Radiation therapy for primary and metastatic tumors of the liver

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Abstract

Background Hepatic tumors can be either primary disease (i.e., hepatocellular carcinoma) or a site of metastases from other solid malignancies. The primary therapy for all liver tumors is resection, but only a minority of patients present with resectable disease. Various nonsurgical ablative techniques have been investigated to cure or palliate unresectable hepatic tumors by improving locoregional control.

Purpose The objective of this article is to review the radiotherapy options in managing primary or metastatic liver cancer.

Design and methods Two emerging radical radiotherapy options include stereotactic body radiation therapy (SBRT) and selective internal radiotherapy (SIRT). SBRT delivers ablative doses of radiation in a hypofractionated course and has been used in metastatic disease to the brain, spine, lung, and liver. The local tumor control for SBRT appears to exceed that of conventional fractionation external beam radiotherapy (EBRT). SIRT, also known as radioembolization, is the intra-arterial delivery of microspheres impregnated with yttrium-90 (Y90) via the hepatic artery. The evidence is limited to cohort and comparative studies with historical controls; nonetheless, results appear to be promising. Both SBRT and SIRT to liver

tumors may serve as a bridge to liver transplantation (LT) and as a treatment strategy for metastasis from colorectal cancer to achieve the effect of metastasectomy. Meanwhile, combining molecular-targeted agents with radiotherapy is an emerging strategy to enhance the therapeutic ratio.

Conclusion SBRT and/or SIRT are promising local ablative modalities for management of unresectable liver tumors. Further well-designed trials are warranted to establish the proper combination of different therapeutic modalities.

Keywords Hepatocellular carcinoma · Liver metastasis · Stereotactic body radiation therapy · Selective internal radiation therapy · Liver transplantation

Introduction

Hepatic tumors arise either from primary liver cancer (i.e., hepatocellular carcinoma) or metastases to the liver, most commonly from a colorectal primary. The standard curative treatment is surgical resection with tumor-free margins or liver transplantation (LT). Unfortunately, only 30–40 % of patients are resectable [1]. Most hepatic tumors are unresectable at diagnosis due to anatomic location, size, and number of lesions; concurrent nonmalignant liver disease; and significant extrahepatic disease or insufficient hepatic reserve. A number of treatments are in use for unresectable tumors including transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT), stereotactic body radiation therapy (SBRT), external beam radiotherapy (EBRT), systemic and hepatic intraarterial chemotherapy, targeted therapy (e.g., sorafenib), radiofrequency ablation (RFA), microwave ablation, cryotherapy, and other ablative techniques.

Prior to the 1990s, EBRT was reserved primarily in the palliative setting for metastatic disease because of the assumed

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low tolerance of the whole liver to RT. Whole-liver RT achieves a palliative goal in the majority of patients with pain [2]. With the advent of intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), higher doses could be delivered safely for partial liver RT. SBRT represents the pinnacle of such technology and permits unprecedented doses of radiation to be delivered with high precision while minimizing radiation exposure to nearby critical structures. Its application is continuously expanding and is currently being used for oligometastases involving the brain, spine, lung, and liver. It is also being used in the management of HCC, mostly as an alternative treatment and in some circumstances as a bridging therapy [3].

SIRT or radioembolization delivers yttrium-90 (Y-90)-labeled microspheres into the arteries that supply the tumor. Y-90 microspheres have several advantages as a potential therapy for liver lesions, including the selective delivery of radiolabeled microspheres via the hepatic artery directly into the tumor, as well as limiting the dose to normal liver parenchyma.

The liver is a common site for metastasis from colorectal cancer because of direct venous drainage from the intestines to the liver. Resection with a negative margin in a single operative procedure is the gold standard for limited liver metastases and offers potential for long-term survival. However, most patients are not amenable to potentially curative resection. SBRT and SIRT have arisen as potential alternative treatment choices [4, 5].

Orthotopic liver transplantation (OLT) in HCC patients is limited, owing to cancer progression and/or death due to underlying liver disease, while the patient is on the waiting list [6, 7]. Bridging therapy is thus needed to halt tumor progression and minimize wait list dropout [8, 9]. Some patients with advanced HCC could benefit from OLT after downstaging the tumor with neoadjuvant treatment [10, 11].

