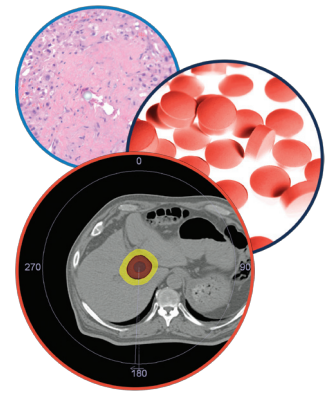
MANAGEMENT PERSPECTIVE

Radiotherapy for liver tumors



Hepatic Oncology

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Practice points

- The incidence of hepatocellular carcinoma (HCC) continues to increase, and patients often present at advanced stages thereby limiting their treatment options. While the historical use of radiotherapy was limited by the risk of radiation-induced liver disease, the development of modern radiotherapy techniques has enabled the safe and effective use of radiotherapy to treat primary hepatic malignancies.
- Stereotactic body radiotherapy (SBRT) is a highly conformal form of radiotherapy which delivers high doses of radiotherapy in a small number of fractions with rapid dose fall-off. Multiple studies have demonstrated the excellent local control and survival rates associated with SBRT for HCC, particularly in patients with early stage (T1–2 tumors).
- Radiotherapy has been safely and effectively delivered in patients who have failed other treatment modalities, including arterially directed therapies.
- Treatment options for patients with HCC with tumor venous thrombosis are particularly limited and survival is poor. Radiotherapy has been shown to improve local control and median survival rates compared with historical controls.
- Continued research on the role of liver-directed radiotherapy, including the optimal fractionation scheme and the role of SBRT in patients receiving systemic therapies, is ongoing.

SUMMARY Many patients with primary hepatic malignancies present with advanced disease that is not suitable for surgical resection, orthotopic liver transplantation, or radiofrequency ablation. Outcomes are particularly dismal in patients with large, unresectable tumors and/or tumor venous thrombosis. Liver-directed radiotherapy, including stereotactic body radiotherapy (SBRT), is able to treat a variety of tumor sizes and tumors with venous involvement and has demonstrated excellent safety and control outcomes. SBRT should be considered a standard option in patients with early-stage hepatocellular carcinoma who are not candidates for surgical resection, orthotopic liver transplantation or radiofrequency ablation. SBRT should be strongly considered in patients with larger tumors and/or tumors with tumor venous thrombosis who have adequate liver function. Radiotherapy should remain a focus of hepatocellular carcinoma research.

KEYWORDS:
• hepatocellular carcinoma • proton therapy • radiation therapy • radiofrequency ablation • stereotactic body radiotherapy • transarterial chemoembolization • tumor venous thrombosis • unresectable hepatocellular carcinoma

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The incidence of primary hepatic malignancies is increasing, with a tripling of the age-adjusted incidence of hepatocellular carcinoma (HCC) in the USA between 1975 and 2005 [1]. In the USA, an estimated 35,560 people will be diagnosed with primary liver or intrahepatic bile duct cancer in the year 2015 [2]. Worldwide, HCC is the second leading cause of cancer-related deaths, accounting for approximately 745,000 deaths per year [3]. While the mainstays of curative intent treatment for HCC are surgical resection and orthotopic liver transplation, or percutaneous thermoablation for lesions less than 2 cm, many patients are not candidates for either therapy due to tumor extent and poor baseline hepatobiliary function. In a SEER-Medicare analysis of 47,040 patients diagnosed with HCC in the USA between 2000 and 2010, only 15% of patients underwent transplantation or resection and 10% of patients underwent ablation [4].

Furthermore, while radiofrequency ablation (RFA) has been employed as definitive therapy and as a bridge to liver transplantation in many patients with HCC [5–7], its efficacy is largely restricted to patients with small tumors, ideally measuring less than 3–4 cm. Local control with RFA declines significantly in larger tumors [8–10]. Proximity of the lesions to large blood vessels also limits the use of RFA, as blood vessels may function as heat sinks, allowing convection of heat away from the lesion itself [11], thereby reducing the degree of necrosis achieved with RFA [12]. Tumor location is also critical. Ablation of lesions in the dome of the liver is challenging due to respiratory motion, and ablation of lesions adjacent to the hilum can damage the biliary tree.

For patients with unresectable HCC who are not candidates for ablation, the National Comprehensive Cancer Network (NCCN) guidelines [13] include several possible treatment options, including arterially directed therapies, systemic therapy and radiotherapy. However, there are currently no randomized data directly comparing these treatment modalities in unresectable HCC.

