Review

What is the role of radiation therapy in treating liver tumors?

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Practice Points

- Radiation therapy can be delivered to the liver either with external beam radiation therapy or with internal radiation delivered via the hepatic artery (radioembolization).
- Numerous advancements in external beam radiation therapy allow for more accurate targeting, such as through the incorporation of 4D computed tomographic simulation, which makes aggressive dose-fractionation strategies possible using techniques such as stereotactic body radiation therapy. Stereotactic body radiation therapy is a state-of-the-art technique whereby ablative doses of radiation are focally delivered to the tumor with a steep dose fall-off within millimeters outside of the target volume, thus significantly sparing normal surrounding tissue.
- In addition to conformal photon external beam delivery, data suggest improving outcomes with charged-particle therapies such as the use of protons.
- Radiation therapy options also offer clinicians the chance to potentially cure or downstage oligometastatic liver lesions not amenable to first-line surgical resection or radiofrequency ablation.
- Radioembolization is a form of brachytherapy that delivers millions of radioactive microspheres directly to the target liver lesion(s). This permits delivery of a high dose to the tumor while significantly sparing normal tissue. It can effectively palliate patients with metastatic disease that is no longer responsive to systemic therapy, as well as those with primary liver cancer not appropriate for other local modalities.
- This review will explore the range of radiation therapy options available to treat primary and metastatic lesions of the liver, as well as emerging innovative strategies that combine these treatments with surgery, radiofrequency ablation and systemic therapies.

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SUMMARY With the liver's dual blood supply and the preferential tumor vasculature from the hepatic artery, liver malignancies offer unique challenges and opportunities for treatment. In the case of primary liver tumors, such as hepatocellular carcinoma and cholangiocarcinoma, the disease burden, when diagnosed, is often extensive and precludes other local forms of therapy. External beam radiation therapy and intravascular brachytherapy, or radioembolization, have been shown to improve outcomes in these patients. Even though many will respond to radiation therapy, long-term cure is unlikely unless they ultimately proceed to resection or transplant. Oligometastases can also be effectively treated with radiation therapy. This review will explore the potential for radiation therapy options to be considered for both primary and metastatic liver malignancies.

Liver malignancies include primary hepatocellular carcinoma (HCC), primary intrahepatic cholangiocarcinoma (IHC) and metastatic disease. While metastatic lesions are the most common form of hepatic malignancy [1,2], HCC is the sixth most common malignancy in the world and the third most common cause of cancer-related mortality [3,4]. Owing to the morbidity and mortality of liver malignancies, significant effort has been invested in improving treatment techniques, especially since many patients are not optimal surgical candidates due to the extent of disease and/or poor liver function.

Patients who are not optimal candidates for hepatic resection can often be selected for a procedure called radiofrequency abalation (RFA), which destroys tumor cells via necrosis through high temperature thermal ablation [5]. Because RFA can be performed percutaneously by an interventional radiologist, or intraoperatively in collaboration with a surgeon via image-guided or manual techniques [6], a multidisciplinary tumor board will often first discuss whether either of these techniques is feasible based on the imaging findings. Since patients often present with advanced disease with intrahepatic locations adjacent to vasculature, margin negative (R0) resections are often not feasible. Such locations are also a contraindication for RFA because it would not be possible for complete eradication due to the heat-sink effect of the nearby vasculature. To obviate the heat sink, a newer technique called irreversible electrocorporation has been developed [7]. Few data are currently available with long-term outcomes for irreversible electrocorporation. There are several methods of evaluating the effect of locoregional therapies that are outside the scope of this review [8].

These nonsurgical options are secondary to the surgical gold standard. Over the past 20 years, surgical series have demonstrated excellent long-term survival and cure rates for patients with limited hepatic disease who undergo surgical management including resection or transplant. This review will focus on the evolution and current practices of radiation therapy in treating these types of tumors in patients who are not candidates for first-line surgery or RFA. Radiation therapy can be delivered using traditional external beam radiation therapy (EBRT) methods or with newer techniques including stereotactic body radiation therapy (SBRT), charged particle therapy or radioembolization. The integration of new technologies has spurred renewed interest in liver tumor radiotherapy with evolving literature to support its efficacy. These advances have been critical in the pursuit of local control or potential cure.

Radiation therapy modalities

■ EBRT

The use of EBRT has expanded over the course of the last several decades. Initially, EBRT was primarily used for palliation due to concern over radiation-induced whole-liver toxicity [9]. Radiation-induced liver disease (RILD), which was historically called 'radiation hepatitis', can potentially cause liver failure and even death. RILD classically presents with anicteric hepatomegaly, elevated liver enzymes from 2 weeks to 4 months postradiation, fatigue and ascites. Occlusion and congestion of the central veins of hepatic lobules can occur while larger veins are spared [10]. In addition, there is a form of nonclassic RILD that typically occurs from 1 week to 3 months after therapy. It is associated with

an elevation of liver transaminases more than five-times the upper limit of normal levels, or a decline in liver function, such as a decline in the Child–Pugh score by at least two [11].

One of the earliest trials to evaluate the efficacy of radiation to the liver was performed by the Radiation Therapy Oncology Group [12]. The Radiation Therapy Oncology Group 8003 randomized 214 patients with liver metastases to whole-liver EBRT alone (21 Gy in seven fractions) with or without the radiosensitizer misonidazole. While adding misonidazole did not offer a significant benefit over EBRT alone, EBRT appeared to provide a significant benefit. In fact, 77% of patients had a decrease in analgesic requirements, 67% of the patients had a decrease in abdominal distension and 40% of patients had a decrease in nausea, anorexia and vomiting.

The advancement from 2D to 3D computerized treatment planning techniques was instrumental in being able to deliver highly conformal doses to the target lesion(s) instead of uniform doses to the whole liver. Selective partial organ volumetric treatment using 3D planning software led to dose-escalation studies. Dawson *et al.* published a series of over 180 patients showing that while the whole liver cannot tolerate high doses of radiation, partial liver doses can be safely escalated without inducing RILD [13]. They found that patients were at a 5% risk of RILD for uniform irradiation of one-third of the liver, two-thirds of the liver and the whole liver at 90, 47 and 31 Gy, respectively [13,14]. Dawson and Ten Haken also reported in a later study, the differences in whole-liver tolerance in the setting of primary versus metastatic liver cancers [14]. A 5% risk of RILD occurred at a mean liver dose of 28 Gy at 2 Gy per fraction for primary liver tumors, while the same risk for RILD was seen at a mean liver dose of 32 Gy at 2 Gy per fraction for metastatic disease.