Molecular-targeted therapy surged as a novel treatment choice for advanced HCC. The randomized controlled trial using target therapy, sorafenib, showed median survival and time to radiologic progression were nearly 3 months longer [12]. This review provides an overview of the novel treatments for primary and metastatic tumors of the liver.

External beam radiotherapy

Historically, the role of EBRT was limited for the liver due to the belief that the normal liver was sensitive to radiation. The dose limitation of whole-liver EBRT is approximately 30 to 35 Gy in 3 to 4 weeks which restricts EBRT to a palliative role [13–17]. In 1987, the Radiation Therapy Oncology Group (RTOG) reported the results of a randomized trial with whole-liver EBRT alone to a dose of 21 Gy in seven fractions

or in combination with the radiosensitizer misonidazole [18]. Although the addition of misonidazole did not significantly improve outcomes, whole-liver EBRT provided a significant palliative benefit, with a decrease in abdominal pain, decreased analgesic requirement in 77 % of patients, less abdominal distention in 67 % of patients, as well as less nausea, vomiting, and anorexia in 40 % of patients.

The subsequent advent of three-dimensional RT treatment planning has expanded the role of EBRT in patients with unresectable liver tumors. Mohiuddin et al. reported an improved median survival if a partial liver boost dose was delivered in conjunction with whole-liver RT for patients with colorectal metastasis to the liver [19]. Later, alternative fractionation schemes were introduced in treating liver tumors. The rapid doubling time of HCC, estimated at 41 days [20], suggests that shortening overall treatment time by hyperfractionation RT may improve response rates. Indeed, twice daily hyperfractionation was used in the University of Michigan series [21–24]. Total dose was individualized based on the volume of normal liver that could be spared without exceeding an estimated 5 % to 10 % risk of radiation-induced liver disease (RILD), considered to be a dose-limiting toxicity. The total dose was the most important factor of survival, with 75 Gy (1.5-Gy fractions twice a day) or more associated with a significantly higher survival (23.9 months) compared to lower doses (14.9 months).

Stereotactic body radiotherapy

With technical advances in tumor localization and motion management, hypofractionated radiotherapy using image-guided RT is being increasingly adopted as a means to ablate liver tumors, whether primary or metastatic. Focal, high-dose SBRT delivers ablative doses in fewer fractions and highly conformal RT volumes. Doses to nearby critical structures and organs are minimized by using very tight margins. Therefore, a robust immobilization device is crucial to ensure reproducible and accurate setup. Respiration-induced tumor motion in the liver is significant and must be controlled during simulation and treatment delivery [25–27]. By doing so, the margin expansion from the gross tumor volume to the planning target volume (PTV) may be reduced. Methods to manage respiratory motion include passive abdominal compression, breath hold, breath coaching, respiratory gating, and respiratory motion tracking [3, 28]. Pretreatment verification of tumor position is needed before each session of SBRT to ascertain precise and accurate delivery of SBRT. Image guidance can be accomplished using a megavoltage/kilovoltage cone beam CT or stereoscopic X-rays.

SBRT for primary liver tumor

Table 1 summarizes the results of SBRT for primary liver tumor. Choi et al. retrospectively analyzed the outcomes of SBRT for 20 HCC patients, 15 with Child-Pugh A and five with Child-Pugh B disease [29]. The dose was 50 Gy in five or 10 fractions. At a median follow-up of 23 months, the overall response rate was 80 % and 1- and 2-year overall survival rates were 70 % and 43.1 %, respectively. The median survival was 20 months. No grade 3 or higher toxicities were noted. In a phase I trial of SBRT (24–54 Gy in six fractions) in 31 patients with primary liver tumor, Tse et al. reported a median survival of 13.4 months, 1-year overall survival of 51 %, and 1-year local control of 65 % [30]. No RILD or treatment-related grade 4/5 toxicity was seen within 3 months of SBRT. Grade 3 elevation of liver enzymes was seen in five patients (12 %). Two patients (5 %) with intrahepatic cholangiocarcinoma (IHC) developed transient biliary obstruction, while seven (five HCC and two IHC) had a decline in liver function from Child-Pugh A to B within 3 months after SBRT.

