Role and Future Directions of External Beam Radiotherapy for Primary Liver Cancer

Florence K. Keane, MD[1], and Theodore S. Hong, MD[1]

Abstract

The incidence of primary liver cancers continues to increase in the United States and worldwide. The majority of patients with primary liver cancer are not candidates for curative therapies such as surgical resection or orthotopic liver transplantation due to tumor size, vascular invasion, or underlying comorbidities. Therefore, while primary liver cancer is the sixth-most common cancer diagnosis worldwide, it represents the second leading cause of cancer-related deaths. Radiotherapy traditionally played a limited role in the treatment of primary liver cancer due to concerns over hepatic tolerance and the inability to deliver a tumoricidal dose of radiotherapy while still sparing normal hepatic parenchyma. However, the development of modern radiotherapy techniques has made liver-directed radiotherapy a safe and effective treatment option for both hepatocellular carcinoma and intrahepatic cholangiocarcinoma. An increasing body of literature has demonstrated the excellent local control and survival rates associated with liver-directed radiotherapy. These data include multiple radiotherapy techniques and modalities, including stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and charged particle therapy, including proton therapy. In this review, we discuss the development of liver-directed radiotherapy and evidence in support of its use, particularly in patients who are not candidates for resection or orthotopic liver transplantation. We also discuss future directions for its role in the management of primary liver cancers.

Introduction

The incidence of primary liver cancer continues to increase in the United States and worldwide. In the United States, it is estimated that there were 39 230 diagnoses and 27 170 deaths from liver and intrahepatic bile duct cancer in the year 2016.[1] Worldwide, hepatocellular carcinoma (HCC) is the sixth most common cancer diagnosis but is the second leading cause of cancer-related deaths, with approximately 745 000 deaths each year[2] and 5-year overall survival (OS) of less than 12%.[3] These outcomes are due in large part to the fact that many patients present with advanced disease and are therefore not candidates for curative treatment modalities such as surgical resection, orthotopic liver transplantation, or radiofrequency ablation. In intrahepatic cholangiocarcinoma (ICC), surgical resection is considered the only curative treatment modality. However, only patients with early-stage disease, such as solitary tumors without vascular invasion or nodal or distant metastases, are candidates for resection. Even in those patients who undergo resection, survival is poor, with a median 5-year OS of 25% to 35%.[4-6] Nearly 70% of patients are not candidates for resection. Median survival is dismal in this population, ranging from 2.3 to 9 months.[7]

Treatment options for patients with advanced primary liver cancer who are not candidates for curative therapies include

[1] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

Corresponding Author:
Florence K. Keane, Department of Radiation Oncology, Massachusetts General Hospital, 32 Fruit Street, Yawkey 7, Boston, MA 02114, USA.
Email: fkeane@partners.org

systemic therapy, arterially directed therapies, and radiotherapy.[8] Liver-directed radiotherapy traditionally had a limited role in the treatment of liver cancer due to concerns over the risk of radiation-induced liver disease (RILD). However, with the development of modern radiotherapy techniques, liver-directed radiotherapy has emerged as an intriguing and effective treatment modality for both HCC and ICC. In this review, we will discuss the development of liver-directed radiotherapy, current evidence in support of its use, and future directions for its role in the management of primary liver cancer.

Hepatic Tolerance to Radiotherapy

Prior to the development of modern conformal radiotherapy, liver-directed radiotherapy often required treatment of the entire liver due to concerns over organ motion and target identification. Treatment of the entire liver was in turn associated with an increased risk of RILD, even at relatively low doses. For example, Radiation Therapy Oncology Group (RTOG) 84-05, a dose escalation study of a trial of whole-liver radiotherapy for patients with solitary or multiple hepatic metastases, closed after 10% of patients treated with 33 Gy in 1.5 Gy twice-daily fractions developed grade 3 radiation hepatitis.[9] There were no cases of radiation hepatitis among patients treated to 27 to 30 Gy, but dose escalation to higher, potentially tumoricidal doses was not feasible.

Classical RILD is characterized by the development of ascites, anicteric hepatomegaly, and elevated alkaline phosphatase with minimal increase in bilirubin and may present as early as 2 weeks or as late as 4 months after the delivery of radiotherapy. The pathologic features of RILD were first described by Reed and Cox in 1966[10] and include veno-occlusive damage with fibrin deposition in central veins. Although the precise mechanism underlying its development is not known, radiation-induced fibrosis is thought to occur in the setting of increased transforming growth factor β expression after radiotherapy, which in turn increases fibroblast migration and collagen deposition.[11]

The risk of developing RILD is also known to vary based on hepatic function, with an increased risk seen in patients with underlying impaired hepatobiliary function. Patients receiving liver-directed radiotherapy for HCC have been found to have an increased risk of RILD when compared with patients receiving the same dose of radiotherapy for liver metastases.[12] Retrospective series have also demonstrated an increased risk of grade ≥2 RILD among patients with Child-Pugh (CP) score B cirrhosis as compared to those patients with CP A cirrhosis.[13] Although many patients recovered from RILD with supportive care, some experienced persistent hepatic damage. Therefore, given the risk of RILD and the resulting inability to deliver a tumoricidal dose of radiotherapy, liver-directed radiotherapy was primarily restricted to the palliative setting.

Development of Modern Radiotherapy Techniques

The development of conformal radiotherapy planning and delivery techniques enabled not only delivery of escalated

doses of radiotherapy but also precise measurement of the radiotherapy dose delivered to both a tumor and surrounding dose-limiting normal structures. These data in turn facilitated better understanding of the interaction between dose and toxicity. The Emami's report first described guidelines for hepatic tolerance based on literature reports of toxicity.[14] Later studies provided a more refined, prospective assessment of the interaction between radiotherapy dose, the irradiated volume of uninvolved parenchyma, and risk of hepatotoxicity. The University of Michigan conducted a series of dose escalation protocols of hyperfractionated conformal radiotherapy with concurrent hepatic arterial chemotherapy and based the total radiotherapy dose on a maximum 10% to 15% risk of RILD as per a normal tissue complication probability (NTCP) model.[12] The NTCP model included several parameters designed to assess the interaction between tumor dose and volume, such as the effective liver volume (Veff), which in turn enabled comparison between radiotherapy treatment plans and modeling of toxicity risks. The median radiotherapy dose was 61.75 Gy in twice-daily 1.5-Gy fractions. Total radiotherapy doses ≥75 Gy were found to be associated with improved OS (23.9 vs 14.9 months, $P < .01$). Of the total cohort of 128 patients, 35 had HCC and 46 had ICC, with median OS of 15.2 and 13.3 months, respectively.