Since the liver follows the parallel architecture model of radiobiology, it is thus desirable to treat focal regions of the liver to high tumoricidal doses, while respecting the volume of liver receiving low-dose radiation to avoid toxicity [11]. Modern radiation dose limits to the liver have been founded on the principles of hepatic resection; the surgical literature notes that 75–80% of a noncirrhotic liver can be safely resected [15]. However, patients with HCC are known to have impaired parenchymal function and liver regeneration [16]. Surgeons thus perform volumetric measurements of total liver volume, as well as an estimation of the volume of the estimated future liver remnant. Similarly, radiation oncologists must determine if the volume of liver irradiated can be restricted such that there will be an adequate volume that is not receiving significant dose.

Finally, based on Quantitative Analyses of Normal Tissue Effects in the Clinic, Pan *et al.* have made the following recommendations when treating HCC with SBRT: a mean liver dose of <13 Gy over three fractions, <18 Gy over six fractions, or <6 Gy in 4–6 Gy per fraction for classical and nonclassical RILD in Child–Pugh Class B patients [17]. For patients with noncirrhotic livers treated for metastases: a mean liver dose of <15 Gy over three fractions and <20 Gy over six fractions. In addition, ≥700 ml of normal liver was recommended to receive ≤15 Gy in three to five fractions [17].

SBRT

Originally developed for the treatment of intracranial malignancies, stereotactic radiotherapy has since been adopted for the treatment of extracranial disease and is called SBRT. SBRT has been most extensively evaluated for the treatment of early stage lung cancer, but has more recently been studied for incorporation into treatment of gastrointestinal malignancies.

SBRT is safely able to deliver a high ablative dose per fraction to small target volumes in only one to five fractions compared with standard fractionation treatment that delivers a much reduced dose per fraction (1.8–2 Gy) over several weeks. It is thought that SBRT may potentially have a unique radiobiologic effect compared with standard fractionation treatment. While the exact mechanism of action is not well understood, preclinical data suggest that ablative dosing occurs at a threshold of 8–10 Gy and is due to an apoptotic effect on the vascular endothelium [18].

Accurate treatment delivery is vital for all patients, but particularly for SBRT patients because such large doses are delivered over five fractions or less. Accuracy within several millimeters can be achieved by using a combination of immobilization devices, image guidance and techniques designed to account for respiratory tumor motion, such as 4D computed tomography (CT) simulation, respiratory gating, abdominal compression and the breath-hold

technique, which will be described further in the next section. Figure 1 illustrates an SBRT treatment plan for a patient with metastatic colon cancer of the liver.

Image-guided radiation therapy

Image-guided radiation therapy can be used to assess the accuracy of the treatment setup prior to treatment delivery using either 2D (i.e., orthogonal x-rays) or 3D (i.e., cone-beam CT) methods [9]. Positional shifts accurate to the millimeter level can then be made to place the patient in the appropriate treatment position. 4D CT simulation allows physicians to visualize tumor movement throughout the respiratory cycle with the patient being immobilized in the treatment position. Treatment volumes can then be created based on the extent of tumor motion to maximize coverage of the target volume while minimizing the dose to normal surrounding structures. For patients whose tumors move a significant distance with breathing, dose to normal tissues can be minimized using several methods including abdominal compression, respiratory gating and breath-hold techniques. Abdominal compression is achieved by placing a device over the abdomen to limit diaphragmatic excursion. Respiratory gating can be used in conjunction with fiducial markers during which the treatment machine will turn on within a predetermined portion of the respiratory phase, typically during end expiration. The breath-hold technique monitors the patient's breathing and can manipulate breathing patterns by restricting air entry at specified intervals [9].

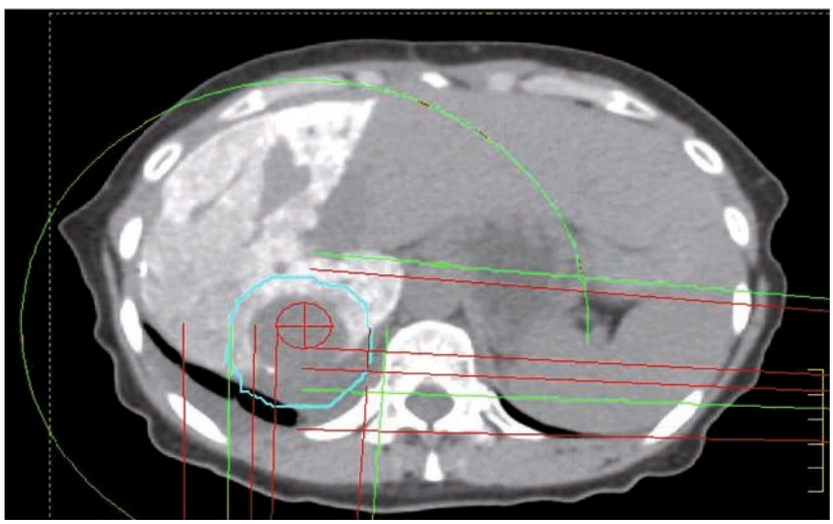

Figure 1. Stereotactic body radiation therapy plan to a posterior liver tumor target treated with arc therapy.

