and quality of life, and for symptom palliation.\(^3^2\) In addition, an internal radiation option in the form of hepatic arterial infusion of radioactive yttrium-90 microspheres has been pioneered with lobar, segmental, and subsegmental techniques to safely deliver a high tumor radiation dose while minimally exposing the adjacent hepatic tissue.\(^3^3\) This review focuses on those nonsurgical strategies that incorporate EBRT.

**External Beam Radiotherapy**

Prior to the 1990s, EBRT to the liver was utilized primarily in the palliative setting for metastatic disease due to concern that tumoricidal doses could not be delivered safely, given the sensitivity of the whole liver to RT. In 1987, the Radiation Therapy Oncology Group (RTOG) reported the results of a trial randomizing patients to whole liver radiation alone to a dose of 21 Gy in 7 fractions or in combination with the radiosensitizer misonidazole.\(^3^4\) Results showed significant palliative benefit. Abdominal pain decreased, with 77% of patients having a decreased analgesic requirement, 67% having less abdominal distention, and 40% experiencing less nausea, vomiting, and anorexia. In this trial, symptoms were recorded by patients as well as their physicians. Mohiuddin et al\(^3^5\) subsequently reported data from a series of patients with colorectal metastasis to the liver and demonstrated an improved median survival if a partial liver boost dose was delivered in conjunction with whole liver irradiation.

**Three-Dimensional Conformal Radiation**

In 1987, investigators at the University of Michigan began studying possible strategies to deliver high doses to a small volume of the liver in order to yield higher tumor control rates while not increasing the potential radiation damage to liver parenchyma. The dose-limiting complication of delivering external beam treatment to the liver is radiation-induced liver disease (RILD), a clinical syndrome consisting of anicteric hepatomegaly, ascites, and elevated liver enzymes occurring from 2 weeks to 4 months following irradiation.\(^3^6\) In severe cases, this syndrome can lead to liver failure and death. Histopathologically, RILD is characterized as veno-occlusive disease with sparing of the larger veins but with significant venous congestion in the central portion of each lobe.\(^3^6\)

With the introduction of computerized treatment planning and the ability to apply three-dimensional conformal treatment techniques for partial liver irradiation, higher doses could be delivered safely (Fig 1).\(^3^7\) To achieve this result, the Michigan group studied factors that determined the partial volume tolerance of the liver to RT. Dawson et al\(^3^8\) reported that based on analyses of over 180 patients, the liver exhibits a large volume effect with a low threshold volume for RILD. They also reported that mean liver dose is associated with RILD and that estimates of a 5% risk for RILD for uniform irradiation of one-third, two-thirds, and the whole liver are 90 Gy, 47 Gy, and 31 Gy, respectively.\(^3^8,3^9\) Further study has shown that the tolerance of the liver is lowered in the setting of primary liver cancer such that the mean liver dose associated with a 5% risk of RILD is 28 Gy at 2 Gy per fraction for primary liver cancer vs 32 Gy at 2 Gy per fraction for metastatic liver cancer.\(^3^9\)

![Fig 1. — Three-dimensional view of a patient undergoing external beam liver radiotherapy.](image-url)
This work at the University of Michigan culminated in the integration of concurrent hepatic fluorodeoxyuridine as a radiosensitizer along with doses up to 90 Gy in 1.5 Gy per fraction delivered twice daily for patients with primary and metastatic liver cancers. Updated results from this series have shown an objective response rate of 56% in patients with HCC, a median survival of 15.2 months, a 1-year survival rate of 57%, and a 5-year survival rate of 11%.40