With the development of conformal radiotherapy, it was also possible to deliver tumoricidal doses of radiotherapy to patients who were not candidates for curative treatments due to underlying hepatobiliary function. A prospective phase II trial of three-dimensional (3D) conformal radiotherapy in Lyon, France,[15] enrolled 27 patients with CP Class A and B cirrhosis with either 1 tumor nodule measuring ≤5 cm or 2 nodules measuring ≤3 cm. Patients were treated to a total dose of 66 Gy in 2-Gy fractions. Response rates were impressive, with a complete response rate of 80% and a partial response rate of 12%. At a median follow-up of 29 months, local control was 78%. There were no instances of grade 4 toxicity in patients with CP A cirrhosis. Among patients with CP B cirrhosis, 2 (22%) of 11 had grade 4 toxicity, all of whom had grade 3 abnormalities at the time of enrollment. These results demonstrated the feasibility of liver-directed radiotherapy in patients with cirrhosis.

Intensity-Modulated Radiotherapy and Stereotactic Body Radiotherapy

The development of highly conformal radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), enabled further dose escalation. These are highly precise forms of radiotherapy which uses multiple beams to deliver high doses to a target with rapid dose falloff, thereby minimizing dose received by adjacent normal tissues. Intensity-modulated radiotherapy is typically administered on a conventional or hypofractionated schedule. By contrast, SBRT is delivered over the course of a few fractions, as opposed to daily treatments over several weeks. In addition to traditional methods of radiotherapy-

induced cell death with DNA damage, SBRT is also thought to have an ablative impact, potentially through vascular injury.[16-22] Given the high doses delivered with both IMRT and SBRT, precise tumor identification, motion management, and advanced treatment delivery systems are essential to ensure safe and effective delivery of treatment.

Radiotherapy Treatment Planning and Delivery

Accurate target identification is essential to ensure maximal dose is delivered to the tumor while also minimizing dose delivered to adjacent normal structures. The classical enhancement patterns of both HCC and ICC have been previously described, with HCC demonstrating rapid arterial enhancement with washout on delayed phases[23,24] and ICC typically showing delayed enhancement.[25-27] However, enhancement patterns for both HCC and ICC can vary significantly on both computed tomography (CT) and magnetic resonance imaging (MRI) due to tumor size and vascular involvement.[24,25,28,29] Multiphasic CT and/or MRI at the time of treatment planning is therefore essential to accurately define the target volume. The RTOG consensus guidelines for HCC recommend contouring the gross tumor volume (GTV) as the union of GTVs from each phase of contrast.[30] Target identification is particularly challenging in patients with tumor vascular involvement or more infiltrative lesions. For example, significant interobserver variability was found among 11 gastrointestinal radiation oncologists when defining the GTV in a patient with portal venous invasion.[30] At our institution, we found that intravenous contrast enhancement patterns varied across lesions and that there was no one optimal phase for tumor visualization.[25] Similar results were demonstrated in patients with ICC.[25] Magnetic resonance imaging–based simulation for radiotherapy planning may be especially helpful in target definition in patients with more infiltrative lesions not easily identified on CT scans.

Immobilization is critical to ensure patients remain in a consistent and reproducible position for both treatment planning and treatment delivery. Target and organ motion must be also assessed at the time of treatment planning. A four-dimensional CT, with individual CT scans obtained throughout the respiratory cycle, facilitates precise target identification. Use of a free-breathing CT is not recommended as this may result in a marginal miss and/or overtreatment of uninvolved hepatic parenchyma. Fiducial markers are typically placed prior to radiotherapy planning. In addition to facilitating assessment of motion,[31-33] fiducial markers are also an integral component of patient setup and treatment delivery and are often more precise than aligning to bony anatomy. For those patients with significant target motion, abdominal compression may be employed to decrease organ and target motion.[34-37] Active breathing control,[36] or respiratory gating, wherein radiotherapy is only delivered during certain portions of the respiratory cycle, may also be used to decrease radiotherapy received by normal hepatic parenchyma. Of note, details of patient immobilization and assessment of intrafraction motion also vary based on the brand of linear accelerator used by a given center. CyberKnife uses real-time orthogonal X-ray tracking of implanted fiducial markers, whereas the Varian Trilogy and the Elekta Synergy use on-board cone-beam CTs.

Outcomes of Modern Liver-Directed Radiotherapy

Prospective phase I and II trials of liver-directed SBRT at Princess Margaret Cancer Centre demonstrated the safety and efficacy of liver-directed radiotherapy in HCC. In the initial phase I series,[38] 41 patients with unresectable HCC (n = 31) or ICC (n = 10) were treated with liver-directed SBRT, with radiotherapy dose based on the maximum allowed Veff and NTCP model detailed above. Dose was escalated within 3 strata of 5%, 10%, and 20% risk of toxicity. The maximum tolerated dose was not reached, and median dose delivered was 36 Gy (range: 24-54 Gy). There were no cases of RILD or grade ≥4 toxicity at 3 months. Median survival was 13.4 months, and 1-year local control was 65%. A subsequent publication of phase I and II trials[39] conducted at Princess Margaret Cancer Centre included 102 patients with locally advanced HCC, the majority of whom had underlying cirrhosis (38% hepatitis C-related, 28% hepatitis B-related, 25% alcohol-related). Patients were treated to a median dose of 36 Gy (range: 24-54 Gy) in 6 fractions. All patients had CP A cirrhosis with at least 700 mL of uninvolved liver. The majority of patients (55%) also had tumor venous thrombosis. Median OS was 17 months, with 1-year local control of 87%. There was 30% rate of grade ≥3 toxicity, but no classic episodes of RILD. Seven patients died within a year after treatment, 2 of whom experienced liver failure in the setting of tumor venous thrombus progression.

Numerous prospective single-arm trials and retrospective series have demonstrated impressive results with liver-directed radiotherapy, with 1-year OS rates ranging from 48% to 100% and local control of 64% to 100%[38-50] (Table 1[38-41,43-46,48-61]). These results are especially encouraging, considering that many series include patients with advanced disease, patients with underlying cirrhosis, and patients who failed prior therapies.

The utility of radiotherapy is especially evident in advanced HCC. Although ablative techniques such as radiofrequency ablation and microwave ablation can be used as definitive therapy in patients with smaller tumors,[63-65] the efficacy declines in larger lesions.[66,67] Arterially directed therapies, including transarterial chemoembolization (TACE), can provide palliation and improve outcomes for patients with advanced HCC compared with supportive care,[68-70] but survival and local control remain poor. Radiotherapy therefore initially gained increasing use as a salvage treatment after arterially directed therapies. For example, a series of 398 patients treated with 3D conformal radiotherapy included 312 patients who previously received TACE. Median OS was 12 months. Although 88 (22.1%) patients had CP B cirrhosis, there was no case of grade 3 or higher toxicities.[71] The encouraging results associated with liver-directed

Table 1. Outcomes After Liver-Directed Radiotherapy for Hepatocellular Carcinoma.