Charged particle radiation therapy

While the majority of EBRT is delivered using photons, other particles, such as protons or carbon ions, can be used due to their unique physical and dosimetric properties. Protons, in contrast to photons, produce no exit dose due to the Bragg–Peak effect, which can significantly limit normal tissue dose [19]. Since patients with HCC typically have coexisting primary liver disease, avoidance of toxicity by minimizing the volume of liver irradiated is of significant concern. Liver toxicity can also manifest itself with the reactivation of viral hepatitis in those patients with hepatitis B-associated HCC [20]. Carbon ion particle therapy has more radiobiological benefit than protons or photons, capable of more effectively killing hypoxic cells [21]. Both protons and carbon ions constitute a type of external beam radiation modality known as charged particles, which has a higher biological effectiveness than photons. These treatments hold significant promise for liver malignancies, especially HCC, given the potential for enhancing focal-dose escalation without increasing the volumes of liver receiving low-dose radiation that could precipitate liver failure [22]. Data from Asia is emerging on the incorporation of charged particle therapies for the treatment of HCC with results of 5-year local control over 80% and overall survival over 35% [23]. In fact, clinical results of 386 tumors treated in Japan with particle therapies in a series of 343 consecutive patients showed a 5-year local control rate of 90.8% and a survival rate of 38.2% [24].

Radioembolization

Radioembolization is the percutaneous intra-arterial injection of micron-sized radioactive particles that become embedded within the tumor and deliver a high-focal dose [1]. Radioembolization for primary or metastatic liver lesions is based on the dual blood supply of the liver and the preferential supply of liver lesions by the hepatic artery, whereas normal hepatocytes receive the majority of blood from the portal vein [25–28]. This difference permits targeted delivery of radioactive particles to the tumor while largely sparing the normal liver [29]. Figures 2–4 highlight the benefit of radioembolization as an option for downstaging to

margin negative resection; the case depicted illustrates a young patient with a solitary colorectal metastasis who remains disease free following radioembolization and hepatic resection.

Liver radioembolization is most commonly performed using yttrium-90 (^{90}Y), which is a pure β-emitter, with a half-life of 64.2 h and an average energy of 0.9367 MeV. ^{90}Y decays to stable zirconium. Commercially available outpatient treatment systems include the glass-based TheraSphere (Nordion, ON, Canada) and the resin-based SIR-Sphere (Sirtex, north Sydney, Australia). Studies have compared these two systems, although there is no clear consensus that one is superior to the other [30].

HCC

HCC accounts for approximately 90% of all primary liver malignancies [9]. Hepatitis C infection is the most common etiology in North America, Japan and Europe, with 2–8% of chronically infected individuals being diagnosed with HCC each year [31]. This is in contrast to hepatitis B infection, which is the most common risk factor of HCC in Asia and Africa [32]. Other risk factors include hemochromatosis, α-1-antitrypsin deficiency, autoimmune hepatitis, primary biliary cirrhosis and alcoholism [31,33]. Liver cirrhosis is also a well-established risk factor of HCC. It is estimated that upwards of 80% of HCC patients have cirrhosis as a comorbidity [34].

Since surgical resection or transplantation are potential curative options for limited HCC, the first priority is to determine the local extent of disease and classify the functional capacity of the diseased liver. Globally, there are a variety of different staging systems and liver functional classification systems [35]. The tumor node metastasis staging system has been adopted by the United Network for Organ Sharing (UNOS) for the staging of HCC patients [36]. In this system, patients eligible for transplant are T2 (solitary tumor with vascular invasion or multiple tumors of <5 cm) or less. Moreover, the model for end-stage liver disease has been adopted by UNOS to stratify patients on the liver transplant waiting list according to the risk of death within 3 months [37]. The model for end-stage liver disease score assigns points for abnormal bilirubin, creatinine and international normalized ratio values and ranges from six (less ill) to 40 (seriously ill). The Child–Pugh scoring system is another commonly used metric to evaluate the patient's clinical status [38,39]. It integrates a score based on five different clinical signs (total bilirubin, prothrombin time, ascites, hepatic

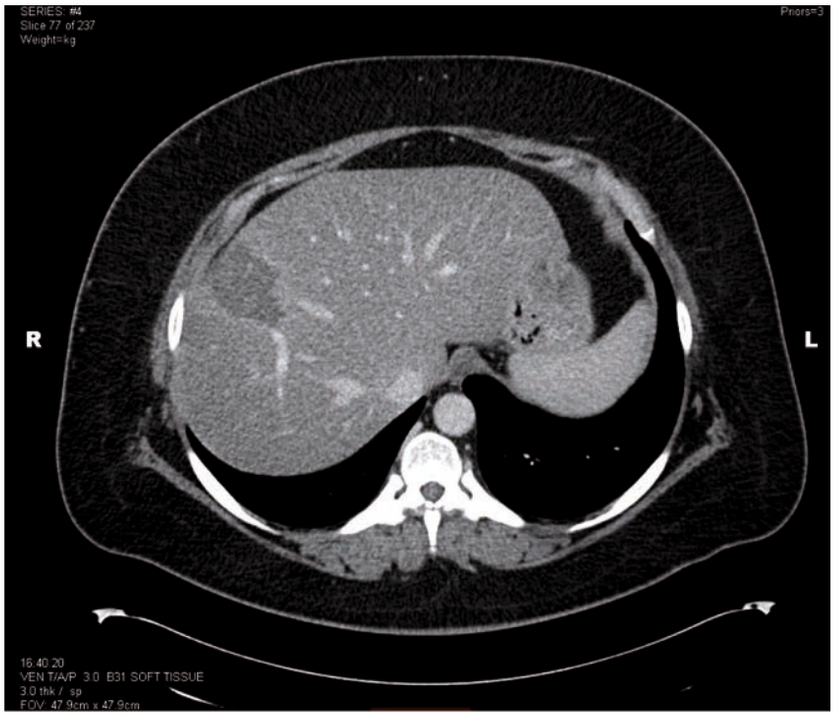

Figure 2. CT scan of liver status postchemotherapy. This image shows a solitary colorectal metastasis.