Extensive data on the feasibility and efficacy of three-dimensional conformal radiation (3DCRT) for HCC has been published in Europe and Asia (Fig 2). Mornex et al41 reported the results of the French phase II trial in which 25 assessable patients with Child-Pugh A/B with either one HCC nodule ≤ 5 cm or 2 nodules ≤ 3 cm received 66 Gy in 33 fractions of 2 Gy. In this study, all patients had cirrhosis, with 16 patients having Child-Pugh A disease and 11 patients having Child-Pugh B disease. Cirrhosis etiologies in this series of patients included alcohol (n = 9), hepatitis C (n = 9), hepatitis B (n = 3), hemochromatosis (n = 2), autoimmune disorder (n = 1), and cryptogenic liver disease (n = 3). The primary endpoint in this trial was the rate of complete tumor response to therapy characterized by the disappearance of contrast enhancement at the arterial-phase CT at 1 and 3 months. Results showed a complete response in 80%, a partial response in 12%, and stable disease in 8%. Grade 4 toxicities developed in 22% of
Child-Pugh B patients only. With a median follow-up of 29 ± 9 months, 22% developed a tumor recurrence outside the irradiated volume and 41% developed a recurrence outside the irradiated volume.

No patient in this study had reactivation of viral hepatitis, which has been shown by other investigators to be a potential occurrence after liver radiation in hepatitis B virus (HBV)-related HCC. The biological mechanism of this was explored by Chou et al in a study in which primary cultures of hepatocytes were prepared from the noncancerous tissue removed peroperatively from 12 HBV carriers with HCC. Results showed that radiation-induced liver toxicity with HBV reactivation was secondary to indirect effects from neighboring nonhepatocytes. In fact, reactivation occurred because of a bystander effect on irradiated endothelial cells releasing cytokines, including interleukin-6.

Chung et al also reported an increase in failures outside the irradiated volume and questioned whether previously dormant subclinical tumors not included in the RT field might be subject to RT-induced vascular endothelial growth factor (VEGF) stimulation. They evaluated HCC outcomes in 276 T3N0M0 patients treated with TACE alone and 64 treated with TACE followed by 3DCRT. The treatment was delivered at 1.8 to 2.0 Gy per fraction to a range of doses, with a maximum dose of 66 Gy, depending on liver toxicity criteria. Results showed a median survival of 19 months in the TACE alone arm and 17 months in the TACE + RT arm (P = .65), indicating that RT did not improve overall survival after TACE. Interestingly, the authors noted a different failure pattern after TACE than after TACE + RT. A significant portion of patients experienced rapid intrahepatic and extrahepatic tumor progression outside the treatment field. In their molecular analysis of the effects of radiation on human hepatoma cells, the investigators found that RT rapidly induced p53-independent transcriptional upregulation of VEGF, increased VEGF secretion in a dose/time/cell-type–dependent manner, and promoted hepatoma cell growth in vivo with enhanced intratumor angiogenesis that correlated with elevated serum levels of VEGF. These results support the rationale for combining anti-VEGF angiogenic modalities with RT.

In another series reported from Asia, Chia-Hsien Cheng et al did not find any difference in rates of intrahepatic tumor recurrence outside the irradiated volumes in patients treated with TACE + RT vs TACE alone (P = .48), but extrahepatic progression-free survival was significantly shorter in patients treated with the combined therapy regimen. In fact, the 2-year rates for the TACE + RT group were 36% compared with 100% in the TACE alone group (P = .002). The patients in this series were treated with a TACE regimen of lipiodol, doxorubicin, cisplatin, and mitomycin C, followed by Gelfoam or Ivalon embolization. The mean dose of delivered EBRT was 46.9 Gy ± 5.8 Gy in daily fraction sizes of 1.8 Gy to 2.0 Gy with a median of two courses of TACE delivered prior to EBRT and a median of two courses after RT. Cheng et al explored the possible molecular mechanisms for such clinical observations of more frequent metastasis in HCC patients undergoing fractionated RT. In their study, three HCC cell lines and normal hepatocyte cell lines were irradiated with different doses. The effect of radiation on cell invasiveness was evaluated with the Boyden chamber assay. Results showed that sublethal doses of radiation could enhance HCC cell invasiveness by MMP-9 expression through the PI3K/Akt/NF-κB signal transduction pathway. This work emphasizes the need to suppress processes that can lead to unwanted metastatic signaling.