Study	Design	Year	Type of RT	Pts	CP Class	Prior Liver-Directed Therapies	Tumor Size (range)	TVT	Multiple Lesions Treated	Dose (Gy)	ORR	1-year LC	1-year OS	Grade ≥3 Toxicity
Bujold et al[39]	Phase I/II	2013	Photon	102	A	52%	1.4-23.1 cm	55%	61%	36 (24-54)	54%	87%	55%	36%
Hong et al[51]	Phase II	2015	Proton	44	A, B	45.8%	1.9-12 cm	29.5%	27.2%	58 GyE (15.1-67.5)	NR	94.8% at 2 y	63.2% at 2 years	2.3%
Bush et al[52]	Phase III	2016	Proton	33	A, B	NR	3.2 cm (1.8-6.5)	0%	54%	70.5 GyE	NR	88% at 2 years	59% at 2 years[a]	NR
Nakayama et al[53]	Retrospective	2009	Proton	318	A, B	45.3%	NR	13.8%	5.3%	72.6 GyE (55.0-79.2)	NR	83.% at 5 years	89.5%	1.6%
Kang et al[44]	Phase II	2012	Photon	47	A, B	100%	1.3-8 cm	11%	17%	57 (42-60)	76.6%	95% at 2 years	69% at 2 years	26%
Bush et al[54]	Phase II	2011	Proton	76	A, B, C	NR	5.5 cm	5%	14.5%	63 GyE	NR	60% PFS at 3 years[b]	70% at 3 years[c]	0%
Cárdenes et al[45]	Phase I	2010	Photon	17	A, B	23.5%	≤6 cm (cumulative)	18%	30%	36-48	81%	100%	75%	18%
Tse et al[38]	Phase I	2008	Photon	31	A	61%	9-1913 mL	42%	1-3 lesions	36 (24-54)	49%	65%	48%	26%
Ibarra et al[43]	Pooled Analysis	2012	Photon	21	A, B	76.2%	9.5-1493.8 mL	NR	23.8%	30 (18-50)	26.8%	64%	87%	8% RILD only
Yamashita et al[50]	Retrospective	2014	Photon	79	A, B, C	100%	0.6-7 cm	NR	NR	48 (40-60)	81%	74.1%	52.9% at 2 years	No RILD
Sanuki et al.[40]	Retrospective	2013	Photon	185	A, B	60%	0.8-5 cm	NR	No	30-40	NR	99%	95%	13%
Jang et al[46]	Retrospective	2013	Photon	108	A, B	100%	1-7 cm	NR	13%	51 (33-60)	NR	87% at 2 years	63% at 2 years	10%[a]
Yoon et al[55]	Retrospective	2013	Photon	93	A, B	98.9%	1-6 cm	0%	10.8%	30-60	61.2%	95%	86%	6.5% RILD only
Huertas et al[56]	Retrospective	2015	Photon	77	A, B	15.6%	0.7-6.3 cm	NR	13%	45 (15-60)	NR	99%	81.8%	5.2%
Bibault et al[48]	Retrospective	2013	Photon	75	A, B	51%	3-4.4 cm	NR	39.6%	45 (24-45)	NR	90%	79%	16%[d]
Honda et al[41]	Retrospective	2013	Photon	30	A, B	100%	1-3 cm	0%	No	48-60	96.3%	100%	100%	7%
Yuan et al[49]	Retrospective	2013	Photon	22	A, B, C	NR	1.6-9.5 cm	NR	No	45 (39-54)	91%	93%	73%	4.5% grade ≥2
Andolino et al[57]	Retrospective	2011	Photon	60	A, B	10%	1-6.5 cm	NR	15%	44 (24-48)	70%	90% at 2 years	67% at 2 years	37%
Son et al[58]	Retrospective	2010	Photon	47	A, B, C	78%	3.0-81.3 mL	NR	NR	30-39	NR	NR	NR	33% grade ≥2
Kwon et al[59]	Retrospective	2010	Photon	42	A, B	81%	3.0-81.8 mL	0%	35.7% multifocal	30-39	85.8%	72%	93%	2%
Seo et al[60]	Retrospective	2010	Photon	38	A, B	100%	<10 cm	NR	NR	33-57	63.1%	79%	69%	3%
Fukumitsu et al[61]	Retrospective	2009	Proton	51	A, B	64.7%	2.8 cm (0.8-9.3 cm)	NR	39.2%	66.6 GyE	76.4%	94% at 3 years	49.2% at 3 years	3 patients grade ≥2

Abbreviations: CP, Child-Pugh cirrhosis; CR, complete response; Fx, fractions; LC, local control; PFS, progression-free survival; Pts, patients; ORR, overall response rate (CR + PR); OS, overall survival; NR, not reported; PR, partial response; RT, radiotherapy; RILD, radiation-induced liver disease; TVT, tumor vein thrombosis.

Adapted from Keane et al.[62] Copyright © 2016 Karger Publishers, Basel, Switzerland.

[a]OS result includes patients treated with transarterial chemoembolization (TACE) alone.

[b]For patients within Milan criteria.

[c]For patients who went on to liver transplantation.

[d]Toxicities may include some redundancies.

radiotherapy suggest that many patients, particularly those with larger tumors, may benefit from earlier use of radiotherapy or integration of radiotherapy with arterially directed therapies. For example, in a series of 72 patients with tumors ≥10 cm who received TACE followed by SBRT, the objective response rate was 76.1% and the median survival was 12.2 months. There were no cases of grade ≥3 toxicities.[72]

Of note, although there are no completed randomized trials of radiotherapy versus arterially directed therapy, the interim analysis of a randomized controlled trial of proton therapy versus TACE for patients with HCC within the Milan or San Francisco criteria reported encouraging results.[52] In addition to a decrease in hospitalization days and needed for retreatment with proton therapy, there was also an improvement in both 2-year local control (88% vs 45%, $P = .06$) and progression-free survival (48% vs 31%, $P = .06$) with proton therapy, suggesting that with longer follow-up, a statistically significant difference may emerge. This trial is discussed in greater detail in the section "Charged Particle Therapy."

In patients with early-stage HCC, liver-directed radiotherapy is associated with especially impressive outcomes. Two series from Japan of tumors measuring 0.8 to 5 cm treated to 30 to 40 Gy in 5 fractions reported 1-year OS rates of 99% to 100% and 1-year local control rates of 95% to 100%.[40,41] A retrospective comparison of gross total resection versus radiotherapy in 26 patients with HCC found similar rates of OS at 3 years (69.2% vs 57.1%, $P = .49$).[41] These results are important as some patients with smaller tumors may not be optimal candidates for resection or ablation due to tumor location. For example, proximity of lesions to blood vessels may hamper the efficacy of ablation as blood vessels may allow convection of heat away from the lesion.[73] Tumors located in the dome of the liver or adjacent to the porta hepatis are also challenging targets for ablative therapies. For these patients, liver-directed therapy represents a safe and effective treatment modality.