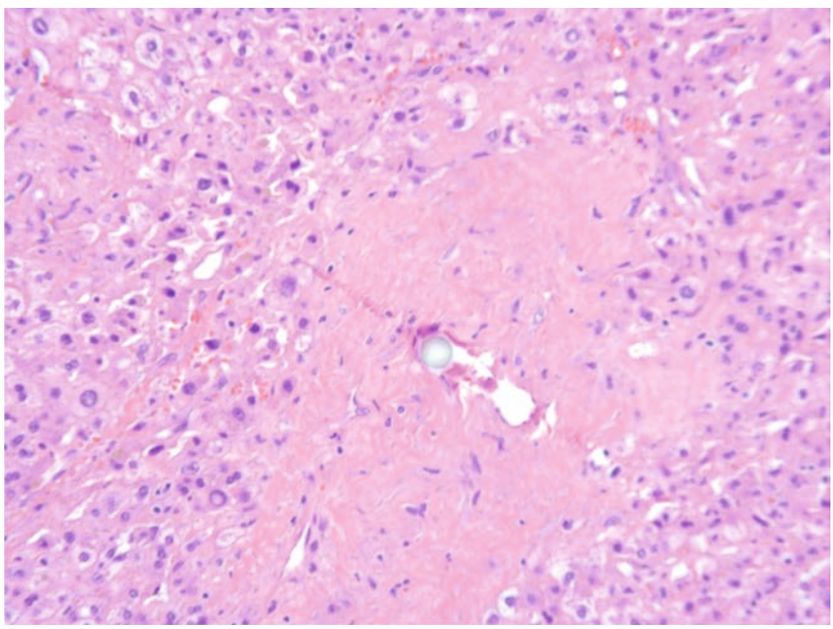

Figure 3. Spheres within the liver. Margin-negative resection specimen shows the embolized spheres.

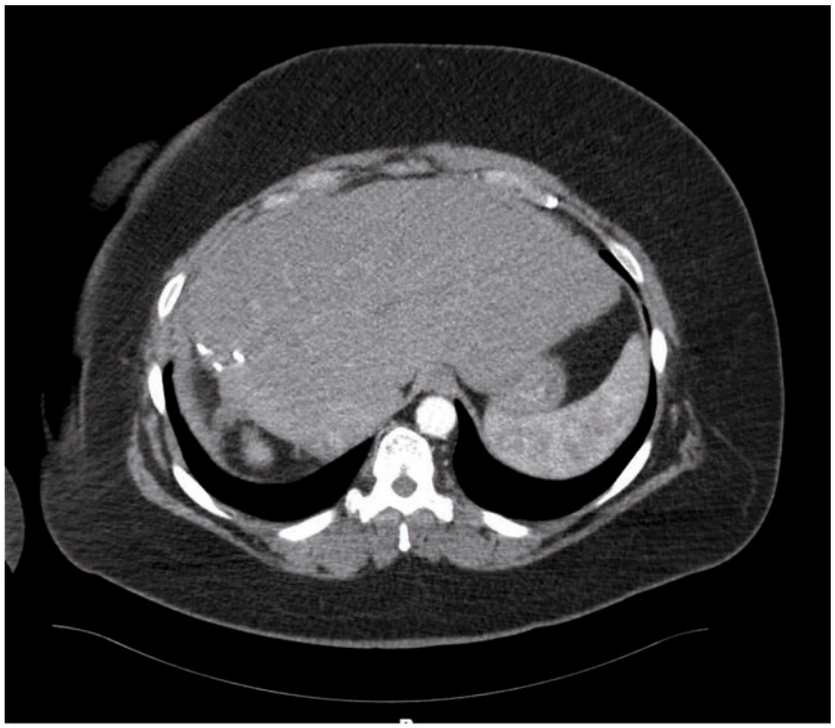

Figure 4. CT scan of liver post-treatment. No evidence of disease 1-year post-chemotherapy/spheres/surgery.

encephalopathy and serum albumin), grading each on a scale from one to three, with one being the mildest condition and three being the most severe. Child–Pugh A, B and C classifications correspond to cumulative scores of 5–6, 7–9 or 10–15, respectively. Child–Pugh A is associated with the best prognosis while Child–Pugh C is associated with the worst. Levy and Sherman provide further information on various staging systems for liver malignancies [40]. **Table 1** compares the different staging systems and the parameters upon which they are based.

Surgical resection is offered to select patients based on specific criteria. If a HCC patient presents with cirrhosis, they may still be a candidate for surgical resection as long as they have normal bilirubin, adequate hepatic reserve, absence of portal hypertension and disease that does not invade major vasculature, such as the inferior vena cava [41]. Unfortunately, only up to 30% of patients initially present with resectable HCC and without evidence of distant metastasis [42]. Even for patients that have undergone surgical resection, the probability of local recurrence after 5 years is as high as approximately 75% [31,43], while overall survival rates range between approximately 30 and 50% [44,45].

While surgical resection is a first-line treatment option for HCC, liver transplantation has gained acceptance as a definitive treatment. Long-term outcomes after liver transplantation for early-stage HCC are excellent. Mazzaferro *et al.* published 4-year overall survival and recurrence-free survival of 85–92% in patients with either a solitary HCC of <5 cm or no more than three tumor nodules of ≤3 cm and absent vascular or extrahepatic spread (Milan criteria) [46]. Cardenes reported a 5-year survival rate of 70% for patients who underwent liver transplantation using the Milan criteria [41].

Surgical resection and/or orthotopic liver transplantation are not always the most optimal due to either unresectable disease or a shortage of donor livers. There are several nonsurgical treatment options. RFA has been used for local tumor control and as a bridge to transplantation [41]. Other nonsurgical options include radiation therapy, transhepatic arterial chemoembolization (TACE), percutaneous ethanol injection, cryotherapy and high-intensity focused ultrasound [9].

EBRT

EBRT has been shown to be effective and well tolerated for patients who are not optimal surgical candidates. Liu *et al.* evaluated a series of 44 patients with unresectable HCC that received EBRT at a median dose of 50.4 Gy [47]. The response rate was 61.4% for tumors of >5 cm. Overall survival at 12, 24 and 36 months was 60.5, 40.3 and 32.0%, respectively. The median survival was 15.2 months. Ben-Josef *et al.* found in a Phase II trial that the addition of concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies with 3D conformal radiation therapy delivered twice-daily at 1.5 Gy up to 90 Gy was associated with a 15.2-month median survival for those patients with HCC with acceptable toxicity. Moreover, the study showed that total dose was the only significant predictor of survival, with little effect of dose below 60 Gy but then a steady increase in survival as the radiation dose was escalated to 90 Gy [48]. In addition, Mornex *et al.* noted the feasibility and efficacy of high-dose 3D conformal radiation therapy in cirrhotic patients in a report of a French Phase II trial, citing a tumor response of over 90% [49]. A dose-escalation study from South Korea of 158 patients with primary HCC showed a dose–response relationship [50]. Response rates

using <40, 40–50 and >50 Gy were 29.2, 68.6 and 77.1%, respectively. Moreover, radiation dose was the only significant factor for predicting an objective response. Data such as these have led investigators to predict that HCC tumors are indeed radiosensitive [51].