Although the current data on exploring antiangiogenic agents with EBRT are limited, there is significant clinical interest in exploring sorafenib in this setting. Sorafenib is an orally active multikinase inhibitor that has been shown to prolong overall survival and delay time to progression in patients with advanced HCC who are not candidates for potentially curative therapy. The drug inhibits cell surface tyrosine kinase receptors such as VEGF receptors and platelet-derived growth factor (PDGF) receptors as well as downstream intracellular serine/threonine kinases.

A recent case report from Asia in a patient refractory to embolization showed initial benefit to sorafenib with a decrease in AFP levels, but the patient developed a grade 3 skin reaction. The dosage of sorafenib was reduced and the skin reaction improved. Reducing the dose, however, also was associated with an increase in AFP levels and development of portal vein thrombosis. When the sorafenib dosage was resumed at 800 mg/day; the tumor did not respond. The patient subsequently received EBRT with IMRT technique concurrently with sorafenib. With this technique, the radiation beam is divided into individual beamlets to maximize dose to the tumor and minimize the dose to surrounding normal tissue. The combination resulted in marked tumor shrinkage but recurrence of the systemic skin reaction. Provocative reports such as these will lead to further interest in combining novel agents with advanced EBRT delivery. There is caution in this setting as well, however, due to concern about potential oversensitization. A recent case report described a fatal bowel perforation in a patient with metastatic renal cell carcinoma who had stopped sorafenib 2 days prior to a single dose of 8 Gy to an anterior-posterior/posterior-anterior field encompassing L3–L5. At autopsy, the transverse and sigmoid colon showed multiple perforations with fecal peritonitis.

At present, there are multiple ongoing clinical trials evaluating outcomes with combining sorafenib and other modalities. In Toronto, the maximum tolerated
dose (MTD) of sorafenib combined with 6-fraction conformal radiation is being evaluated in a phase I trial. In the United States, sorafenib is being evaluated in combination with chemoembolization with LC Beads or TACE, with RFA, and with radioembolization as well as in the adjuvant setting following resection or following transplant for high-risk patients.

In addition to targeted agents, immunotherapy is also being explored in HCC in combination with EBRT. Chi et al reported a phase I study from Asia in patients with advanced/metastatic disease who were not suitable for surgery or transarterial chemoembolization. In their 14-patient study, a dose of 8 Gy was delivered with conformal EBRT followed by 1 to 2 doses of immature dendritic cells injected intratumorally. The treatment was well tolerated and was associated with decreases in the AFP level of more than 50% in 3 patients and partial responses in 2 patients. AFP-specific immunologic improvements were also noted in 8 out of 10 patients. These data suggest that intratumoral injection of dendritic cells not only can be combined with EBRT safely, but also can induce tumor-specific immunity.

**3DCRT in Combination With TACE**

Since the majority of recurrences after focal liver RT occur within the liver but outside the high-dose irradiated liver volume, there is strong rationale for combining RT with other therapies such as TACE. Three strategies combining TACE with EBRT have been extensively studied in Asia and shown to be both feasible and tolerable.

One approach involves treating portal vein tumor thrombus (PVTT) and inferior vena cava tumor thrombus (IVCTT) with RT to complement TACE without irradiation of the primary liver tumor. The rationale for this approach is that TACE is less effective in patients with PVTT and RT may make TACE more effective if PVTT can be eradicated. Thus, HCC patients with PVTT or IVCTT may benefit from EBRT. Zeng et al have reported experience in China with 158 HCC patients. Of these, 44 were classified as the EBRT group because they received local EBRT to a median of 50 Gy targeted to tumor thrombi in addition to other treatment modalities. Their outcome was compared with 114 patients who had tumor thrombi but did not receive EBRT. Results showed a median survival of 8 months and a 1-year survival rate of 34.8% in the EBRT group compared with a median survival of 4 months and 1-year survival rate of 11.4% in the non-EBRT group. In a stepwise multivariate analysis, EBRT showed a strong protective value (relative risk = 0.324, \( P < .001 \)). In their updated experience, involving 136 patients with tumor thrombi receiving EBRT, the authors reported a median survival of 9.7 months. Survival rates at 1, 2, and 3 years for patients with PV tumor thrombi were 31.8%, 17.5%, and 8.8% for patients with PVTT, respectively, compared with 66.3%, 21.1%, and 15.8% for patients with IVCTT and 25%, 8.3%, and 0% for PVTT plus IVCTT. Indeed, the data suggest that 50 Gy to 60 Gy over 5 to 6 weeks can be delivered safely to macrovascular disease with limited liver volume required to be irradiated.