The use of radiotherapy for the treatment of hepatic tumors was historically limited by concerns over hepatic tolerance and the risk of radiation-induced liver disease (RILD). However, the development of more advanced radiotherapy techniques such as stereotactic body radiotherapy (SBRT) has prompted increased interest in the application of radiotherapy as a potentially curative nonoperative treatment modality for primary hepatic tumors. While there have been no large randomized trials comparing radiotherapy with surgical resection or nonoperative treatments such as RFA or transarterial chemoembolization (TACE), the excellent local control rates and low toxicity in a variety of HCC cohorts make SBRT an attractive nonoperative treatment of HCC and justify its inclusion as a standard treatment option, especially for early-stage HCC not well suited for transplant, surgical resection or RFA. We will discuss the development of modern radiotherapy techniques, the excellent local control and survival rates currently associated with radiotherapy and discuss radiotherapy in the context of limitations associated with the two dominant treatment modalities in unresectable HCC, ablation and arterially directed therapies.

Background

• Development of modern radiotherapy techniques

Historical radiation techniques often required irradiation of the entire liver due to limitations in imaging and treatment delivery [14]. This is turn led to a risk of radiation-induced liver disease (RILD) [15], which can occur 2 weeks to 4 months after radiotherapy and is classically defined as the triad of anicerteric hepatomegaly, ascites and elevated alkaline phosphatase out of proportion to bilirubinemia or transaminitis. The pathologic features of RILD were first described in 1966 and included veno-occlusive injury with chronic changes including hyperemia and hepatic cell atrophy [16]. Patients were treated with doses that were far below those needed for tumor control [15,17] to minimize the risk of RILD, thereby limiting liver-directed radiotherapy to the palliative setting. For example, in the 1991 Emami report, the liver tolerance doses or TD 5/5 (dose expected to result in 5% complication rate in 5 years) were set as 50 Gy for one-third of the liver, 35 Gy for two-thirds of the liver, and 30 Gy for the whole liver [18].

Advancements in radiation treatment planning and delivery techniques led to increased interest in the use of radiotherapy for treatment of hepatic tumors. The development of 3D conformal radiation therapy (3D-CRT) enabled delivery of increased doses of radiotherapy to the tumor while sparing uninvolved portions of the liver, as well as assessment of the interaction between radiation dose, treatment volumes and

toxicity [19,20]. A series of dose-escalation protocols from the University of Michigan based radiotherapy doses on the risk of RILD according to a normal tissue complication probability ('NTCP') model and demonstrated the safety and excellent local control and survival rates with increasing radiotherapy doses [20–22].

Specifically, the Lyman–Kutcher–Burman (LKB)-NTCP model enabled assessment of the dose-volume risk of RILD in patients receiving liver-directed radiotherapy by including the following paramters: the effective volume ('V_{eff}') parameter, which allows volume-dose distrubtion comparisons between plans; the TD50, or tolerance dose associated with 50% chance of complication for uniform liver irradiation; 'm', which represents to the steepness of dose response at TD50; and 'n' which defines the effect of the volume on a scale from zero to one. The refined LKB-NTCP model was employed in a Phase II trial of hyperfractionated conformal radiotherapy with concurrent hepatic arterial chemotherapy in 128 patients (37 with liver metastases, 46 with cholangiocarcinoma and 35 with HCC) who received radiotherapy doses on maximum 10–15% risk of RILD based on the model [23]. Median survival was 15.2 months in patients with unresectable HCC, and tumor dose ≥75 Gy was associated with improved overall survival on multivariate analysis (23.9 months vs 14.9 months, $p < 0.01$).

A trial of 25 HCC patients with Child–Pugh (CP) Class A and B cirrhosis in Lyon, France, demonstrated the feasibility of dose-escalated 3D-CRT in cirrhotic patients. Patients were treated to 66 Gy in 2-Gy fractions, with impressive rates of complete and partial response of 80 and 12% respectively, and local control rates of 78% at median follow-up of 29 months [24]. Among CP B patients, 22% developed grade 4 toxicities, while no CP A patients developed grade 4 toxicity. These data underscored the importance and feasibility of delivering tumoricidal doses of radiotherapy to HCCs.

Outcomes of modern liver-directed radiotherapy

• Stereotactic body radiotherapy

The development of SBRT, which uses multiple conformal beams to deliver high doses of radiotherapy in a single or small number of fractions with rapid dose fall-off [25], has enabled increasing use of radiotherapy to treat HCC. The high radiation doses associated with SBRT are thought to result in vascular injury and an ablative effect on the tumor [26–29] in addition to the double-stranded DNA breakage associated with conventionally fractionated radiotherapy, but the full mechanism underlying SBRT-induced cell death has not been fully determined [28,30–32]. Strategies to account for breathing motion and change in HCC position day-to-day include four-dimensional CT scanning [33–35], abdominal compression [36–39], active breathing control [40,41] and image-guided radiation therapy.