In a phase I dose escalation trial, Cardenes et al. conducted the feasibility of SBRT for HCC in 17 patients with 25 lesions [31]. The dose was escalated from 36 Gy to 48 Gy in three fractions (one to two fractions per week). No dose-limiting toxicities were observed in the Child-Pugh A patients. Two patients with Child-Pugh B disease developed grade 3 hepatic toxicity at the 42 Gy (in three fractions) level. The protocol was changed for five subsequent patients with Child-Pugh B to 40 Gy in five fractions, of which one patient experienced progressive liver failure. The only factor related to grade 3 or higher toxicity or death within 6 months after treatment was a Child-Pugh score greater than 8.

To determine the safety of SBRT for large HCC lesions (>10 cm), Shin et al. evaluated the outcomes of six patients using regimen of 32–40 Gy in four fractions [32]. Overall, treatment was well tolerated and one patient with a partial response underwent lobectomy after SBRT. Due to advanced disease, 1-year overall survival was only 33 %.

SBRT for liver metastases

Table 2 summarizes the published results of clinical trials of SBRT for liver tumors. From Princess Margaret Hospital, Lee et al. reported on a phase I risk-adapted dose escalation study of SBRT for liver metastases [33]. Individualized radiation doses over six fractions were selected to maintain the same nominal risk of RILD for three estimated risk levels (5 %, 10 %, and 20 %). The median SBRT dose was 41.8 Gy in six fractions, with the maximum dose of 60 Gy. The 1-year local control rate was 71 %, and the 18-month overall survival rate was 47 %. Improved local control with

Table 1 Summary of SBRT for primary liver tumor

Author	No. of patients	No. of liver lesions	Tumor volume/ tumor diameter	Type of disease	RT_dose	Toxicity $\geq$ grade 3	Response	Median follow-up	Local control comments	Median survival	Overall survival	Reference
Choi et al.	20	20	2–6.5 cm (average: 3.8 cm)	Primary HCC	10 Gy $\times$ 5 5 Gy $\times$ 10	0 %	CR 20 % PR 60 % SD 20 %	23 months	1y 65 % 2y 32.5 %	20 months	1y 70.0 % 2y 43.1 %	[29]
Tse et al.	41	NR	9–1,913 ml (median, 173 ml)	Primary (31 HCC, 10 IHC)	4–9 Gy $\times$ 6	44 % acute 2 % late gastroin- testinal bleed	CR 5 % PR 44 % SD 51 %	17.6 months	1y 65 %	Total 13.4 months HCC 11.7 months	HCC 1y 48 %	[30]
Cardenes et al.	17	25	8–95 ml (median, 34 ml)	Primary HCC	12–16 Gy $\times$ 3 8 Gy $\times$ 5	11 %	SD 42 % Transplantation CR 2 patients PR 3 patients SD 1 patient	24 months	2y 100 %	IHC 15.0 months Not reached	IHC 1y 58 % 1y 75 % 2y 60 %	[31]
Shin et al.	6	6	1,008–1,574 ml (average: 1,288 ml)	Primary HCC	8–10 Gy $\times$ 4	17 %	PR 66 % SD 17 % PD 17 %	25.6 months	50 %	10 months	1y 33 %	[32]

NR not reported, CR complete response, PR partial response, SD stable disease, PD disease progression, Dx ml dose to x ml, HCC hepatocellular carcinoma, IHC intrahepatic cholangiocarcinoma