A second strategy employs RT as a “consolidation” planned procedure to target residual hepatic tumor after TACE; this is done with curative-intent. The rationale for this approach is that RT targets cancer cells at the tumor periphery that may remain viable through blood supply from collateral circulation or recanalization of the embolized artery and that the chemotherapy agents used during TACE may act as radiosensitizers. Seong et al reported the Korean experience with 30 patients prospectively treated with TACE followed by EBRT in unresectable HCC. In this trial, TACE was performed with lipiodol and doxorubicin followed by gelatin sponge particle embolization. This was followed 7 to 10 days later by local RT with a mean tumor dose of 44 Gy at 1.8 Gy per fraction. Response was assessed by CT scan 4 to 6 weeks after treatment and then at 1-
to 3-month intervals. The combination treatment was associated with a 63.3% response rate and a median survival of 17 months, and there were no treatment-related deaths. A planned combined approach may have some advantage over reserving RT as salvage therapy.

Lastly, a salvage approach is to use either TACE or RT up front, with the other modality as therapy for recurrences. The most common of these approaches include the use of a TACE procedure followed by RT, RT sandwiched between TACE procedures, or repetitive TACE until optimal response followed by RT.57 The interval between TACE and RT has been variable in the literature. Liu et al62 reported 44 patients with unresectable HCC who received a median tumor dose of 50.4 Gy at standard fractionation. The objective response rate for this series, of which the majority of lesions were > 5 cm, was 61.4%, with survival rates at 1, 2, and 3 years of 60.5%, 40.3%, and 32.0%, respectively. The median survival time was 15.2 months. Seong et al63 reported similar data from Korea with a study of 27 patients who failed TACE and received 3DCRT to a median dose of 51.8 Gy at standard fractionation. Results showed a tumor response rate of 66.7%, with a 3-year survival rate of 21.4% and a median survival time of 14 months. Indeed, reduction of tumor volume after TACE may allow less uninvolved liver to be irradiated, permitting the use of higher doses of radiation with less toxicity.

Despite variations in techniques and timing, the majority of studies have suggested a benefit of RT and TACE in patients with advanced HCC, often with macrovascular invasion, compared with contemporaneous patients treated without RT. The partial response rates range from 25%67 to 78%64 at 1 month after RT, with complete response rates as high as 13%.62,65 Survival rates range from 10.2% to 53.8% at 2 years and from 9% to 19% at 5 years.64,66,67 Since RT combined with TACE appears to be a promising therapeutic approach, this option should be investigated in a randomized trial.

**Advanced Radiation Technologies**

Modern radiation oncologists have more treatment tools available than ever before for highly precise delivery of partial liver radiation. With the advent of 4DCT scans, there is now the ability to set up the patient in the desired position with a body cradle for immobilization with the capability to measure how much the liver tumor moves with respect to respiration. Fiducial markers may be implanted percutaneously into the liver to guide treatment (Fig 3).68 HCCs are best visualized in the arterial dominant phase of the three-phase liver CT scan (Fig 4).69 Along with advances in imaging, there also has been significant progress in managing liver motion for reproducible radiation treatment delivery. With image-guided radiation therapy (IGRT), radiation
oncologists can now document the intended treatment position prior to dose delivery. Radiation treatment units are increasingly equipped with kilovoltage x-ray and megavoltage CT units that can verify organ position. These CT images generated while the patient is in the treatment position on the table are used to verify localization prior to activating the machine to enhance the precision of dose delivery (Fig 5). This increasing treatment certainty has allowed smaller margins of normal tissue and thus more liver sparing.