Clinically, patients with advanced HCC often present with tumor thrombus, often involving the portal vein, with reports of invasion up to 42% [52]. This type of major vascular invasion is associated with a worse prognosis, with untreated patients having a median survival time of 2.7–4.0 months [43]. EBRT has been reported to be effective in this setting [53]. Investigators from Asia reported a 10.6-month median survival when the radiotherapy volume included the portal vein tumor thrombus and the primary intrahepatic HCC was managed by TACE [54], and a 17.4-month median survival for a thrombus location in the inferior vena cava [55].

SBRT

SBRT, which delivers very high doses over one to five fractions to small volumes, has more recently been evaluated for use in HCC [17,56–59]. Tse *et al.* published the Princess Margaret experience of 31 patients with Child–Pugh A HCC that were deemed unsuitable for standard therapies [57]. These patients received a median dose of 36 Gy (24–54 Gy) over six fractions. The median overall survival was 11.7 months and no patient experienced RILD. The median tumor volume was 173 ml. Data from Asia also support the safety and efficacy of SBRT [60,61].

SBRT has been evaluated as a means to bridge to transplantation. In a study reported by O'Connor *et al.* from the Baylor University Medical Center, ten patients were treated with SBRT to a median dose of 51 Gy in three fractions followed by liver transplantation [58]. The median size of the 11 HCCs in this study was 3.4 cm (range = 2.5–5.5 cm) with a median follow-up of 62 months. The overall survival rate and disease-free survival rate were both 100% at 5 years. Explant pathology showed a complete response rate of 27% with no viable tumor in three out of the 11 tumors. The other eight tumors were stable or had decreased. The treatment was tolerated with minimal toxicity.

In a SBRT Phase I dose-escalation trial, investigators from Indiana University (USA) reported differences in toxicity experienced by 17 patients with either Child–Pugh Class A or B [59].

Table 1. Selected staging systems in hepatocellular carcinoma.

Parameter	Albumin	Bilirubin	INR	Ascites	Encephalopathy	Alkaline phosphatase	Tumor extent/ stage	Portal vein thrombosis	α-fetoprotein	Symptoms	Performance status	Ref.
JIS	✓	✓	✓	✓	✓		✓					[129]
Okuda	✓	✓		✓			✓					[130]
CLIP	✓	✓	✓	✓	✓		✓	✓	✓			[131]
CUPI		✓		✓		✓	✓		✓	✓		[132]
TNM							✓					[133]
BCLC	✓	✓	✓	✓	✓		✓	✓			✓	[134]
GRETCH		✓				✓		✓	✓		✓	[135]

BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of the Liver Italian Program; CUPI: Chinese University Prognostic Index; GRETCH: Groups d'Etude et de Traitement du Carcinoma Hepatocellulaire; INR: International Normalized Ratio; JIS: Japanese Integrated System; TNM: Tumor node metastasis treatment.
Reproduced with permission from [136].

Starting at 36 Gy in three fractions, the dose was escalated in 2 Gy per fraction increments, ending at 48 Gy over three fractions. None of the patients with Child–Pugh Class A had dose-limiting toxicities, while two with Child–Pugh Class B developed grade three liver toxicities when the dose was escalated to 42 Gy over three fractions. For the entire cohort of patients, the complete response, partial response and stable disease rates were 25, 56 and 19%, respectively. At a median follow-up of 24 months, the local control rate was 100%. In fact, the 12-month overall survival for Child–Pugh Class A was 100%, while the Child–Pugh Class B 12-month overall survival was 60%. Six patients in the study were able to undergo orthotopic liver transplantation after SBRT. Two patients had pathological complete responses in the explanted livers, three had a partial response and one had stable disease. Cardenes *et al.* also reported no dose-limiting toxicities in Child–Pugh Class B patients when they were treated with a dose regimen of 40 Gy over five fractions compared with 42 Gy over three fractions received by the Child–Pugh Class A patients [59].

Recently, Andolino *et al.* updated the Indiana University experience, reporting outcomes on 60 patients with liver-confined HCC [56]. Of these patients, 36 were Child–Pugh Class A with a median number of fractions, dose per fraction and total dose of 3, 14, and 44 Gy. There were 24 patients treated with Child–Pugh Class B with a median number of fractions, dose per fraction, and total dose of 5, 8 and 40 Gy, respectively. In this series, 23 patients underwent transplantation with a median time to transplant of 7 months. There were no grade three or greater nonhematologic toxicities. The 2-year local control rate was 90% with a progression-free survival of 48% and an overall survival of 67%. The median tumor volume in this updated series was 27 ml.