Table 2 Summary of clinical trials of SBRT for liver tumors

Author	No. of patients	No. of liver lesions	Tumor volume/ tumor diameter	Type of metastases	RT_dose	Toxicity ≥ grade 3	Response	Median follow-up	Local control comments	Median survival	Overall survival	Reference
Rule et al.	27	37	9.01–247.31 ml (median, 43.04 ml)	CRC [12] Carcinoid [3]	6 Gy×5 10 Gy×5	0 %	60-Gy cohort 90 % 50-Gy cohort 50 %	20 months	2y 60-Gy cohort 100 % 50-Gy cohort 89 % 30-Gy cohort 56 % MTD not reached	37 months	2y 60-Gy cohort 50 % 50-Gy cohort 67 % 30-Gy cohort 56 %	[35]
				Melanoma [2] Pancreas [2]	12 Gy×5		30-Gy cohorts 30 %					
				Renal [2] Other [6] HCC [2] IHC [5] CRC [6] Pancreatic [3] Gastric [2] Ovarian [2] Other [6]	18–30 Gy×1	0 %	NR	17.3 months	77 % MTD not reached	28.6 months	2y 50.4 %	[34]
Goodman et al.	26	33	0.8–146.6 ml (median, 32.6 ml)									
Lee et al.	68	141	1.2–3,090 ml (median, 75.9 ml)	CRC [15] Lung [10] Breast [4] Ovarian [3] Esophageal [3] HCC [2] Other [10] CRC [15] Lung [10] Ovarian [3] Breast [4] Esophageal [3] HCC [2] Other [10] CRC [14] Lung [1] Breast [1] Carcinoid [1]	Median 7 Gy×6 27.7–60 Gy/6 fractions, variable, NTCP-based	10 %	CR 6 % PR 43 % SD 30 %	10.8 months	1y 71 % Better for higher dose, smaller volume	17.6 months	18-month 47 %	[33]
Rusthoven et al.	47	63	0.4–5.8 cm (median, 2.7 cm)		12–20 Gy×3	2 %	NR	16 months	2y 92 % ≤3 cm 100 % >3 cm 77 % (<i>P</i> =0.015)	20.5 months	2y 30 %	[4]
Mendez Romero et al.	25	45	1.1–322 ml (median, 22.2 ml)/ 0.5–7.2 cm (median, 3.2 cm)		12.5 Gy×3 10 Gy×3 5 Gy×5	16 % acute 4 % late	NR	12.9 months	2 year 82 %	NR	1y 82 % 2y 54 %	[37]

Table 2 (continued)

Author	No. of patients	No. of liver lesions	Tumor volume/ tumor diameter	Type of metastases	RT_dose	Toxicity ≥ grade 3	Response	Median follow-up	Local control comments	Median survival	Overall survival	Reference
Herfarth et al.	37	60	1–132 ml (median, 10 ml)	4 primary, 56 mets	14–26 Gy × 1	0 %	CR 7 % PR 51 %	5.7 months	18-month 68 % (81 % for 20–26 Gy)	NR	1y 72 %	[17, 36]
Hoyer et al.	44	–	1–8.8 cm (median, 3.5 cm)	CRC	15 Gy × 3	2 % liver failure 5 % severe late GI toxicities	SD 40 % NR	4.3 years	79 %, 2-yr LC 86 % (by tumor)	1.6 years	1y 67 % 2y 38 %	[38]
									64 % (by patient)		3y 22 % 4y 13 % 5y 13 %	

CRC colorectal, NR not reported, CR complete response, PR partial response, SD stable disease, Dx % dose to x %, D_x ml dose to x ml, MTD maximum tolerated dose, HCC hepatocellular carcinoma, IHC intrahepatic cholangiocarcinoma, mets metastases, NTCP normal tissue complication probability

higher doses was found in a univariate analysis. There were only two grade 3 liver enzyme changes but no RILD.

In another phase I dose-escalation study, Goodman et al. reported on the outcomes of 18–30 Gy in a single-fraction SBRT for primary (five patients with IHC, two patients with HCC) or metastatic liver tumors (19 patients) in 26 patients with Child-Pugh A disease [34]. No patients developed dose-limiting toxicities. Across the entire study cohort, the 1-year local control rate was 77 % and the 2-year actuarial overall survival was 50 %. The 1- and 2-year overall survival rates in patients treated for primary liver tumors were 71 % and 53 %, and in those treated for metastatic disease, 61 % and 49 %, respectively.

In a phase I dose-escalation study, Rule et al. compared outcomes of 30 Gy in three fractions, 50 Gy in five fractions, and 60 Gy in five fractions [35]. Dose-dependent effects on local control of 100 %, 89 %, and 56 % for SBRT doses of 60 Gy, 50 Gy, and 30 Gy, respectively, were observed.

Herfarth et al. assessed single-fraction SBRT from 14 to 26 Gy at University of Heidelberg [17, 36]. Thirty-seven patients with 60 tumors were treated, with no toxicity greater than grade 2 observed. The 18-month local control rate was 68 % for all patients and 81 % for patients who received 20–26 Gy, suggesting a dose response effect. Mendez Romero et al. reported the outcomes of SBRT in 25 patients with primary or metastatic liver lesions. In patients with metastases, HCC without cirrhosis, and HCC < 4 cm, the SBRT dose was mostly 37.5 Gy in three fractions [37]. In patients with HCC ≥ 4 cm and cirrhosis, the dose was 25 Gy in five fractions or 30 Gy in three fractions. The 1- and 2-year local tumor control rate for the entire cohort was 94 % and 82 %, respectively. The actuarial 1- and 2-year local control rates were 100 % and 86 % in the metastasis group, respectively. In the HCC group the 1-year local control rate was 75 %.