The optimal dose and fractionation for liver-directed radiotherapy remains a subject of research. Retrospective series have reported improvement in outcomes with dose escalation, particularly in patients with larger tumors. For example, in a series of 82 patients with HCC with tumors measuring up to 7 cm, total radiotherapy dose ≥54 Gy was associated with a 100% local control rate and 68% OS rate at 4.5 years. There were no episodes of RILD.[46] A retrospective series of liver-directed conformal radiotherapy from South Korea also demonstrated an improvement in survival rates with increasing radiotherapy doses, with tumor response rates measuring 29.2% in patients treated with total doses <40 Gy, 68.6% in patients treated with total doses of 40 to 50 Gy, and 77.1% in patients treated to total doses >50 Gy.[74] Although control is improved with larger doses of radiotherapy, particularly in larger lesions, smaller total doses of radiotherapy may be sufficient, particularly in patients with smaller primary tumors or those with CP B cirrhosis. This is particularly important as many patients with HCC and ICC have compromised hepatobiliary function and would therefore especially benefit from increased sparing of uninvolved hepatic parenchyma. For example, a retrospective series of 185 patients

with HCC with tumors measuring 0.8 to 5 cm treated to 30 to 40 Gy in 5 fractions reported 3-year local control of 91% and OS of 70%.[40] Further prospective study is needed.

Hepatocellular Carcinoma With Tumor Venous Thrombosis

Management of patients with tumor venous thrombosis is particularly challenging. These patients are not candidates for traditional curative therapies and have especially poor outcomes, with reported median survival of less than 4 months.[75] Arterially directed therapies have traditionally been the cornerstone of management in patients with advanced HCC who are not candidates for resection or ablation. However, in patients with portal tumor vein thrombosis (TVT), arterially directed therapies are associated with increased risk of mortality and are often contraindicated.[76] In addition to the inherent risks associated with arterial embolization in a patient with portal vein thrombosis, the presence of a TVT has also been shown to alter the vasculature in HCC. This in turn interferes with effective localization of arterially directed therapies such as TACE or selective internal radiation therapy. Unlike arterially directed therapies, external beam radiotherapy does not rely on preserved hepatic vasculature for efficacy.

Multiple series of liver-directed radiotherapy have included patients with HCC with tumor venous thrombosis. For example, in the prospective trials from Princess Margaret Cancer Centre discussed above, 55% of patients had tumor venous thrombosis. Median OS ranges from 3.8 to 22 months in published series, with response rates of TVT of 50% to 79%.[39,47,77-82] Of note, in some series, radiotherapy was typically directed only to the tumor thrombus instead of both the thrombus and intrahepatic disease due to concerns over toxicity. Although the tumor venous thrombus represents a significant acute risk of morbidity, management of the full extent of intrahepatic disease is also critical. Sugahara et al reported a series of 31 patients with TVT treated with proton beam therapy with a median OS of 22 months. Although patient numbers were low, those patients who received radiotherapy to the full extent of intrahepatic disease in addition to the area of TVT had a significant improvement in survival compared with patients who only received radiotherapy to the area of TVT, with a 2-year OS of 20% versus 0% ($P = .019$).[77]

Some series have explored liver-directed radiotherapy in conjunction with arterially directed therapies, particularly in those patients who do not have extensive TVT precluding TACE. In a retrospective series of 412 patients with HCC with TVT, patients were treated to a median dose of 40 Gy in 2 to 5 fractions directed to the thrombosis in conjunction with TACE. At 1 year, OS was 42.5% and progression-free survival was 85.6%.[47]

Of note, although radiotherapy has been safely delivered in patients with CP B cirrhosis, we do not recommend treating patients with CP C cirrhosis off-study. Radiotherapy has not shown a survival benefit in these patients in a retrospective series, and TACE is contraindicated.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is associated with particularly poor survival rates, even in patients who are able to undergo resection.[83,84] The data are complicated in that many series are heterogeneous and comprised of patients with extrahepatic cholangiocarcinoma, ICC, or gallbladder cancer. For example, a meta-analysis by Horgan et al[85] of 20 institutional and registry series on the role of adjuvant therapy in cholangiocarcinoma included only one series of patients with intrahepatic tumors. There was a significant improvement in outcomes in patients who received adjuvant therapy in the setting of involved lymph nodes (odds ratio [OR]: 0.49, 95% confidence interval [CI]: 0.3-0.8) or positive resection margins (OR: 0.36, 95% CI: 0.19-0.68).[85] Retrospective series also support the role of adjuvant therapy in this population.[4,86] For example, a series from Fudan University of 90 patients with resected ICC with involved lymph nodes reported an improvement in OS with the use of radiotherapy (19.1 vs 9.5 months).[86]

Nearly 70% of patients are unresectable at diagnosis due to nodal or distant metastases, vascular invasion, or tumor extent.[7] For patients with unresectable disease, median survival is 2.3 to 9 months,[7] and chemotherapy is the mainstay of treatment. The ABC-02 trial, which included patients with metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer, demonstrated an improvement in OS in patients who received cisplatin and gemcitabine over gemcitabine alone, with a median OS of 11.4 versus 8.1 months (HR: 0.64, 95% CI: 0.52-0.80, $P < .0001$).[87] A meta-analysis of ABC-02 and BT-22, a randomized trial conducted in Japan, also demonstrated an improvement in survival with gemcitabine and cisplatin compared with gemcitabine monotherapy.[88]

Although there are no randomized data on radiotherapy in this population, single-arm prospective and retrospective series do show an improvement in local control and survival with radiotherapy. A phase I dose escalation study of SBRT for primary liver cancers included 10 patients with ICC. Median OS was 15 months.[38] A retrospective series of 84 patients with unresectable ICC also reported an improvement in outcomes with radiotherapy, with 1-year OS of 38.5% in patients who received radiotherapy versus 16.4% in patients who did not receive radiotherapy.[89] A SEER analysis of 3839 patients with ICC also found an improvement in survival with the use of radiotherapy.[90] Although there are several caveats associated with SEER data, including the lack of information on chemotherapy and comorbidities, it does provide some evidence of improved outcomes in those patients who are able to receive radiotherapy. Several retrospective series of SBRT and IMRT for primary liver tumors have also included patients with ICC,[43,91,92] with encouraging outcomes (Table 2[89,91-97]).