Strategies have evolved that can minimize liver motion prior to daily treatment. First, there is the option of abdominal compression whereby a mechanical belt-like device is used to physically limit the excursion of the liver. Second, there is the option of respiratory gating such that the machine is only “on” during a specified phase of the breathing cycle. Third, there is the option of various breath hold techniques such as active breathing control. In these techniques, the patient’s breathing is monitored by the radiation therapist on the treatment unit with a device that can hold the patient’s breath by restricting air entry. When the patient’s breathing is held in the desired phase of the respiratory cycle, the treatment machine is turned on and the dose delivered.

In addition to advances in imaging, treatment planning, and delivery, extracranial stereotactic body radiation therapy (SBRT) has been developed for the treatment of liver tumors (Fig 6). The origins of stereotactic treatment date back to the 1940s with the neurosurgical halo device that was designed to screw into the patient’s skull so that the device could then be rigidly fixed to the treatment table. Over the last 10 to 15 years, these neurosurgical beginnings have found fertile ground in the treatment of extracranial sites since modern radiation oncology has overcome problems with body immobilization and motion. Given the complexity of liver tumor motion, coupled with the priority of minimizing the volume irradiated to reduce the risk of RILD, SBRT has emerged as a promising modality for treatment of liver tumors.

Initial experience for treatment of liver tumors has been with liver metastases. One of the first studies was from the University of Heidelberg, reported by Herfarth et al. They delivered single-fraction treatment to 60 liver tumors (4 primary tumors and 56 metastases) with a median tumor size of 10 cm and a dose ranging from 14 Gy to 26 Gy. A recent update from this series reported a local control rate of 66% at 18 months with a single dose of 22 Gy. Recent data from the US multi-institutional phase I/II trial of patients with 1 to 3 hepatic lesions with 6 cm as the individual maximal tumor size allowed was reported by Rusthoven et al. A delivered dose of 60 Gy in 3 fractions has shown a 2-year local control rate of 100% with a lesion size of 3 cm or smaller and only 1 patient with grade 3 or higher toxicity. This series included 47 patients with 63 lesions, with 2.7 cm as the median individual maximal tumor diameter. The median survival was reported to be 20.5 months, with a 2-year overall survival rate of 30%.

Experience with SBRT for HCC is now emerging as well. Tse et al. reported data on 31 patients with HCC not suitable for standard therapies who were treated with 6-fraction SBRT at Princess Margaret Hospital in Toronto. The median tumor size was 173 mL, with a median dose of 36 Gy (24 Gy to 54 Gy). No RILD was noted, and the median survival was 11.7 months. Henderson et al. reported preliminary data from an Indiana University dose escalation study that included 10 patients with HCC with tumors ≤ 6 cm and ≤ 3 lesions. This study started at dose level 1 with 36 Gy in 3 fractions with escalation in 6 Gy increments up to an anticipated total dose of 60 Gy in 3 fractions. No patients at dose level 1 experienced dose-limiting toxicity (DLT). However, 2 patients at the next dose level experienced DLT, both of whom were Child-Pugh B cirrhotics. O’Connor et al. reported data from Baylor University Medical Center suggesting the SBRT may be an effective bridge to transplant. In this study of 5 patients and 6 tumors with a median tumor size of 3.2 cm, patients were given a median dose of 48 Gy in 3 fractions. Following SBRT and liver transplant, pathological examination of the explants revealed that 2 of the 6 tumors had no evidence of viable tumor and 3 of the 6 tumors decreased in size following SBRT. One tumor increased in size.