In a compelling multi-institutional dose-escalation phase I/II trial of SBRT for liver metastases, Rusthoven et al. reported on the outcomes of SBRT in 47 patients [4]. The 2-year local control rate was 92 % for all lesions, 100 % (lesions ≤ 3 cm) and 77 % (lesions > 3 cm). The radiation dose was escalated from 36 to 60 Gy in three fractions and no dose-limiting toxicity was observed. Grade 3 or greater toxicity was observed only in one patient.

Hoyer et al. reported on the outcomes of SBRT for patients with liver metastasis from colorectal carcinoma using a dose of 45 Gy in three fractions [38]. Median follow-up was 4.3 years. The 2-year actuarial local control rate was 79 %. In tumor- and patient-based analyses ($n=141$ total lesions; $n=64$ patients, respectively), the 2-year local controls were 86 % and 63 %, respectively. Nineteen percent had no local or distant progression after 2 years, and 2- and 5-year overall survival rates were 38 and 13 %, respectively.

In terms of toxicities, one patient died of hepatic failure, one patient underwent surgery for a colonic perforation, and two patients were conservatively treated for duodenal ulcerations [38].

In summary, survival outcomes are better in patients with liver metastasis than HCC. In both groups, there appears to be a dose response for local control. For HCC, the dose of SBRT should be based on the cirrhotic status. For patients with Child-Pugh A cirrhosis, 48 Gy or higher in three fractions is recommended. For patients with Child-Pugh B cirrhosis, more fractionated schemes are recommended (e.g., 40 Gy in five fractions). For liver metastasis, doses greater than 48 Gy in three fractions or 14–26 Gy in one fraction is recommended. Grade 3 or higher toxicities were more common (up to 44 %) in patients with HCC and Child-Pugh class B cirrhosis. In patients with liver metastasis, no treatment-related grade 4/5 toxicity after SBRT was observed, with grade 3-elevated liver enzymes in less than 20 %.

SIRT

SIRT or radioembolization refers to the delivery of microspheres loaded with radioactive isotopes into the arteries feeding liver tumors. The microsphere is an implantable medical device consisting of resin-based or glass-based biocompatible microspheres loaded with Y-90 [39]. Y-90 is a beta emitter with a half-life of 2.6 days and an average penetration depth in tissues of 2.4 mm. SIRT demonstrated an 89 % treatment response with resin microspheres and 78 % with glass microspheres, respectively, in patients with HCC [40]. In a large retrospective review, Kennedy et al. reported 515 patients receiving 680 treatments of SIRT [41]. Stable disease was seen in 76.8 %, partial response in 9.5 %, complete response in 4.5 %, and progressive liver disease in 9 %. The treatment was well tolerated with an incidence of RILD of only 4 % and nonliver grade 3 or greater toxicity of 6 %. No relationship was identified in terms of response rates or toxicity by tumor type. Table 3 summarizes the results using SIRT for liver tumors.

SIRT in HCC

Sangro et al. reported 24 patients treated with resin-based Y-90 microspheres, with the delivered activity of 106.3 Gy [42]. The median survival was 7 months, and the time to progression (TTP) was 3 months. In another study by Hilgard et al., HCC patients treated with Y-90 were assessed [43]. Although the median TTP for all patients was 10.0 months, the TTP ranged from 8.0 months for patients with portal vein thrombosis (PVT) to 11.8 months for those without