A pilot study of SBRT included nine patients with primary liver tumors treated with 16–66 Gy in one to three fractions demonstrated an objective average response rate of 70% [42]. A Phase I study of SBRT in 41 patients with unresectable, locally advanced HCC (n = 31) and intrahepatic cholangiocarcinoma (n = 10) at Princess Margaret Cancer Centre demonstrated the safety of SBRT. Radiotherapy doses were based on the volume of liver irradiated and the risk of RILD as per the NTCP model detailed above. Doses were escalated within three liver volume-irradiated strata of 5, 10 and 20% risk of toxicity. The median dose delivered was 36 Gy (range 24–54 Gy) in six fractions. There were no cases of RILD or treatment-related early grade ≥4 toxicity within 3 months after SRBT, and maximum tolerated dose was not achieved. While 17% of patients experienced a decline in liver function from CP A to CP B within 3 months of radiotherapy, the contribution from SBRT versus progression of cirrhosis was not known. The median survival was 13.4 months, with one year local control of 65% [43].

While there have been no prospective randomized trials of SBRT published to date, multiple single-arm studies and institutional series have been published with impressive rates of local control and overall survival, with 1-year local control ranging from 64 to 100% and 1-year overall survival ranging from 48 to 100% (Table 1). These series contain a wide variety of patients, and often include patients with advanced disease and patients who have failed prior locoregional therapies, including arterially directed therapies. Several series have included patients with tumor vein thrombosis, CP B cirrhosis, and/or large primary tumors, which rendered them ineligible for other locoregional therapies. Of note, the optimal staging system for predicting prognosis after SBRT is not yet known. Table 1 summarizes the results of several single-arm and retrospective series on SBRT for HCC [43–60].

Table 1. Stereotactic body radiotherapy in hepatocellular carcinoma.

Author	Institution	Design	Pts	CP class	Prior non-RT therapies (%)	Tumor size (range)	TVT (%)	Dose (Gy)	Fx	ORR (%)	1-year OS	1-year LC (%)	Grade ≥3 toxicity (%)	Ref.
Bujold *et al.*	Princess Margaret Hospital	Phase I/II	102	A	52	1.4–23.1 cm	55	36 (24–54)	6	54	55	87	36	[44]
Mendez-Romero *et al.*	Erasmus MC, Netherlands	Phase I/II	8	A, B	NR	0.5–7.2 cm	25	25–37.5	3–5	NR	75	75	12.50	[45]
Kang *et al.*	KIRMS	Phase II	47	A, B	100	1.3–8 cm	11	57 (42–60)	3	76.6	69 at 2 years	95 at 2 years	26	[46]
Cárdenes *et al.*	Indiana	Phase I	17	A, B	23.5	≤6 cm (cumulative)	18	36–48	3–4	81	75	100	18	[47]
Tse *et al.*	Princess Margaret Hospital	Phase I	31	A	61	9–1913 ml	42	36 (24–54)	6	49	48	65	26	[43]
Ibarra *et al.*	Multi-institutional	Pooled Analysis	21	A, B	76.2	9.5–1493.8 ml	NR	30 (18–50)	1–10	26.8	87	64	8 RILD only	[48]
Yamashita *et al.*	Multi-instiutional	Retrospective	79	A, B, C	100	0.6–7 cm	NR	48 (40–60)	4	81	52.9 at 2 years	74.1	No RILD	[61]
Sanuki *et al.*	Tokai University, Japan	Retrospective	185	A, B	60	0.8–5 cm	NR	30–40	5	NR	95	99	13	[49]
Jang *et al.*	KIRMS	Retrospective	108	A, B	100	1–7 cm	NR	51 (33–60)	3	NR	63 at 2 years	87 at 2 years	10[†]	[50]
Yoon *et al.*	Asan Medical Center, Korea	Retrospective	93	A, B	98.9	1–6 cm	0	30–60	3–4	61.2	86	95	6.5 RILD only	[51]
Bibault *et al.*	Lille, France	Retrospective	75	A, B	51	3–4.4 cm	NR	45 (24–45)	3	NR	79	90	16[†]	[52]
Honda *et al.*	Hiroshima, Japan	Retrospective	30	A, B	100	1–3 cm	0	48–60	4–8	96.3	100	100	7	[53]
Yuan *et al.*	Tianjin Medical University, China	Retrospective	22	A, B, C	NR	1.6–9.5 cm	NR	45 (39–54)	3–8	91	73	93	4.5 Grade ≥2	[54]
Huang *et al.*	Taipei, Taiwan	Retrospective	36	A, B, C	100	1.1–12.3 cm	NR	37 (25–48)	4–5	58.6	64 at 2 years	98	3	[55]
Andolino *et al.*	Indiana	Retrospective	60	A, B	10	1–6.5 cm	NR	44 (24–48)	3–5	70	67 at 2 years	90 at 2 years	37	[56]
Son *et al.*	Gyeongsang University, Korea	Retrospective	47	A, B, C	78	3.0–81.3 ml	NR	30–39	3	NR	NR	NR	33 Grade ≥2	[57]
Kwon *et al.*	Catholic University, Korea	Retrospective	42	A, B	81	3.0–81.8 ml	0	30–39	3	85.8	93	72	2	[58]
Seo *et al.*	KIRMS	Retrospective	38	A, B	100	<10 cm	NR	33–57	3–4	63.1	69	79	3	[59]
Louis *et al.*	Liege, Belgium	Retrospective	25	A, B	36	1.8–10 cm	16	45	3	86	79	95	8	[60]

[†]Toxicities may include some redundancies.