Charged particle therapy

Carbon ion therapy is emerging as a potential option in Asia. Kato *et al.* reported results from a Phase I/II trial that treated patients with HCC to a dose of 50–80 Gy with 5-year local control of 81% and survival of 25% [62]. Proton-beam data has suggested efficacy in this setting as well [63,64]. Chiba *et al.* have reported data from Japan with proton-beam therapy to a dose of 72 Gy in 16 fractions for 162 patients with unresectable HCC [65]. The findings of minimal toxicity, an overall survival of 23.5% and a 5-year local control rate of 87% are provocative. In this dataset, the subset of Child–Pugh A patients with solitary tumors had a 5-year survival rate of 53.5%. Other groups have reported similar findings, suggesting that long-term survival may be possible with noninvasive therapies [63,64,66]

Radioembolization

Radioembolization, a form of intravascular brachytherapy, is a safe and effective treatment for HCC [51,67,68]. Like EBRT, radioembolization can also be used for tumor downstaging, stabilization of disease as a bridge to transplantation or palliation [46,69]. In a series of 150 patients, Kulik *et al.* report outcomes on 35 patients who were initially staged as having unresectable T3 disease [70]. After radioembolization, 56% were successfully downstaged to T2 after treatment and of these, 32% were downstaged to a tumor size of ≤3 cm. Moreover, 23% of these patients were ultimately able to undergo orthotopic liver transplant. Survival rates at 1, 2 and 3 years were 84, 54 and 27%, respectively. Data confirming the efficacy of radioembolization from a histopathologic standpoint have been accumulating. In a study of 35 patients with 38 lesions that were treated with ^{90}Y radioembolization prior to transplant, Riaz *et al.* showed that all target lesions showed some degree of histologic necrosis at explant [71]. In patients with lesions of <3 cm, 89% had complete histologic necrosis. Overall, 61% of target lesions showed complete pathologic necrosis.

Prior to the widespread use of radioembolization, TACE was the predominant option for liver-directed therapy [72]. Although no prospective data exist, Salem *et al.* conducted a comparative effectiveness study retrospectively between chemoembolization and ^{90}Y radioembolization in a cohort of 245 patients treated at Northwestern University (IL, USA) [73]. Radioembolization was delivered to 123 patients while 122 were treated with TACE; none of the patients in either cohort had evidence of extrahepatic metastases or portal vein thrombosis. Patients receiving radioembolization had a higher response rate (49 vs 36%). The median survival for patients receiving radioembolization was also longer, although this difference was not statistically significant (20.5 vs 17.4 months; p = 0.232) [73,74]. Salem *et al.* recently presented their

outcomes of 526 radioembolization treatments noting response rates of 42% using the WHO criteria and 57% using European Association for the Study of the Liver (EASL) criteria [75]. Patients with Child–Pugh A disease fared the best, with a median survival of 17.2 compared with 7.7 months in those with Child–Pugh B disease. Patients with Child–Pugh A disease and portal vein thrombosis benefited from treatment, but those with Child–Pugh B disease and portal vein thrombosis had a median survival of only 5.6 months. Raoul *et al.* compared chemoembolization and radioembolization in a prospective randomized trial of 142 patients [74]; however, instead of ^{90}Y-based, ^{131}I-labeled iodized oil (Guerbet LLC, IN, USA) was used. Overall survival was similar between the treatment modalities. Overall survival rates were reported at 6, 12, 24, 36 and 48 months. For the ^{131}I-lipiodol patients, the overall survival rates were 69, 38, 22, 14 and 10%, respectively. For the chemoembolization patients, the overall survival rates were 66, 42, 22, 3 and 0%, respectively. The number of patients achieving a complete versus partial response was similar between the groups.

Cholangiocarcinoma

IHC comprises approximately 10% of all primary liver malignancies. The only known curative treatment for IHC is surgical resection, which is not commonly feasible due to its aggressive and infiltrative nature [76,77]. Even for those that are fortunate enough to receive surgery, local recurrence at the site of resection is common [76,78]. The prognosis for unresectable IHC, even with nonsurgical treatment, is poor, with an expected median survival rate of approximately 9 months and a 5-year overall survival rate of <5% [79].

■ EBRT

EBRT can be used to improve prognosis and lessen morbidity in patients with IHC. Chen *et al.* reported the effectiveness of EBRT in 84 patients diagnosed with unresectable IHC [80]. Of these, 35 patients received EBRT to a median dose of 50 Gy (range 30–60 Gy) in 2 Gy fractions. The median overall survival for the EBRT and non-EBRT groups were 9.5 and 5.1 months, respectively. The 1- and 2-year overall survival rates for the EBRT cohort was 38.5 and 16.4%, respectively, while it was 9.6 and 4.9%, respectively, for the patients who did not receive EBRT.

■ SBRT

SBRT has been evaluated in the setting of IHC. Barney *et al.* explored the use of SBRT at Mayo Clinic (MN, USA) in a cohort of ten patients with 12 unresectable primary tumors (n = 6) or recurrent IHC (n = 6) [81]. SBRT was delivered over three (n = 2) or five (n = 10) consecutive fractions to a median dose of 55 Gy (range 45–60 Gy). After a median follow-up of 14 months, freedom from progression within the SBRT treatment field was 100%, but four patients developed intrahepatic recurrence in other areas of the liver. Overall survival was 83% at 6 months and 73% at 12 months. Five patients experienced grade two nausea and vomiting, while one patient experienced grade five liver failure. As noted above, Tse *et al.* reported the Princess Margaret Hospital experience with SBRT for primary liver malignancies [57]. In their series, the ten patients with IHC had a median survival of 15 months. Ibarra *et al.* reported a 75% 6-month overall survival and a 45% 1-year overall survival in a multicenter study of SBRT for nonresectable primary liver tumors with low rates of toxicity [82].

■ Radioembolization

Radioembolization may also be a therapeutic option for patients with IHC. Ibrahim *et al.* reported results from Northwestern University showing a median overall survival of 14.9 months in the 24-patient study [83]. The median survival was improved (31.8 months) for patients who had an excellent performance status (Eastern Cooperative Oncology Group 0). Over 50% of tumor necrosis was demonstrated using the EASL criteria in 77% of patients. German investigators also suggest potential benefit, reporting the results in 33 patients with ^{90}Y [84]. Median overall survival was 22 months with time to progression of 9.8 months. Similar to the US study, the median survival in patients with Eastern Cooperative Oncology Group 0 was 29.4 months [84].

Metastases

Treatment of liver-only metastases is of significant interest due to the expanding range of treatment options. The term oligometastasis is relevant because there may be subsets of patients who only have a limited number of metastatic tumor clones that can potentially be completely eradicated. Due to the vascular nature of the

liver, it is a common site of metastasis, particularly from primary gastrointestinal cancers, especially for colorectal carcinomas (CRCs) [85]. Approximately 25% of CRC patients have hepatic metastases at the time of diagnosis, while nearly half of all patients with CRC have tumor recurrences in the liver in the span of 5 years [86].