Table 3 Summary of studies using SIRT for liver tumors

Author	Type of microspheres	Activity delivered	Type of metastases	No. of patients	Response rate	Median follow-up	TTP (months)	Median survival (months)	Reference
Salem et al.	Glass-based microspheres	102–115 Gy (median 110 Gy)	HCC	Y-90: 123 TACE: 122	Y-90: 49 % TACE: 36 %	Y-90: 32.6 months TACE: 22.7 months	⁹⁰ Y: 13.3 TACE: 8.4	90Y: 20.5 TACE: 17.4	[44]
Hilgard et al.	Glass-based microspheres	Median 120 Gy	HCC	108	EASL: CR 3 % PR 37 % SD 53 % PD 6 %	NR	10	16.4	[43]
Sangro et al.	Resin-based microspheres	0.75–3.02 GBq (median 2.20 GBq)	HCC	24	RECIST: response rate 23.8 %, disease control 100 %	12.5 months	1–7 (median 3)	7 months	[42]
Hendlisz et al.	Resin-based microspheres	1.32–2.15 GBq (mean 1.79 GBq)	CRC metastases	FU alone: 23 Y-90+FU: 21	EASL: FU alone: response rate 0 %, disease control 35 % Y-90+FU: response rate 9.5 %, disease control 86 %	24.8 months	FU alone: 2.1 Y-90+FU: 4.5	FU alone: 7.31 Y-90+FU: 10	[46]
Kennedy et al.	Resin-based microspheres	0.1–2.9 GBq (mean 1.7 GBq)	CRC metastases	208	CT: 35 %; PET: 91 %; CEA: 70 %	13 months	NR	Responders: 10.5 Nonresponders: 4.5	[45]

TTP time to progression, CRC colorectal, HCC hepatocellular carcinoma, TACE transcatheter arterial chemoembolism, Y-90 yttrium-90, EASL response criteria of European Association for the study of liver, CR complete response, PR partial response, SD stable disease, PD progression of disease, RECIST Response Evaluation Criteria in Solid Tumors, FU fluorouracil, CT computed tomography partial response, PET positron emission tomography response, CEA reduction in carcinoembryonic antigen

PVT. The 6-month survival probability in the PVT group was 65 % and the median survival was 10.0 months, as compared to 76 % and 16.4 months in patients without detectable PVT.

Recently, Salem et al. analyzed the outcomes comparing Y-90 with transcatheter arterial chemoembolism (TACE) for HCC [44]. There was a trend that patients treated with Y-90 had a higher response rate than with TACE (49 % vs. 36 %, $P=.104$). Although TTP was longer following Y-90 than TACE (13.3 months vs. 8.4 months, $P=.046$), the median survivals were not statistically different (17.4 months vs. 20.5 months, $P=.232$). Among patients with intermediate-stage disease, survival was similar between groups of TACE (17.5 months) and Y-90 (17.2 months, $P=.42$). They concluded that Y-90 leads to longer TTP and less toxicity than TACE, with no survival difference.

SIRT in liver metastases

SIRT has been used to treat patients with liver metastases. Kennedy et al. assessed Y-90 as a salvage therapy for unresectable colorectal liver metastases [45]. A total of 208 heavily pretreated patients underwent Y-90 delivered through hepatic arterial vessels. Encouraging tumor response was observed on computed tomography, positron emission tomography, and the reduction in carcinoembryonic antigen levels of 35 %, 91 %, and 70 %, respectively. The maximum response occurred at approximately 3 months after treatment. Median survival was 10.5 months in the responders but only 4.5 months in the nonresponders.

Hendлиз et al. compared intravenous fluorouracil alone (FU) with the combination of Y-90 and intravenous fluorouracil (Y-90+FU) [46]. The median survival were 7.3 and 10.0 months in FU and Y-90+FU, respectively ($P=.80$). The median TTP was 2.1 and 4.5 months, respectively ($P=.03$). Grade 3 or 4 toxicities were recorded in six patients after FU and in one after Y-90+FU ($P=.10$). They concluded that combination therapy is a safe and effective therapeutic option for chemotherapy-refractory liver metastases.

In summary, Y-90 is another promising treatment for patients with multifocal liver tumors that have failed from previous treatments. Response rates range from 24 % to 49 % in HCC and 9.5 % to 91 % in liver metastasis. Treatment-related complications, such as ulceration of stomach or duodenum and RILD, were few and manageable. No patient experienced RILD after SIRT.

SIRT and SBRT as a bridge to LT

LT is an effective treatment for HCC other than surgical resection. LT has the advantages of a resected malignancy

and elimination of parenchymal liver disease that initially led to HCC. A landmark study from the Milan group reported survival at 4 years of 85 %, with a recurrence rate of 8 % in an appropriately selected patient group [47]. The Milan criteria suggested in this study remain the benchmark for providing a priority status for HCC patients who are otherwise candidates for LT [48]. The major criteria include a single tumor ≤ 5 cm, up to three nodules ≤ 3 cm each, and no macrovascular invasion.