Similar to HCC, the optimal radiotherapy dose for ICC is not yet known. There is suggestion of improvement in outcomes with dose escalation, particularly in patients with larger tumors. A retrospective series from MD Anderson Cancer Center reported improvements in both local control and OS in patients treated to a higher biologic equivalent dose (BED).[93]

A total of 79 patients with unresectable ICC were treated with sequential chemotherapy followed by IMRT or proton therapy with passive scattering to a median dose of 58.05 Gy in 15 fractions. In some patients with larger tumors, the GTV was treated with a simultaneous integrated boost to 75 Gy in 15 fractions or 100 Gy in 25 fractions. Care was taken to achieve hepatic normal parenchyma and surrounding normal organ dose constraints. In patients who were treated to doses corresponding to BED >80.5 Gy, both OS and local control were improved at 3 years. Specifically, 3-year OS was 73% in patients treated with BED >80.5 Gy versus 38% in patients treated with BED <80.5 Gy ($P = .017$); 3-year local control was 78% with BED >80.5 Gy versus 48% with BED <80.5 Gy ($P = .04$). Despite the escalated doses delivered, there were no cases of RILD. Five patients were hospitalized within 90 days of the completion of treatment, 3 with cholangitis due to stent failure or tumor progression, 1 due to gastric bleeding, and 1 with radiation pneumonitis. A total of 7 patients developed biliary stenosis, although at least 4 of these patients had evidence of disease progression contributing to stenosis. This report demonstrated both the feasibility and efficacy of dose-escalated radiotherapy in ICC. These results are especially encouraging as the majority of patients with ICC are unable to undergo resection due to disease extent.

Charged Particle Therapy

Background

Charged particle therapy, including proton beam therapy and carbon ion therapy, has been assessed in both retrospective and prospective trials in primary hepatic malignancies. Unlike photon-based radiotherapy, which is absorbed exponentially in tissue, particle-based radiotherapy is characterized by rapid energy deposition at the end of range followed by sharp dose falloff. These properties in turn enable delivery of increasing doses of radiotherapy to a given target while still minimizing dose received by surrounding normal parenchyma, making charged particle therapy a particularly intriguing treatment modality for both HCC and ICC. A retrospective comparison of proton and photon treatment plans found that proton therapy was associated with increased sparing of normal tissues, with lower mean hepatic doses, lower maximum spinal cord dose, and lower dose to the stomach.[98] A comparison of carbon ion therapy also showed improvements in normal tissue sparing when compared with photon radiotherapy.[99] This may facilitate the use of liver-directed radiotherapy in patients with tumors ≥10 cm. Of note, as in photon radiotherapy, target identification and motion management are critical elements in treatment planning and delivery for charged particle therapy.

Outcomes of Charged Particle Therapy

The largest series of proton radiotherapy for primary liver cancer included 318 patients with HCC treated at the University of Tsukuba from 2001 through 2007.[53] One-year OS was 89.5%,

Table 2. Outcomes After Liver-Directed Radiotherapy for Intrahepatic Cholangiocarcinoma.

Study	Design	Year	Type of RT	Pts	Prior Liver-Directed Therapies	Tumor Size (Range)	Multiple Lesions	Dose (Gy)	1-Year LC	1-Year OS	Grade ≥3 Toxicity
Hong et al[51]	Phase II	2015	Proton	39	45.8%	2.2-10.9 cm	12.8%	58 GyE (15.1-67.5 GyE)	94.1% at 2 years	46.5% at 2 years	7.7%
Tse et al[38]	Phase I	2008	Photon	10	50%	172 (10-465) mL	a	36 (24-54)	65%	58%	2 transient biliary obstruction, 2 with decline to CP B
Goodman et al[94]	Phase I	2010	Photon	5	NR	32.6 (0.8-146.4) mL	NR	18-30	77%[b]	71.4%[b]	None
Tao et al[93]	Retrospective	2016	Proton or IMRT	79	NR	2.2-17 cm	39%	58.05 (35-100)	81%	87%	15.2%[c]
Chen et al[89]	Retrospective	2010	Photon	35	42.9%	7.7 ± 3.2 cm	25.7%	30-60	32.2%	38.5%	8.6%
Ibarra et al[43]	Retrospective	2012	Photon	11	50%	80.2 (31.6-818.5) mL	18.2%	36-60	50%	45%	7 patients
Barney et al[92]	Retrospective	2012	Photon, IMRT or 3D-CRT	6	83.3%	16-412.4 mL	NR	55 (45-60)	100%	73%	1 grade 3, 1 grade 5 due to hepatic failure
Liu et al[91]	Retrospective	2013	Photon	6	54%[b]	8.8 (0.2-222.4) mL[b]	51%[b]	20-50	93%[b]	81.8%[b]	None
Goyal et al[95]	Retrospective	2010	Photon	3	100%	384 (80-818)	0%	34 (24-45)	82% at 8 months	NR	None
Dewas et al[96]	Retrospective	2012	Photon	6	50%	6.3 (3.6-11.2) cm	0%	45 (29-45)	100%	NR	NR
Lanciano et al[97]	Retrospective	2012	Photon	4	36.7%[b]	25.3 (0.53-316) mL[b]	26.7%[b]	36-60	92%[b]	73%[b]	None

Abbreviations: CRT, chemoradiotherapy; 3D, 3-dimensional; LC, local control; IMRT, intensity-modulated radiotherapy; NR, not reported; OS, overall survival; Pts, patients; RT, radiotherapy; .
[a]All patients had tumor venous thrombosis or extrahepatic disease.
[b]Results include patients with other primary liver cancers included in publication.
[c]Toxicities may include some redundancies, may be due to progression in some instances.

and 5-year OS was 44.6%. Underlying hepatobiliary function had a significant impact on outcomes, with OS significantly increased in patients with CP A cirrhosis compared with those patients with CP B cirrhosis (1-year OS 93.9% vs 55.9%, $P <$ .01). There were 5 cases of grade $\geq$3 toxicity. Proton therapy has also been shown to be effective in patients with larger primary tumors—in a phase II study of 76 patients with HCC treated at Loma Linda University, 54% of patients had tumors outside of Milan criteria. Median progression-free survival was 36 months. There were no cases of grade $\geq$3 toxicities. Of note, 18 patients in this trial subsequently underwent liver transplantation, 6 of whom were found to have had a pathologic complete response.[54] The properties of proton beam therapy may facilitate dose escalation while minimizing associated toxicity. For example, a retrospective series[61] of hypofractionated proton beam therapy reported on 51 patients with tumors located at least 2 cm from the hilum who were treated at 66.6 GyE in 10 fractions. At 3 years, local control was 94.5% and OS was 49.2%. There were only 3 cases of grade $\geq$2 toxicities and no treatment-related deaths.