CP class: Child–Pugh class; Fx: Fractions; KIRMS: Korea institute of radiological and medical sciences; LC: Local control; NR: Not reported; ORR: Overall response rate (CR+PR); OS: Overall survival; Pts: Patients; RILD: Radiation-induced liver disease; RT: Radiotherapy; TVT: Tumor vein thrombosis.

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Prospective Phase I and II trials from Princess Margaret Cancer Centre of SBRT in 102 patients with locally advanced HCC demonstrated the excellent local control and survival rates of liver-directed radiotherapy. Patients were treated to a mean dose of 36 Gy (range 24–54 Gy) in six fractions delivered every other day over 2 weeks. While all patients had CP A cirrhosis with at least 700 ml of uninvolved liver, the trials did include 56 patients with tumor venous thrombosis. Results were quite impressive despite the number of patients with advanced disease, with an overall response rate of 54% (11% complete response, 43% partial response) and 1-year local control and overall survival rates of 87 and 55%, respectively [44].

In patients with early-stage HCC, retrospective series of SBRT have demonstrated especially impressive results, even in patients treated with lower doses of radiotherapy. Two series from Japan of SBRT for tumors measuring 1–5 cm reported 1-year rates of local control and overall survival of 95–100% and 99–100%, respectively [49,53]. For example, in a series of 185 patients with lesions measuring 0.8–5 cm, patients were treated with SBRT to 30–40 Gy in five fractions, with 1- and 3-year rates of local control of 99 and 91%, respectively, and 1- and 3-year rates of overall survival of 95 and 70%, respectively [49]. A series from Tianjin Medical University in China compared 26 patients who underwent gross total resection (R0) with 22 patients treated with CyberKnife SBRT and found no significant difference in overall survival between the two groups (3-year overall survival measuring 69.2% in surgery vs 57.1% in SBRT, p = 0.49) [54]. Prospective Phase II trials are ongoing at these centers; however, given the excellent control rates seen with SBRT and the comparative poor outcomes associated with arterially directed therapies, SBRT should become standard for patients with early stage HCC tumors that are not suitable for surgical resection or ablation.

For patients with especially large tumors (e.g., >10 cm), TACE is often the primary recommended treatment. However, survival remains poor with TACE alone and radiotherapy in conjunction with TACE may help optimize control. Zhong *et al.* reported a series of 72 patients with HCC tumors measuring ≥10 cm who received TACE followed by SBRT to a median dose of 35.6 Gy (2.6–3 Gy/fraction, six fractions per week). The objective response rate was 76.1% with median survival of 12.2 months, respectively. There were no reported cases of ≥grade 3 toxicity [63].

The optimal dose and fractionation scheme for HCC are not yet known and remain a subject of research. HCC is radiation-sensitive and responses with lower RT doses have been seen, particularly in patients with early-stage disease [49] or impaired hepatobiliary function such as CP B cirrhosis [49,64]. Some dose-escalation series have found improvements in local control and overall survival in patients receiving higher doses of radiotherapy. In a pooled multi-institution analysis of 82 patients with 111 lesions treated with median SBRT doses of 36 Gy (range 18.6–60 Gy) with median biologic effective dose (BED) of 79.2 Gy (range 30.1–180 Gy), 1-year rates of local control and overall survival were 91 and 70%, respectively, and BED >100 Gy was associated with improved local control [65]. Jang *et al.* reported their series of 82 patients with HCC tumors ≤7 cm (median 3.0 cm) who received a median dose of 51 Gy (range 33–60 Gy) in three fractions. There were excellent 2-year rates of local control and overall survival in the entire cohort, measuring 87 and 63%, respectively. In patients receiving SBRT doses >54 Gy, local control and overall survival rates at the time of last follow-up (4.5 years) were 100 and 68%, respectively [50]. No patients experienced classic RILD, while four patients had an elevation in CP score not related to disease progression. These abnormalities resolved with supportive care in three of four patients.

In summary, these results require validation in larger series and randomized trials, but provide impressive evidence supporting the efficacy and highlighting potential applications of SBRT in HCC.