However, some patients initially meeting the Milan criteria may not make it to LT because of tumor progression. There are also a significant number of patients with advanced stage of disease at diagnosis who were not ideal candidates for LT. Therefore, several bridging strategies have been developed, including RFA, percutaneous ethanol injection (PEI), and TACE [49–52]. In the first prospective study on downstaging of HCC prior to LT, a combination of TACE, RFA, PEI, and/or surgical resection was investigated [53]. In this carefully selected patient group, 70 % were successfully downstaged, and 53 % eventually had a LT. At a median follow-up of 16 months, no HCC recurrence was observed.

The role of SIRT with Y-90 for downstaging HCC has also been investigated [7, 54]. For T3 unresectable HCC, 56 % were downstaged from T3 to T2, while 23 % were downstaged and underwent LT following treatment. Comparing the downstaging efficacy of TACE and SIRT with Y-90, the partial response rate was more favorable by SIRT and Y-90 than TACE (61 % vs. 37 %). HCC downstaged to T2 was achieved in 31 % by TACE and 58 % by SIRT and Y-90.

SBRT is now emerging as another treatment option for bridging therapy [10, 55–57]. Table 4 summarizes the results of SBRT as a bridge for LT.

Al Hamad et al. published the first report of a HCC patient undergoing SBRT with 50 Gy in five fractions while awaiting LT. Following LT, pathological examination of the liver explant revealed only scarring at the irradiated site [58].

Sandroussi et al. reported their experience in 10 patients with either failure from prior local therapies or unsuitability for standard local therapies [56]. The safety and efficacy of SBRT as a bridging therapy was evaluated. The median SBRT delivered dose was 33 Gy (range 8.5–54 Gy) in one to six fractions. Nine patients completed their SBRT as planned and one patient was transplanted after the first fraction. Two tumors remained stable, and the others had 10–50 % regression, sustained on follow-up images. Two patients were delisted as a result of cancer progression outside the treated field. Three patients were still waiting for LT. Five patients who underwent LT had a demonstrable pathological response with the degree of necrosis ranging from 40 % to 90 %. With a median follow-up of 14 months, all five patients survived with no disease progression.

Table 4 Summary of studies using SBRT as a bridge for liver transplantation

Author	No. of patients	Lesions	No. of patients who received previous treatment (TACE/RFA)	RT_dose	Tumor volume/tumor diameter	MC ⁺	MC [−]	Toxicity ≥ grade 3	Radiographic tumor response after RT	Pathology response	No. of months to transplant	Median follow-up	Local control	No. of patients who received liver transplant	No. of patients delisted	No. of patients who received hepatic resection	No. of patients still on wait list	OS	DFS	Reference
O'Connor et al.	1018	11	4	33–54 Gy/3 frx	2.5–5.5 cm (median 3.4 ml)	0	10	0 %	SD: 5 patients PR: 1 patients	CR: 27 %	0.3–26 (median 3.7)	62 months	100 %	10	0	0	0	5y 100 %	5y 100 %	[55]
Katz et al.	21	3	3	50 Gy/10 frx	31–137 ml (median 63 ml)	3	15	0 %	PR: 4 patients SD: 7 patients NR: 7	100 % necrosis: 2 lesions >50 % necrosis: 3 lesions ≤50 % necrosis: 4 lesions No necrosis: 2 lesions	0.6–11.6 (median 6.3)	19.6 months	100 %	11	6	1	0	2y 100 %	NR	[10]
Andolino et al.	23	32	0	32–48 Gy/3–5 frx	2–77 ml (median 16 ml)	NR	NR	35 % ^a	CR: 30 % ^a PR: 40 % SD: 25 %	NR	Median 7	22 months	100 %	23	0	0	0	2y 96 %	2y 69 %	[57]
Sandroussi et al.	10	NR	5	8.5 Gy/1 frx 23–54 Gy/5–6 frx	15–798 ml (median 79 ml)	8	10	0 %	SD: 2 patients PR: 7 patients NR: 1	40–90 % necrosis: 5 patients	9–17 (median 11)	14 months	100 %	5	2	0	3	NR	NR	[56]