As previously noted, a randomized controlled trial of proton therapy versus TACE for patients with HCC within the Milan or San Francisco criteria has demonstrated encouraging results in a planned interim analysis.[52] The interim analysis reported on 69 patients who were randomized to proton therapy (n = 33) to a total dose of 70.2 Gy in 15 daily fractions versus TACE (n = 36). Within the proton therapy cohort, 23 patients were within Milan criteria and 10 patients were within San Francisco criteria; while within the TACE cohort, 29 patients were within Milan criteria and 7 were within San Francisco criteria. Patients randomized to TACE received additional courses of TACE for persistent disease, with 58% receiving 1 chemoembolization and 42% receiving up to 4 chemoembolizations. By contrast, of the 33 patients randomized to protons, 27 (82%) received one course of proton therapy, while the remaining 6 patients received additional proton therapy to other sites of disease. Days of hospitalization was reported as a surrogate for treatment toxicity; there was an increase in the number of patients hospitalized within 30 days of treatment and the overall number of hospitalization days in TACE patients as compared to patients receiving proton therapy (166 vs 24 days, $P <$ .001). This result does include postprocedure hospitalization days. There was no significant difference in median OS, with a 2-year OS rate of 59% and median OS of 30 months for the entire study cohort. There was an improvement in 2-year local control (88% vs 35%, $P =$ .06) and progression-free survival (48% vs 31%, $P =$ .06) with proton therapy, which trended toward statistical significance. It is possible that with increased follow-up, a significant difference may emerge. Of note, this trial also included patients who were awaiting liver transplantation. A total of 22 patients underwent orthotopic liver transplantation (12 from the proton therapy arm and 10 from the TACE arm). There was a clinically but not statistically significant difference in the rate of pathologic complete response, with a rate of 10% after TACE versus 25% after proton therapy ($P =$ .38). As the authors noted, this is an interim analysis and

the final results are needed, but the results thus far are encouraging and demonstrate the feasibility and efficacy of liver-directed radiotherapy in this cohort.

As in photon radiotherapy, dose and fractionation must be tailored based on proximity to normal structures and to maximize sparing of uninvolved hepatic parenchyma. A phase II multi-institutional trial of hypofractionated proton radiotherapy enrolled 92 patients with biopsy-proven, unresectable HCC or ICC. Median tumor dimension was 5.0 cm (range: 1.9-12.0 cm) for patients with HCC and 6.0 cm (range: 2.2-10.9 cm) for patients with ICC. A total of 29.5% of patients with HCC and 28.2% of patients with ICC had tumor vascular thrombosis. Radiotherapy dose was selected based on tumor proximity to the porta hepatis as well as the mean liver dose.[51] Specifically, peripheral tumors, which were defined as tumors located more than 2 cm from the porta hepatis, received up to 67.5 GyE in 15 fractions, while central tumors received up to 58.05 GyE in 15 fractions. Both dose schemas were further tailored to ensure that mean liver dose remained less than or equal to 24 GyE. Two-year OS rates were 63.2% for HCC and 45.8% for ICC, and 2-year local control rates were 94.8% for HCC and 93.1% for ICC. Treatment was well tolerated with this risk-adjusted dosing approach. Only 3 (3.6%) patients had a decline in CP score from CP A to CP B, and only 4 (4.8%) patients had grade $\geq$3 toxicity.

Conclusion

As demonstrated in the multiple prospective and retrospective series discussed above, modern liver-directed radiotherapy is a safe and effective treatment option for patients with HCC and ICC, including patients who were previously relegated to palliative treatments.

Further prospective study is needed to determine the optimal role of liver-directed radiotherapy in the management of HCC and ICC. Tumor characteristics, underlying hepatobiliary function, and performance status must all be carefully assessed to ensure each patient is presented with the optimal treatment recommendations. At our institution, all patients with primary liver tumors are discussed at a weekly multidisciplinary tumor board including medical oncologists, hepatobiliary and transplant surgeons, radiation oncologists, and interventional radiologists. We recommend consideration of liver-directed radiotherapy in patients with early-stage disease who are not candidates for resection, orthotopic liver transplantation, or ablation. For patients with larger tumors, radiotherapy should also be considered if there is a sufficient volume of uninvolved liver. We favor trial enrollment whenever possible.

Patients with advanced disease may benefit from a combination of liver-directed radiotherapy with either systemic treatment or arterially directed therapies. RTOG 1112 (NCT01730937) is a currently accruing randomized phase III trial of sorafenib with or without SBRT in patients with unresectable BCLC stage B or C HCC. Patients are to be stratified by vascular invasion, etiology of cirrhosis, and extent of HCC volume relative to overall hepatic volume. Dose level is to be

based on the mean liver dose, with constraints applied to uninvolved liver and surrounding organs at risk. It is important to note that patients with TVT are eligible for enrollment on RTOG 1112, as this is a population that has often been excluded from trials.