• Charged particle therapy

The role of charged particle therapy, including proton radiotherapy and carbon ion therapy, in HCC is also being explored. The rapid dose fall-off of particle-based radiotherapy can be exploited in the treatment of hepatic tumors to maximize dose to the lesion while minimizing dose to normal hepatic parenchyma and surrounding structures [66]. The largest series of proton radiotherapy was published by the University of Tsukuba and included 318 patients with primarily CP A cirrhosis and HCC who were treated with adjusted doses based on proximity to digestive organs and the porta hepatis [67].

Overall survival at 5 years was 44.6% with only five cases of grade 3 toxicities. In addition, 20% of patients received additional proton radiotherapy for synchronous tumors or salvage with 5-year survival of 51%. A Phase II study of high-dose proton radiotherapy from Loma Linda also included several patients with advanced disease, including 54% outside the Milan criteria and 24% with CP C cirrhosis [68]. Despite the poor prognosis of this cohort, median progression-free survival was 3 years and there were no grade ≥3 toxicities. Additional prospective trials on the use of charged particle therapy for HCC are ongoing.

Treatment of patients with radiotherapy after failure of arterially directed therapies

TACE and transarterial embolization have typically been employed in patients with larger unresectable tumors which are not suitable candidates for ablative techniques. Unfortunately, while arterially directed therapies do provide palliation and improved outcomes when compared with supportive care [69–72], long-term control and survival remain poor. While there have been studies of TACE in conjunction with ablative techniques [73,74] or systemic therapies such as Tamoxifen or 5-fluorouracil [75], there have been no randomized trials of TACE versus radiotherapy or SBRT.

There are also several potential complications and limitations associated with the use of TACE. One meta-analysis reported a 5.6% rate of severe adverse events after TACE, with the most common being liver failure, sepsis and gastrointestinal bleeding [71]. Furthermore, while TACE has been performed in the setting of portal tumor vein thrombosis in patients with otherwise preserved hepatic function and collateral circulation [76], the presence of a tumor vein thrombosis is often a contraindication to arterially directed therapies in many patients, given the risk of treatment-related ischemic injury [77–79]. The efficacy of transarterial radioembolization (TARE), or selective internal radiation therapy (SIRT), also declines significantly in patients with more advanced liver disease or portal vein thrombosis. A prospective cohort study of 291 patients reported median survival of 7.7 months in patients with CP B cirrhosis and 5.6 months in patients with CP B cirrhosis and portal vein thrombosis compared with 17.2 months for patients with CP A cirrhosis [80]. TARE is also not without risks – a retrospective series of 118 patients who received TARE with 90-Y for HCC reported 90-day mortality rates of 18%, with 12 patients experiencing a major complication resulting in death [81,82].

By contrast, radiotherapy is not hampered by the same vascular limitations as arterially directed therapies and has been safely and effectively administered in numerous patients with main branch and occlusive tumor vein thromboses, thereby improving local control, hepatobiliary function and survival (see **Table 2**). In many early series, radiotherapy was employed as salvage therapy, often after several courses of arterially directed therapies **(Table 1)** [83]. For example, in a small series of 24 patients with unresectable HCC who received conventionally fractionated liver radiotherapy to a mean dose of 51.8 Gy after the failure of TACE, 3-year survival was 21.4%, with median survival of 14 months [84]. In a subsequent publication of 398 patients with HCC treated with radiotherapy (81.9% 3D-CRT), 312 patients (78.4%) had previously undergone TACE [83]. The 2-year overall survival was 27.2%, with median survival of 12 months and no reported grade 3 or higher toxicities. On multivariate analysis, tumor size <5 cm, an absence of lymph node involvement, and a BED ≥ 53.1 Gy were associated with improved survival. Of note, CP A cirrhosis was also associated with an improved prognosis compared with CP B disease, but 88 patients (22.1%) with CP B cirrhosis successfully underwent treatment without significant toxicity. Finally, a prospective Phase II trial of 31 patients with HCC who received salvage 3D-CRT after TACE (no more than three courses) demonstrated impressive in-field (radiotherapy target volume) rates of overall response, complete response and partial response rates of 83.9, 22.6 and 61.3% [85]. These series demonstrated both the safety and value of radiotherapy as a salvage treatment modality after TACE. Moreover, these results raise questions about the typical order of treatments in HCC – instead of reserving radiotherapy as a salvage treatment, many patients would likely benefit from earlier administration of radiotherapy to optimize local control and therefore improve overall survival.

Of note, the treatment of patients with HCC with CP C cirrhosis is particularly challenging given their significant risk of death from their underlying hepatobiliary disease. Arterially directed therapies are contraindicated in these patients, and radiotherapy has not been proven

Table 2. Liver directed radiation outcomes for hepatocellular carcinoma with tumor vein thrombosis.