It is with this rationale that oncologists have found that treating liver oligometastases is potentially curative. In the case of CRC, for example, surgical resection is associated with the potential for a long-term cure. The 5-year overall survival rates for selected patients with resected CRC liver metastases are approximately 60% [87–93]. A 10-year survival rate has also indicated that surgical resection is potentially curative, with multiple institutions reporting overall survival of up to approximately 30% [88,91,92,94–97]. In terms of surgical resection for CRC liver metastases, Fong *et al.* have reported that patients with a solitary tumor of <5 cm, long disease-free interval (>1 year), carcinoembryonic antigen of <200 ng/ml and negative surgical margins had 5-year overall survival of 60% [88]. Patients who did not meet these criteria had 5-year OS of only 14% [88]. In this series, patients were not treated with prior systemic chemotherapy. While a large body of literature has been collected on CRC oligometastases over the past 30 years, there are also documented cases of long-term survival from liver oligometastases originating from non-CRCs, such as breast cancers and sarcomas, although treatment options for non-CRC metastases are less defined [98].

As 80–90% of patients with metastatic liver disease are considered unresectable, due to either large tumor size or location, nonsurgical interventions are the only options available for these patients [99]. The possibility of curative treatment for liver metastases raises the question of whether other treatment options can provide similar results to surgical resection when resection is not possible. If so, then what is the maximum number and size of tumors before the chance of survival decreases? Also, what role does tumor location provide in noninvasive therapies?

In patients with liver metastases not appropriate for surgery, RFA is often considered by multidisciplinary tumor boards as a potential option. Aloia *et al.* performed an analysis comparing the efficacy of RFA against surgical resection in the setting of solitary CRC liver metastasis [100]. They noted that RFA, while having similar rates of intrahepatic and extrahepatic failure, had a seven-times higher risk of local failure. The risk of death was also three-times higher with RFA [100]. A study by Otto *et al.* reported a local failure rate of 32%, with a 12-month local control rate of 58% and a 12-month rate of hepatic retreatment of 33% in 28 patients with CRC liver oligometastases [101]. Finally, a study conducted by Livraghi and Solbiati found local failures occurring in 70 out of 179 patients (39%) treated with RFA for CRC liver oligometastases, with an 18-month local control rate of 56% [102]. There has also been a trend of decreasing macroscopic local recurrence with smaller tumor size in patients treated with percutaneous RFA. In 2001, Solbiati *et al.* reported that, in a series of 117 patients with 179 tumors with an average size of 2.8 cm, the patients had a macroscopic local recurrence rate of 39% [103]. In 2006, Solbiati *et al.* reported that, in a series of 121 patients with 320 tumors with an average size of 2.1 cm, the macroscopic local recurrence rate was 14% [104]. Although RFA can effectively provide improved local control in liver oligometastases, RFA may not be optimal due to tumor size and location.

EBRT

Safety and efficacy data supporting the role of conformal partial liver EBRT for the treatment of metastatic colorectal carcinomas was reported by investigators at the University of Michigan (USA) in the 1990s [105]. Robertson *et al.* noted a response rate of 50% in patients treated with hyperfractionated 3D conformal radiation therapy to a maximum dose of 72.6 Gy in fractions of 1.50–1.65 Gy [105]. In this 22-patient study, the median survival was 20 months. The Michigan group has also reported that higher doses are associated with improved median survival in patients with colorectal cancer metastatic to the liver [48,106]. They noted a 17.2-month median survival rate in a series of 47 patients who were treated at 1.5 Gy twice-daily to a median dose of 60.75 Gy along with concurrent continuous-infusion hepatic-arterial floxuridine [48].

SBRT

The SBRT literature for the treatment of liver metastases has been expanding with an evolving foundation of clinical outcomes data [107]. One of the first SBRT studies for liver metastases was conducted at the University of Heidelberg

(Germany), where patients were treated with 14–26 Gy in a single fraction. Forty three of the 55 lesions treated were locally controlled at a median follow-up of 5.7 months. Furthermore, by using a single fraction of 22 Gy, Herfarth *et al.* were able to show a local control rate of 66% after 18 months [108,109]. Hoyer *et al.* also concluded that SBRT is reasonable for treatment with curative intent in a series of 64 patients with 141 CRC tumors (44 of which were unresectable) [110]. While SBRT can be used for palliation, it may also be used to bridge potentially curable patients with oligometastases to complete disease eradication. Adam *et al.* have shown that downstaging of CRC liver metastases to allow tumor resection has a survival benefit, especially in a population of patients that have been pretreated with chemotherapy [111].

A multi-institutional, prospective study conducted by Chang *et al.* at Princess Margaret Hospital (ON, Canada), University of Colorado (USA) and Stanford University (CA, USA) attempted to establish the standard of care therapy for patients with CRC metastases of the liver using SBRT by determining outcomes of a large patient cohort [112]. In their study, they found that active extrahepatic disease correlated with a decrease in overall survival time ($p = 0.04$), coinciding with surgical studies that have established active extrahepatic disease correlating with worse survival in patients undergoing hepatic resection [113–116]. This study limited the maximum number of tumor lesions to four, while having a solitary lesion versus two to four lesions did not provide any survival benefit [112]. They formulated that a three-fraction regimen to a total dose of 48 Gy provided optimal ablative therapy while minimizing radiation toxicity to the liver and surrounding normal tissue.

Recently, Rusthoven *et al.* have reported their experiences from a multi-institutional Phase I/II trial with 47 patients with 63 lesions treated with SBRT [117]. The patients contained one to three lesions, with 6 cm as the individual maximal tumor size allowed. By delivering a total dose of 60 Gy over three fractions, they were able to maintain a 100% local control rate in the patients with tumor sizes of ≤3 cm. However, one patient in the study suffered from grade three or higher toxicity. The median individual maximal tumor diameter was 2.7 cm and the median overall survival was 20.5 months, while the 24-month overall survival rate was 30%.