In unresectable ICC, prospective series are also focusing on the optimal integration of liver-directed radiotherapy with systemic therapy. NRG GI001, a phase III trial of cisplatin and gemcitabine with or without focal hypofractionated radiotherapy, is currently enrolling patients.[100] Patients are randomized to chemotherapy alone, consisting of cisplatin and gemcitabine for 5 cycles, versus chemoradiotherapy consisting of 1 cycle of cisplatin and gemcitabine followed by radiotherapy followed by an additional 4 cycles of cisplatin and gemcitabine. Patients are to be stratified by tumor size and the presence or absence of satellite lesions. Radiotherapy dose is based on the mean liver dose and proximity of the target to the porta hepatis.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
2. *Global Cancer Facts & Figures*. 3rd ed. Atlanta, GA: American Cancer Society; 2015.
3. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011; 365(12):1118-1127.
4. Maithel SK, Gamblin TC, Kamel I, Corona-Villalobos CP, Thomas M, Pawlik TM. Multidisciplinary approaches to intrahepatic cholangiocarcinoma. *Cancer*. 2013;119(22):3929-3942.
5. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer*. 2015;121(22):3998-4006.
6. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA Surg*. 2014;149(6):565-574.
7. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg*. 2008;248(1):84-96.
8. National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 2.2016). www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed April 3, 2017.
9. Russell AH, Clyde C, Wasserman TH, Turner SS, Rotman M. Accelerated hyperfractionated hepatic irradiation in the management of patients with liver metastases: results of the RTOG dose escalating protocol. *Int J Radiat Oncol Biol Phys*. 1993;27(1):117-123.
10. Lines DR, Derrington AW. Non-fatal listeria monocytogenes septicaemia in a neonate. *Med J Aust*. 1967;1(8):390-391.
11. Keane FK, Wo JY, Ferrone CR, et al. Intraoperative radiotherapy in the era of intensive neoadjuvant chemotherapy and chemoradiotherapy for pancreatic adenocarcinoma [Published online October 12, 2016]. *Am J Clin Oncol*.
12. Ben-Josef E, Normolle D, Ensminger WD, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. *J Clin Oncol*. 2005;23(34):8739-8747.
13. Jung J, Yoon SM, Kim SY, et al. Radiation-induced liver disease after stereotactic body radiotherapy for small hepatocellular carcinoma: clinical and dose-volumetric parameters. *Radiat Oncol*. 2013;8:249.
14. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21(1): 109-122.
15. Mornex F, Girard N, Beziat C, et al. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies—mature results of the French Phase II RTF-1 trial. *Int J Radiat Oncol Biol Phys*. 2006;66(4):1152-1158.
16. Song CW, Cho LC, Yuan J, Dusenbery KE, Griffin RJ, Levitt SH. Radiobiology of stereotactic body radiation therapy/stereotactic radiosurgery and the linear-quadratic model. *Int J Radiat Oncol Biol Phys*. 2013;87(1):18-19.
17. Song CW, Kim MS, Cho LC, Dusenbery K, Sperduto PW. Radiobiological basis of SBRT and SRS. *Int J Clin Oncol*. 2014;19(4): 570-578.
18. Kocher M, Treuer H, Voges J, Hoevels M, Sturm V, Müller RP. Computer simulation of cytotoxic and vascular effects of radiosurgery in solid and necrotic brain metastases. *Radiother Oncol*. 2000;54(2):149-156.
19. Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70(3):847-852.
20. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys*. 2014;88(2):254-262.
21. Pan T, Lee TY, Rietzel E, Chen GT. 4D-CT imaging of a volume influenced by respiratory motion on multi-slice CT. *Med Phys*. 2004;31(2):333-340.
22. Rietzel E, Chen GT, Choi NC, Willet CG. Four-dimensional image-based treatment planning: target volume segmentation and dose calculation in the presence of respiratory motion. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1535-1550.
23. Araki T, Itai Y, Furui S, Tasaka A. Dynamic CT densitometry of hepatic tumors. *AJR Am J Roentgenol*. 1980;135(5):1037-1043.
24. Baron RL, Oliver JH III, Dodd GD III, Nalesnik M, Holbert BL, Carr B. Hepatocellular carcinoma: evaluation with biphasic, contrast-enhanced, helical CT. *Radiology*. 1996;199(2):505-511.

25. Niska JR, Keane FK, Wolfgang JA, et al. Impact of intravenous contrast enhancement phase on target definition for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC): observations from patients enrolled on a prospective phase 2 trial. *Pract Radiat Oncol*. 2016;6(1):e9-e16.

26. Kim TK, Choi BI, Han JK, Jang HJ, Cho SG, Han MC. Peripheral cholangiocarcinoma of the liver: two-phase spiral CT findings. *Radiology*. 1997;204(2):539-543.

27. Iavarone M, Piscaglia F, Vavassori S, et al. Contrast enhanced CT-scan to diagnose intrahepatic cholangiocarcinoma in patients with cirrhosis. *J Hepatol*. 2013;58(6):1188-1193.

28. Kanematsu M, Semelka RC, Leonardou P, Mastropasqua M, Lee JK. Hepatocellular carcinoma of diffuse type: MR imaging findings and clinical manifestations. *J Magn Reson Imaging*. 2003; 18(2):189-195.

29. Kim SA, Lee JM, Lee KB, et al. Intrahepatic mass-forming cholangiocarcinomas: enhancement patterns at multiphasic CT, with special emphasis on arterial enhancement pattern—correlation with clinicopathologic findings. *Radiology*. 2011;260(1): 148-157.

30. Hong TS, Bosch WR, Krishnan S, et al. Interobserver variability in target definition for hepatocellular carcinoma with and without portal vein thrombus: Radiation Therapy Oncology Group consensus guidelines. *Int J Radiat Oncol Biol Phys*. 2014;89(4): 804-813.

31. Lax I, Blomgren H, Naslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol*. 1994;33(6):677-683.

32. Heinzerling JH, Anderson JF, Papiez L, et al. Four-dimensional computed tomography scan analysis of tumor and organ motion at varying levels of abdominal compression during stereotactic treatment of lung and liver. *Int J Radiat Oncol Biol Phys*. 2008; 70(5):1571-1578.

33. Langen KM, Jones DT. Organ motion and its management. *Int J Radiat Oncol Biol Phys*. 2001;50(1):265-278.

34. Case RB, Sonke JJ, Moseley DJ, Kim J, Brock KK, Dawson LA. Inter- and intrafraction variability in liver position in non-breath-hold stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009;75(1):302-308.

35. Eccles CL, Patel R, Simeonov AK, Lockwood G, Haider M, Dawson LA. Comparison of liver tumor motion with and without abdominal compression using cine-magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 2011;79(2):602-608.

36. Wong JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Radiat Oncol Biol Phys*. 1999;44(4):911-919.

37. Dawson LA, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. *Semin Radiat Oncol*. 2001;11(3):240-246.

38. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2008; 26(4):657-664.

39. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol*. 2013;31(13): 1631-1639.

40. Sanuki N, Takeda A, Oku Y, et al. Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. *Acta Oncol*. 2014;53(3):399-404.

41. Honda Y, Kimura T, Aikata H, et al. Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2013;28(3):530-536.

42. Méndez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase i-ii study. *Acta Oncol*. 2006;45(7):831-837.

43. Ibarra RA, Rojas D, Snyder L, et al. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. *Acta Oncol*. 2012;51(5):575-583.

44. Kang JK, Kim MS, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer*. 2012;118(21):5424-5431.

45. Cárdenes HR, Price TR, Perkins SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clin Transl Oncol*. 2010;12(3):218-225.

46. Jang WI, Kim MS, Bae SH, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. *Radiat Oncol*. 2013;8:250.

47. Yoon SM, Lim YS, Won HJ, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. *Int J Radiat Oncol Biol Phys*. 2012;82(5):2004-2011.

48. Bibault JE, Dewas S, Vautravers-Dewas C, et al. Stereotactic body radiation therapy for hepatocellular carcinoma: prognostic factors of local control, overall survival, and toxicity. *PloS One*. 2013;8(10):e77472.

49. Yuan Z, Tian L, Wang P, Song Y, Dong Y, Zhuang H. Comparative research on the efficacy of CyberKnife(R) and surgical excision for stage I hepatocellular carcinoma. *Onco Targets Ther*. 2013;6:1527-1532.

50. Yamashita H, Onishi H, Murakami N, et al; Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG). Survival outcomes after stereotactic body radiotherapy for 79 Japanese patients with hepatocellular carcinoma. *J Radiat Res*. 2015;56(3):561-567.