Recent data from Asia reported on the feasibility of combining SBRT with TACE. Takeda et al. reported the Japanese experience of 16 Child-Pugh A/B patients with solitary HCC treated with SBRT. Fourteen patients received TACE prior to SBRT. The median time to TACE and SBRT was 13 days. The SBRT was delivered in 5 to
7 fractions to a total dose of 35 Gy to 50 Gy. At the median follow-up of 611 days, all patients were alive, with 8 of the 16 noted to have a complete response and 7 others with stable disease. One patient recurred locally after 489 days, and in 6 patients, intrahepatic recurrence developed outside the treated volume. Choi et al\textsuperscript{78} have reported data from Korea in a series of 31 patients with 32 HCC lesions. In this study, 23 lesions were treated using stereotactic technique on a linear accelerator with a mounted robotic arm to guide tracking of the tumor with respiration to a small, non-resectable primary HCC, and 9 lesions were treated to the PVTT with TACE to follow, with at least 4 weeks in between TACE and SBRT. The overall response rate was 71.9\%, with a median survival of small HCC of 12 months and advanced HCC with PVTT of 8 months. No patients experienced grade 4 toxicity. For patients who do present with metastases, Jang et al\textsuperscript{79} reported that tomotherapy can be safely delivered; in their study, the reported median survival time was 12.3 months.

In addition to SBRT, other advanced EBRT strategies such as proton beam therapy and other charged particle therapy have been utilized in this disease. The Japanese reported encouraging local control rates after carbon ion and proton beam therapy. Kato et al\textsuperscript{80} reported results from a phase I/II dose escalation trial of 25 patients with a range of 49.5 Cobalt gray equivalents (GyE) to 79.5 GyE over 15 fractions. At 5 years, the local control rate was 81\% with a survival rate of 25\%. At 71 months of follow-up, the majority of recurrences were in untreated portions of the liver, with 25\% of patients developing systemic metastases. Fukumitsu et al\textsuperscript{81} reported a series of 51 patients with HCC at least 2 cm away from the porta hepatic or gastrointestinal tract with a maximum tumor size of 10 cm treated with protons to 66 GyE in 10 fractions. In this study, metallic fiducial markers were implanted percutaneously into the hepatic parenchyma adjacent to the tumor. The median observation period for survival in all patients was 34 months. The local control rate at 5 years was 88\% with a 39\% survival rate. There were no treatment-related deaths; 20\% of the patients were in Child-Pugh class B.

The EBRT experience to date demonstrates that cure of localized HCC lesions might indeed be possible, but at what optimal dose and fractionation schema and with what technique? Data from Aoki et al\textsuperscript{82} demonstrated that all patients with HCC treated with localized radiation to a dose of 50 Gy to 70 Gy in standard fractionation still had viable tumor cells remaining at autopsy. With the ability to deliver higher ablative doses to focal liver tumors while accounting for organ motion, the answers to these questions may be available in the near future. Dawson\textsuperscript{32} notes that patients with tumors < 6 cm and at the dome of the diaphragm are those most likely to be safely treated with biologically potent photon therapy, whereas proton therapy would provide the greatest benefit in patients with Child-Pugh B class liver function or large > 8 cm central tumors. In contrast, patients with diffuse multifocal disease or Child-Pugh C liver function are not optimal candidates for either modality but might be candidates for radioembolization in which yttrium-90 microspheres are delivered through the hepatic arterial system to treat the intrahepatic disease.\textsuperscript{83}

**Conclusions**

Modern external RT options can be safely delivered to patients with HCC. Biologically potent EBRT can be tumoricidal and may offer cure. In a disease where the whole liver is at risk for carcinogenesis, given that the majority of patients have underlying cirrhosis, strategies that offer potential tumor downstaging and conversion to resectable or transplantable status hold significant promise. By employing novel tools in combination with RT, such as advanced imaging\textsuperscript{84} and immunotherapy,\textsuperscript{51} we may make further advancements with respect to cancers of the liver. The issue of how to maximize radiation delivery with other therapies such as TACE and sorafenib is the subject of ongoing investigation.

**References**

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