The main concern with SBRT to the liver is hepatotoxicity. Radiation oncologists are conservative in their dose–volume constraints when treating liver tumors because of concerns of causing RILD. To be safe, a standard guideline of 700 ml of normal liver tissue receiving no more than 15 Gy delivered over three fractions (or 7 Gy in one fraction) has been established in order to minimize toxicities [118]. Also, radiation oncologists must try to keep the radiation dose low enough, such that 30% of the liver volume receives no more than 21 Gy in three fractions (or 12 Gy in one fraction) [119,120].

Radioembolization

Radioembolization for liver metastases is another viable alternative to surgical resection [121]. Kennedy *et al.* reported a modern US experience with a cohort of 208 heavily pretreated patients with metastatic colorectal liver metastases, reporting an encouraging median survival of 10.5 months for responders [122]. In a series of patients treated at Northwestern University and William Beaumont Hospital (MI, USA), Sato *et al.* reported on a cohort of 51 patients with CRC liver metastases who received ^{90}Y radioembolization [123]. Median survival time was 15.2 months. Mulcahy *et al.* reported that ^{90}Y radioembolization for liver metastases resulted in median survival of 14.5 months from time of initial treatment and a time to hepatic progression of 15.4 months after initial treatment [124]. More recently, Nace *et al.* reported a median survival of 17 months in patients without extrahepatic disease and an even longer median overall survival of 18.3 months in the patients without extrahepatic disease that had not received cetuximab prior to radioembolization [125]. The patients in this series had metastatic CRC and were not candidates for surgical resection or RFA, and had received either first- or second-line chemotherapy.

There has been interest in exploring combinations of systemic chemotherapy with radioembolization. Two randomized controlled Phase III trials showed benefits for SIR-SPHERES combined with chemotherapy compared with chemotherapy alone in patients with CRC liver metastases [126,127]. With more effective systemic therapies that have been introduced into the metastatic CRC paradigm, future studies will continue to evaluate potential efficacy of combined modality regimens.

Discussion

Over the last 20 years, significant progress in the localization of hepatic tumors that move with respiration and the careful delivery of focal high-dose EBRT have created new opportunities for noninvasive liver treatment. Technological advances are now leading the way for improved outcomes, with studies documenting dose-related efficacy with low toxicity. Internal radiation with intravascular microsphere brachytherapy has also emerged as a well-tolerated, effective treatment, with a potential role in downstaging to surgery or RFA, as well as palliating patients with large disease burden. **Table 2** summarizes key studies and survival outcomes for patients with primary or metastatic liver disease using different radiotherapy techniques.

Conclusion & future perspective

Patients with primary and metastatic hepatic tumors can significantly benefit from liver-directed radiation therapy. Despite the recent advances in radiation treatment delivery, there are still many unanswered questions that will hopefully be answered over the next 5–10 years.

For metastatic lesions of the liver, the question of a potential cure for oligometastases is indeed appealing. Optimal patient selection, however, is unclear. When should patients who have limited hepatic metastases with a favorable primary cancer be considered for external radiation modalities? How should systemic therapy be integrated with such treatment? What is the optimal number and size of lesions to be considered for a potentially curative, tumoricidal approach?

The case with primary liver malignancies is especially unclear. Focal irradiation of HCC lesions is associated with high in-field control rates but progression outside of the treatment field is common [128]. How best to optimize liver-directed therapies potentially capable of treating microscopic disease in the whole lobe, along with focal EBRT to the macroscopic disease, is an important question. Given the promising charged-particle data, what is the role of radiation sensitizers to improve the excellent 5-year outcomes even further? Is a long-term cure possible without surgery, transplantation or RFA?

Finally, the future possibilities of how best to integrate radioembolization into the existing treatment paradigm for liver malignancies is expanding. With the potential of delivering selective treatment based on tumor blood supply, radiation oncologists have the ability to deliver extremely high doses to a small volume, such as a particular liver segment. Ablation of a focal liver segment by radioembolization could potentially become a standalone, curative treatment. This could yield more options for patients with isolated disease that may not be feasible for resection or RFA due to tumor location within the liver. As systemic therapies continue to evolve and improve, future trials are needed to explore novel combinations of local radiation treatment with such agents.

Table 2. Summary of survival outcomes for patients with primary or metastatic liver cancer who received radiation therapy.

Study (year)	Patients (n)	Histology	Concurrent chemotherapy	Technique	Median survival (months)	Ref.
Salem *et al.* (2007)	123	HCC	No	Radioembolization	20.5	[28]
Liu *et al.* (2004)	44	HCC	No	3D-CRT	15.2	[47]
Ben-Josef *et al.* (2005)	35	HCC	Yes	3D-CRT	15.2	[48]
Tse *et al.* (2008)	31	HCC	No	SBRT	11.7	[57]
Cardenes *et al.* (2010)	17	HCC	No	SBRT	NR	[59]
Chiba *et al.* (2005)	162	HCC	No	Proton therapy	26.4	[65]
Chen *et al.* (2010)	35	IHC	No	3D-CRT	9.5	[80]
Barney *et al.* (2012)	10	IHC	No	SBRT	NR	[81]
Ibrahim *et al.* (2008)	24	IHC	No	Radioembolization	14.9	[83]
Hoffmann *et al.* (2012)	33	IHC	No	Radioembolization	22	[84]
Sato *et al.* (2008)	51	Met	No	Radioembolization	15.2	[123]
Nace *et al.* (2011)	51	Met	No	Radioembolization	18.3	[125]
Van Hazel *et al.* (2004)	11	Met	Yes	Radioembolization	29.4	[127]
Rusthoven *et al.* (2009)	38	Met	No	SBRT	20.5	[117]
Chang *et al.* (2011)	47	Met	No	SBRT	14.4	[112]

CRT: Conformal radiation therapy; HCC: Hepatocellular carcinoma; IHC: Intrahepatic cholangiocarcinoma; Met: Metastasis; NR: Not reported; SBRT: Stereotactic body radiation therapy.

Since so many patients experience liver involvement as a component of their disease, the enlarging range of safe and effective radiation options is indeed appealing. Bolstered by the evolving efficacy data of both internal and external radiation modalities, the promise of better outcomes shines brighter than ever before due to more effective tools in our treatment armamentarium.

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