51. Hong TS, Wo JY, Beow YY, et al. A multi-institutional phase II study of high dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2016;34(5): 460-468.

52. Bush DA, Smith JC, Slater JD, et al. Randomized clinical trial comparing proton beam radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: results of an interim analysis. *Int J Radiat Oncol Biol Phys*. 2016;95(1): 477-482.

53. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. *Cancer*. 2009;115(23):5499-5506.

54. Bush DA, Kayali Z, Grove R, Slater JD. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular

carcinoma: a phase 2 prospective trial. *Cancer*. 2011;117(13): 3053-3059.

55. Yoon SM, Lim YS, Park MJ, et al. Stereotactic body radiation therapy as an alternative treatment for small hepatocellular carcinoma. *PloS One*. 2013;8(11):e79854.

56. Huertas A, Baumann AS, Saunier-Kubs F, et al. Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma. *Radiother Oncol*. 2015;115(2):211-216.

57. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e447-e453.

58. Son SH, Choi BO, Ryu MR, et al. Stereotactic body radiotherapy for patients with unresectable primary hepatocellular carcinoma: dose-volumetric parameters predicting the hepatic complication. *Int J Radiat Oncol Biol Phys*. 2010;78(4):1073-1080.

59. Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. *BMC Cancer*. 2010;10:475.

60. Seo YS, Kim MS, Yoo SY, et al. Preliminary result of stereotactic body radiotherapy as a local salvage treatment for inoperable hepatocellular carcinoma. *J Surg Oncol*. 2010;102(3):209-214.

61. Fukumitsu N, Sugahara S, Nakayama H, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2009; 74(3):831-836.

62. Keane FK, Wo JY, Zhu AX, et al. Liver-directed radiotherapy for hepatocellular carcinoma. *Liver Cancer*. 2016;5(3):198-209.

63. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol*. 2012;57(4):794-802.

64. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. 2006; 243(3):321-328.

65. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg*. 2010;252(6):903-912.

66. Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. *Radiology*. 2000;214(3):761-768.

67. Ruzzenente A, Guglielmi A, Sandri M, et al. Surgical resection versus local ablation for HCC on cirrhosis: results from a propensity case-matched study. *J Gastrointest Surg*. 2012;16(2): 301-311; discussion 311.

68. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002;359(9319):1734-1739.

69. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002; 224(1):47-54.

70. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003;37(2):429-442.

71. Seong J, Lee IJ, Shim SJ, et al. A multicenter retrospective cohort study of practice patterns and clinical outcome on radiotherapy for hepatocellular carcinoma in Korea. *Liver Int*. 2009;29(2):147-152.

72. Zhong NB, Lv GM, Chen ZH. Stereotactic body radiotherapy combined with transarterial chemoembolization for huge (≥10 cm) hepatocellular carcinomas: a clinical study. *Mol Clin Oncol*. 2014;2(5):839-844.

73. Crocetti L, de Baere T, Lencioni R. Quality improvement guidelines for radiofrequency ablation of liver tumours. *Cardiovasc Intervent Radiol*. 2010;33(1):11-17.

74. Park HC, Seong J, Han KH, et al. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2002;54(1):150-155.

75. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology*. 1999; 29(1):62-67.

76. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;35(5):1164-1171.

77. Sugahara S, Nakayama H, Fukuda K, et al. Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. *Strahlenther Onkol*. 2009;185(12):782-788.

78. Choi BO, Choi IB, Jang HS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer*. 2008;8:351.

79. Xi M, Zhang L, Zhao L, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. *PloS One*. 2013;8(5):e63864.

80. Huang YJ, Hsu HC, Wang CY, et al. The treatment responses in cases of radiation therapy to portal vein thrombosis in advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2009; 73(4):1155-1163.

81. Chuma M, Taguchi H, Yamamoto Y, et al. Efficacy of therapy for advanced hepatocellular carcinoma: intra-arterial 5-fluorouracil and subcutaneous interferon with image-guided radiation. *J Gastroenterol Hepatol*. 2011;26(7):1123-1132.

82. Rim CH, Yang DS, Park YJ, Yoon WS, Lee JA, Kim CY. Effectiveness of high-dose three-dimensional conformal radiotherapy in hepatocellular carcinoma with portal vein thrombosis. *Jpn J Clin Oncol*. 2012;42(8):721-729.

83. Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg*. 2011;254(5):824-829; discussion 830.

84. Ribero D, Pinna AD, Guglielmi A, et al; Italian Intrahepatic Cholangiocarcinoma Study Group. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. *Arch Surg*. 2012; 147(12):1107-1113.

85. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2012;30(16):1934-1940.

86. Jiang W, Zeng ZC, Tang ZY, et al. Benefit of radiotherapy for 90 patients with resected intrahepatic cholangiocarcinoma and

concurrent lymph node metastases. *J Cancer Res Clin Oncol.* 2010;136(9):1323-1331.

87. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010; 362(14):1273-1281.

88. Valle JW, Furuse J, Jitlal M, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol.* 2014;25(2):391-398.

89. Chen YX, Zeng ZC, Tang ZY, et al. Determining the role of external beam radiotherapy in unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 84 patients. *BMC Cancer.* 2010;10:492.

90. Shinohara ET, Mitra N, Guo M, Metz JM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys.* 2008;72(5):1495-1501.

91. Liu E, Stenmark MH, Schipper MJ, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors. *Transl Oncol.* 2013;6(4):442-446.

92. Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity using stereotactic body radiotherapy (SBRT) for advanced cholangiocarcinoma. *Radiat Oncol.* 2012;7:67.

93. Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. *J Clin Oncol.* 2016;34(3):219-226.

94. Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys.* 2010;78(2):486-493.

95. Goyal K, Einstein D, Yao M, et al. Cyberknife stereotactic body radiation therapy for nonresectable tumors of the liver: preliminary results. *HPB Surg.* 2010;2010. pii:309780.

96. Dewas S, Bibault JE, Mirabel X, et al. Prognostic factors affecting local control of hepatic tumors treated by stereotactic body radiation therapy. *Radiat Oncol.* 2012;7:166.

97. Lanciano R, Lamond J, Yang J, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. *Front Oncol.* 2012;2:23.

98. Wang X, Krishnan S, Zhang X, et al. Proton radiotherapy for liver tumors: dosimetric advantages over photon plans. *Med Dosim.* 2008;33(4):259-267.

99. Abe T, Saitoh J, Kobayashi D, et al. Dosimetric comparison of carbon ion radiotherapy and stereotactic body radiotherapy with photon beams for the treatment of hepatocellular carcinoma. *Radiat Oncol.* 2015;10:187.

100. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg.* 2007;245(5):755-762.