RT radiotherapy, MC[−] does not meet the Milan criteria, MC⁺ meets Milan criteria, OS overall survival, DFS disease-free survival, frx fractions, CR complete response, PR partial response, SD stable disease, PD progression of disease, NR not reported

^a Included patients who were not transplanted. All were of grade 3 hematologic/hepatic toxicity

The largest series, reported by Andolino et al., described 23 of 60 patients with liver-confined HCC undergoing LT after SBRT [57]. The median dose was 44 Gy in three fractions for those with Child-Pugh A cirrhosis and 40 Gy in five fractions for those with Child-Pugh B cirrhosis. The median time to transplant was 7 months. Neither median progression-free survival nor overall survival has yet to be achieved at the time of the report. The actuarial rates at 2 years were 69 % and 96 %, respectively. For the entire cohort, the rates of complete response, partial response, and stable disease were 30 %, 40 %, and 25 %, respectively. Of the 21 patients (35 %) who developed grade 3 hematologic/hepatic toxicity, 17 had preexisting grade 2 dysfunction. Patients who did not undergo transplant were 2.7 times more likely to experience progression and 17.1 times more likely to die than were patients who did undergo transplant.

Another study by Katz et al. retrospectively reviewed 18 patients receiving SBRT with a median dose of 50 Gy in 10 fractions [10]. Six of 18 patients were delisted because of disease progression or other causes. Twelve patients successfully underwent major hepatic resection (one patient) or LT (11 patients). Ten patients with 11 lesions were evaluable for pathological response, and five of them had more than 50 % necrosis. All patients were alive after LT and/or hepatic resection at a median follow-up of 19.6 months. Only one patient developed intrahepatic recurrence.

O'Connor et al. reported a series of 10 HCC patients undergoing SBRT as a bridge to LT [55]. The median dose was 51 Gy in three fractions. Median time from SBRT to LT was 62 months. Based on explant pathology, 27 % of patients had complete tumor necrosis. All the remaining patients' tumors decreased or remained stable in size. The median survival was not reached. The 5-year overall and disease-free survival were 100 %.

In summary, SIRT and SBRT may be practically considered as a bridge to LT while awaiting a donor. Some patients may benefit from SIRT (23–53 %) or SBRT (50–100 %) with the downstaging effect to meet the LT criteria [7, 53]. The results of SIRT and SBRT are complimentary to each other as an adjunct to LT.

Future directions

Sorafenib (Nexavar; Bayer, West Haven, CT, and Onyx, Richmond, CA) is a molecular-targeted therapy used in the palliative treatment of advanced HCC in Child-Pugh A or selected patients with Child-Pugh B. Its clinical use is supported by the results of two randomized phase III trials (the SHARP trial and the Asia Pacific trial). In the SHARP trial, the median TTP was 5.5 months and 2.8 months with sorafenib and placebo, respectively [12]. The 1-year survival rates were 44 % and 33 % with sorafenib and placebo,

respectively. Among patients with hepatitis C, median overall survival (14.0 vs. 7.9 months) and median TTP (7.6 vs. 2.8 months) were significantly prolonged with sorafenib. In the Asia Pacific trial, the median TTP were 2.8 months and 1.4 months with sorafenib and placebo, respectively [59]. The 6-month survival rates were 53 % and 37 % with sorafenib and placebo, respectively. Of note is that no patient in both trials achieved a complete response.

Because of the modest benefits by sorafenib, the combination of sorafenib and RT is being studied. In a case report, combined sorafenib and RT resulted in marked tumor shrinkage [60]. In an early experience of 20 HCC patients receiving the combined regimen, 22 % in-field response was observed. Other potential radiosensitizers are under investigation, such as sunitinib (Sutent; Pfizer, New York, NY) and AR-42 (Armo Therapeutics, Inc., Fairfield, NJ). [61, 62]. To date, there is no randomized trial evaluating the combination of a molecular-targeted radiosensitizer with RT in the treatment of HCC.

Conclusion

SBRT and/or SIRT are promising local ablative modalities for patients with unresectable liver tumors. Currently, supportive data is limited to phase 1 or 2 studies. Future research will focus on combining different therapeutic modalities, including SBRT, SIRT, TACE, and novel targeting agents.

Conflict of interest The authors declare that they have no conflicts of interest.

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