Author	Institution	Study design	Pts	Tumor size (range)	Prior non-RT trtmt (%)	Trtmt	Dose (range) in Gy	Fx	ORR† (%)	1-year OS (%)	MS (mo)	Grade ≥3 toxicity (%)	Ref.
Bujold *et al.*	Princess Margaret Hospital	Prospective	56	1.8–23.1 cm	52‡	SBRT	36 (24–54)	6	NR	44	10.6	36†	[44]
Xi *et al.*	Guangzhou, China	Retrospective	41	NR	100	SBRT	36 (30–48)	6	75.6	50	13	2.40	[86]
Sugahara *et al.*	University of Tsukuba, Japan	Retrospective	35	2.5–13 cm	77.8	Proton	72.6 (55–77) GyE	2.2–5.5 GyE/fx	63 Primary 55.6 TVT	48 at 2 years	22	8.60	[87] [87]
Choi *et al.*	Catholic University, Korea	Retrospective	9	3.9–47.7 ml	83.9§	SBRT	36 (30–39)	3	44.4	43.20	8	16†	[88]
Yoon *et al.*	Asan Medical Center, Korea	Retrospective	412	2–21 cm	NR	3D-CRT + TACE	40 (21–60)	2–5 Gy/fx	28 Primary 39.6 TVT	43	10.6	10	[89] [89]
Rim *et al.*	Korea University Medical Center	Retrospective	45	1.5–17.3 cm	93.3	3D-CRT	61.2 (38–65)	1.8–2.5 Gy/fx	62.3 TVT	52	13.9	2	[90]
Chuma *et al.*	Hokkaido University, Japan	Retrospective	20	6–14.5 cm	55	3D-CRT + intra-arterial-5FU and SubQ-IFN	30–48	6–20	60 TVT	NS	10.6	15	[91]
Huang *et al.*	Kaohsiung Medical Center, Taiwan	Retrospective	326	≥10cm in 39%	NR	3D-CRT	60	20–30	17.1 TVT	17	3.8	0	[92]
Kang *et al.*	Navy General Hospital, Beijing, China	Retrospective	101	NR	NR	SBRT → TACE	40.2 (21–60)	6	88.2	58.8	17	32.4	[93]
						TACE → SBRT			89.2	54.1	15	40.5	[93]
						SBRT			83.3	500	12	30.0	[93]
Lin	Taipei, Taiwan	Prospective	9 7	6.5 cm (median) 13.8 cm (median)	NR	Fractionated SBRT 3D-CRT	45 45	15 25	75 84	NR	6 6.7	NR	[94]

†Grade 3+ toxicity reported for all patients with and without TVT.

‡Did not specify prior trtmt for patients w/ versus w/o TVT.

§Includes additional pts without TVT.

3D-CRT: 3D conformal radiation therapy; CP Class: Child–Pugh class; Fx: Fractions; LC: Local control; KIRMS: Korea institute of radiological and medical sciences; NR: Not reported; MS: Median survival; ORR: Overall response rate (CR+PR), specified response for primary tumor and TVT when available; OS: Overall survival; Pts: Patients; SBRT: Stereotactic body radiotherapy; SubQ-IFN: Subcutaneous interferon; TACE: Trans-arterial chemoembolization; Trtmt: Treatment; TVT: Tumor vein thrombosis.

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effective in retrospective series. Given the significant risk of liver toxicity in these patients, SBRT is not recommended off-study.

Treatment of patients with HCC with tumor vein thrombosis

Treatment options are particularly limited for patients with HCC with tumor vein thrombosis (TVT) of the portal or hepatic veins, and median survival of untreated patients is 2–4 months [95]. These patients are ineligible for many treatments, including surgery, percutaneous ethanol injection and RFA. TACE has had been administered in some retrospective series, but treatment is limited by the risk of liver failure and treatment-related ischemic injury [77–79]. For example, in a meta-analysis of TACE versus supportive care, TACE was associated with a significantly increased risk of posttreatment mortality in patients with TVT of the portal vein on multivariate analysis (odds ratio 3.24; 95% CI: 1.28–8.22; p = 0.013) [71]. Furthermore, while TARE can be more readily performed in the setting of TVT and portal vein thrombosis [96], its pattern of distribution is not always clear due to the disorganized vasculature seen in HCC, potentially resulting in undertreatment of the tumor thrombosis.

Given the poor outcomes and lack of treatment options for patients with HCC with TVT, studies have explored the use of radiotherapy with or without TACE as a potential treatment option. Takagi *et al.* first reported a series of radiation to portal venous tumor thrombosis after arterially directed therapy in 1989, with a histologic and/or angiographic response seen in two of seven patients (29%) [97]. Table 2 summarizes several recent studies of radiotherapy for patients with HCC with TVT [44,86–94]. Response rates to radiotherapy range from approximately 50 to 89.2% [86,93–94,98], with 1-year overall survival rates of 25–58.8% [86,89,93,98–100] and median overall survival of 3.8–22 months [44,86–87,89–90,92–94]. For example, a series of 412 patients with HCC with portal TVT (200 patients with main or bilateral portal TVT, 212 patients with unilateral portal TVT at the first branch point) were treated to a median dose of 40 Gy (range 21–60 Gy) in 2–5 Gy fractions to the portal TVT before or after TACE. Of note, only 16.7% of patients received radiotherapy to the portal TVT and the primary tumor. The response and progression-free rates were 39.6 and 85.6%, respectively, with median overall survival of 10.6 months and 1-year overall survival rate of 42.5%. There was a 10% rate of grade 3–4 hepatotoxicity in the 3 months after completion of radiotherapy, but the treatment combination was otherwise well tolerated [89]. Patients may also benefit from planned multimodality treatment with SBRT and TACE, particularly in instances where the entire tumor and TVT cannot by the radiotherapy target volume. Retrospective series of SBRT with TACE, including a series by Kang *et al.*, have demonstrated impressive rates of local control and median survival [93]. Prospective studies are needed to determine the optimal use of both treatment modalities in patients with HCC with TVT.

There were impressive response rates in a series by Xi *et al.*, where the portal and/or inferior vena cava tumor thrombosis of 41 patients were treated to a median dose of 36 Gy (range 30–48 Gy) in six fractions, with rates of complete response, partial response and stable disease of 36, 39 and 17%, respectively [86]. Median survival was 13 months and 1-year overall survival was 50.3%. Another series by Zhang *et al.* demonstrated a significant improvement in 1-year survival (32 vs 6.9%, p < 0.01) with the addition of radiotherapy to percutaneous transhepatic portal vein stenting with TACE [100]. In another retrospective series of 158 patients with HCC with PVT, patients who received radiotherapy had an improvement in local control and survival compared with patients who only received TACE and did not receive radiotherapy (1-year overall survival of 34.8 vs 11.4%) [101].

Of note, many series of radiotherapy for TVT only radiated the TVT and not the full extent of intrahepatic disease. For example, in a retrospective series of 994 patients with HCC with portal TVT treated at 10 Korean institutions from 1998 to 2011, 427 patients (43%) received radiotherapy to the portal TVT only [102]. Historically, the extent of intrahepatic disease often precluded treatment of both the TVT and intrahepatic disease with radiotherapy; therefore, radiotherapy was limited to the TVT, while TACE was used to target the bulk of the intrahepatic disease. However, as noted in the above discussion of SBRT, recent advancements in treatment delivery have enabled increasing doses of radiotherapy to larger tumor volumes while still safely sparing adequate volumes of uninvolved liver. A series from the University of Tsukuba, Japan, noted the importance of targeting not only the TVT but also active intrahepatic disease. In this series, 35 patients with portal TVT were treated with fractionated proton therapy to a

median dose of 72.6GyE in 2.2–5.5 GyE fractions, with a median survival of 22 months and median local progression-free survival of 21 months [87]. There was a significant difference in overall survival in patients who received proton therapy to the portal TVT alone versus patients who received proton therapy to the portal TVT and additional sites of active disease.

The optimal fractionation scheme for treatment of TVT is also a matter of study. In a series by Kim *et al.* of 3D-CRT for HCC with portal TVT, 59 patients were treated to a dose of 30–54 Gy in 2–3 Gy daily fractions, or a BED of 39–70.2Gy_{10} assuming an α/β ratio of 10. On multivariate analysis, BED ≥ 58 Gy_{10} was significantly associated with an increased response rate. An objective response was seen in 27 patients (45.8%), with median survival in responders of 10.7 months versus 5.3 months in nonresponders [103]. Other series have focused on a hypofractionated approach. Bujold *et al.* reported the largest series of SBRT for TVT as part of their Phase I/II trials of HCC for SBRT. A total of 56 patients with TVT were treated to a median dose of 36 Gy (range 24–54 Gy) in six fractions [44], with 1-year overall survival of 44% and median survival of 10.6 months. The presence of TVT was the strongest adverse prognostic factor for survival on multivariate analysis (HR 2.47; 95% CI: 1.25–4.88; p = 0.01).

In summary, the outcomes in these series represent substantial improvements in outcomes post-radiation therapy compared with historical data. Given the dismal results typically seen in patients with HCC with TVT, broader administration of radiotherapy would benefit many patients.

Ongoing investigations

Further study is needed to determine the optimal role of SBRT in the treatment of unresectable HCC, the optimal staging system to predict prognosis after SBRT, the most suitable patients for SBRT and the risk/benefit ratio in different patient subsets, especially in locally advanced HCC with main portal vein tumor thrombosis and/or small bulk extrahepatic HCC. For patients with advanced HCC, RTOG 1112 [104], a Phase III randomized trial of sorafenib with or without SBRT in patients, is currently accruing and will provide valuable prospective data on the impact of SBRT on overall survival in HCC patients treated with sorafenib. Specifically, the trial is open to accrual for patients with unresectable Barcelona Clinic Liver Cancer (BCLC) stage B (intermediate) or C (advanced) HCC who are not candidates for RFA or TACE, or were refractory to TACE. Patients with vascular involvement (including the inferior vena cava or portal vein) and large tumors (including patients with >40% of liver volume replaced by HCC) are eligible for enrollment and will be stratified between the two treatment arms. To assess the impact of SIRT in BCLC stage B and C HCC, a currently accruing study in Singapore [105] is randomizing patients with locally advanced HCC to sorafenib versus SIRT with SIR-Spheres (SIRTex Medical, IL, USA). The protocol is open to patients who are not candidates for resection, transplant or ablation and who have had at most two prior courses of hepatic arterially directed therapies. Of note, complete main portal vein thrombosis is one of the exclusion criteria for this protocol.

The role of SBRT versus TACE in patients with HCC is being explored via a Phase III trial at Loma Linda University Medical Center of proton beam radiotherapy versus TACE [106]. Based on single-arm trials and retrospective series, SBRT appears to provide better cancer control outcomes compared with TACE, but this trial will provide an important prospective assessment of local control and survival.

Conclusion

While the incidence of HCC increases worldwide, treatment of patients with unresectable HCC remains challenging. Adoption of radiotherapy has been limited in some instances by recollections of historical series of palliative liver radiotherapy, but it is important to remember that these series were conducted prior to the development of modern radiotherapy techniques and therefore used doses of radiotherapy which were far too low to impact local control or survival. As the field of radiation oncology has advanced, liver-directed radiotherapy has become a safe and effective treatment option for patients with HCC. The multiple series cited above highlight this point and represent the successful implementation of SBRT at numerous institutions worldwide. SBRT should be considered a standard treatment option in patients with early-stage HCC who are not candidates for orthotopic liver transplantation, surgical resection or RFA. Specifically, we would recommend SBRT prior to arterially directed therapies for patients with single or few HCC lesions measuring 3–6 cm. Radiotherapy should not be

excluded for patients with larger tumors (6–10 cm) as these patients can be safely treated if there is a sufficient volume of uninvolved liver. Charged particle therapy, which is characterized by sharper dose fall-off, may be of particular benefit to these patients.

Cooperation across specialties is key to optimizing patient care. At our institution, all hepatobiliary patients are discussed at a weekly multidisciplinary tumor board with hepatobiliary and transplant surgery, medical oncology, radiation oncology and interventional radiology. We favor enrollment of patients on appropriate clinical trials whenever feasible. As discussed above, ongoing clinical trials, including RTOG 1112, will provide valuable information on the role of SBRT in the treatment of advanced HCC. Enrollment onto RTOG 1112 is particularly important for patients with tumor vein thrombosis given the especially poor outcomes seen in this patient population. For patients with advanced HCC who are not suitable candidates for sorafenib, we would consider SBRT off-protocol. In patients who fail TACE, enrollment onto clinical trials of SBRT such as RTOG 1112 should be encouraged whenever possible. We recognize that there may be a small window to treat some of these patients who have failed prior therapy and therefore if clinical trial enrollment were not possible we would recommend SBRT off-protocol. Of note, we would not recommend SBRT off-protocol for patients with CP C cirrhosis. Of course, collection of outcomes on registries is important, especially for higher-risk patients.

In summary, further research on the treatment of unresectable HCC is needed, ideally in the form of randomized controlled trials. Radiotherapy is a safe treatment option for many patients who are not candidates for other treatment options such as resection and ablation and should be a focus of research. Many patients will benefit from increased integration of radiotherapy into current treatment paradigms.

Future perspective

Multiple studies have demonstrated that radiotherapy can be safely and effectively delivered in patients with primary hepatic malignancies, including HCC. The local control and survival rates from these studies are impressive. Furthermore, while promising Hepatitis C treatments have recently emerged [107–110], it is likely that over the next decade the incidence of HCC will continue to increase in the US and worldwide. Given the number of patients who present with advanced disease and are therefore not eligible for surgical resection, orthotopic liver transplation or radiofrequency ablation, the application of liver-directed radiotherapy must remain a focus of research. The results of ongoing clinical trials, including RTOG 1112, will provide valuable data on the role of SBRT in patients with advanced HCC receiving Sorafenib. Further studies are needed to determine the optimal fractionation pattern and patient characteristics for liver-directed radiotherapy.

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