Chapter 11
Radiation Oncology in the Treatment of Hepatocellular Carcinoma

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Abstract Optimizing the therapeutic ratio and achieving an adequate safety profile in the treatment of hepatocellular carcinoma (HCC) with radiation therapy (RT) has historically been a challenge. Although HCC is a radiosensitive tumor, it is surrounded by highly radiosensitive organs, including the remainder of the liver and hollow gastrointestinal viscera. As technology has advanced to the point of allowing a highly conformal dose to be delivered to the tumor while sparing the surrounding normal tissues, RT has re-emerged as a viable treatment modality for many patients with HCC, pending randomized controlled trials to confirm its efficacy. Options for RT include stereotactic body radiotherapy (SBRT), external beam radiation therapy (EBRT), and radioembolization. SBRT, which involves the precise delivery of highly conformal, image-guided, ablative doses of external beam radiation, has been shown to be an effective alternative to other ablative procedures in nonsurgical candidates with tumors up to 6 cm in size, including HCC in patients with cirrhosis. Radioembolization involves catheter-based infusion of radioactive particles (such as Yttrium-90-labeled microspheres) targeted at the hepatic artery branches that feed the tumor. Typical prescription doses are in the range of 120–150 Gy, significantly higher than those possible with EBRT. Radioembolization may be used in patients with unresectable primary HCC with liver-dominant tumor burden and life expectancy >3 months. For patients with large HCCs, treatment options include conventionally fractionated EBRT. EBRT is considered safe for all patients with Child-Pugh class A or B.

Keywords Personalized medicine · Hepatocellular carcinoma · Treatment · Locoregional therapy · Radiation therapy · Stereotactic body radiotherapy (SBRT) · External beam radiation therapy (EBRT) · Radioembolization · Yttrium-90 microspheres

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11.1 Introduction

Optimizing the therapeutic ratio and achieving an adequate safety profile in the treatment of hepatocellular carcinoma (HCC) with radiation therapy (RT) has historically been a challenge, as although HCC is a radiosensitive tumor, it is surrounded by highly radiosensitive organs, including the remainder of the liver and hollow gastrointestinal viscera. As technology has advanced to the point of allowing a highly conformal dose to be delivered to the tumor while sparing the surrounding normal tissues, radiotherapy has re-emerged as a viable treatment modality for many patients with HCC, pending randomized controlled trials to confirm its efficacy.

11.1.1 External Beam Radiotherapy in the Treatment of Hepatocellular Carcinoma

Some of the earliest trials of irradiation for HCC involved treating the whole liver, though outcomes were generally poor, with 2-year survival rates < 10 %. The advent of computed tomography (CT)-based treatment planning, intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy has allowed for better targeting of the tumor and sparing of surrounding tissue, which in turn has led to a series of trials evaluating whether increasing the dose of radiation improves tumor control and survival. Dawson et al. reported that patients with unresectable tumors who received doses > 70 Gy had a better median survival (> 16.4 mo) than those who received a lesser dose, with a 68 % response rate overall [1]. Mornex et al. showed similar encouraging results in a small Phase II trial, in which tumors < 5 cm were treated to a dose of 66 Gy in 2 Gy fractions, resulting in an 80 % complete response (CR) rate. Grade 4 toxicity was observed in 22 % of patients in this study, though all of them had Child-Pugh class B cirrhosis prior to treatment [2]. Determining dose allocation can be aided with the use of the normal tissue complication probability (NTCP) model for intrahepatic malignancy, which can predict the probability of radiation-induced liver disease (RILD) after treatment to a given dose and volume of liver [3]. Based on this model, patients are to receive a maximum possible dose to the tumor while being subjected to no more than a 10 % risk of RILD. Of note, the NTCP model is limited by the fact that it was not validated for patients with moderate-severe liver disease, which unfortunately represents the majority of patients with HCC. As such, caution should be used when adopting the NTCP model to this group of patients.

The safety and efficacy of conventionally fractionated external beam radiation therapy (EBRT) has also been studied in combination with transarterial chemoembolization (TACE), in an attempt to improve outcomes with a dual modality approach. Seong et al. reported on 158 patients, with a median tumor size of 9 cm, who received 48 Gy either in combination with or after failure of TACE. The objective response rate in this study was 67 %, with a 16 month median survival [4]. Zeng et al. also reviewed 203 patients with unresectable HCC who received TACE with

or without radiation therapy (RT), finding that RT appeared to improve survival in each of the first 3 years after treatment [5]. Finally, Oh et al. reported on prospectively treating 40 unresectable HCC patients who had an incomplete response to 1–2 courses of TACE with 54 Gy, achieving a response rate of 63 % with 2-year overall survival of 46 % [6]. Though none of these studies were randomized, they all support the premise that conventionally fractionated radiotherapy may have some survival benefit in combination with TACE, and is well tolerated overall.

Another potential indication for radiotherapy is in the setting of portal vein tumor thrombosis (PVTT). These patients have a poor prognosis, and in many institutions are not considered candidates for TACE. Tazawa et al. treated 24 patients with PVTT with 50 Gy RT delivered focally to the thrombus, achieving an objective response rate of 58 % and 1-year overall survival of 41 % [7]. A similar approach, using either conventionally fractionated and hypofractionated radiotherapy targeted at the portal vein thrombus, has yielded response rates in the range of 45–83 % in several studies [8–10].

Overall, patients with unresectable, liver-confined HCC treated with conventionally fractionated, conformal radiotherapy can achieve durable tumor responses with an acceptable safety profile, though no RCTs have been carried out to demonstrate a survival benefit. Local control rates range from 40 to 90 % and median survival 10–25 months in various trials [11], depending on several patient and treatment-related factors. Indications for RT may include large unresectable tumors in a patient who is not a candidate (or has failed) other local therapy. Relatively good liver function is necessary for maintaining an adequate safety profile, and the predicted risk of RILD should be kept below 10 % for a given treatment plan. Within these parameters, dose escalation up to a maximum of 90 Gy is associated with the best outcomes.

11.1.2 Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT), which involves the precise delivery of highly conformal, image-guided, ablative doses of external beam radiation in an abbreviated course of five fractions or less, has been shown to be an effective alternative to other ablative procedures in nonsurgical candidates with tumors up to 6 cm in size. SBRT is also unique from all other therapeutic options in that it is noninvasive. To ensure that enough residual liver is spared from RT, it is important to keep the target volume as small as possible, which has been made feasible through the use of advanced treatment-planning technologies like multi-phasic and multi-modality imaging, breathing motion management, highly conformal plans, and image-guided treatment delivery. The safety and efficacy of SBRT has been shown in several prospective studies of metastatic lesions in noncirrhotic livers [12, 13], and in the past few years data has also emerged from several groups reporting success in treating HCC with SBRT in patients with cirrhosis.

The largest series of patients enrolled in a prospective trial in the United States comes from Indiana University [14, 15], with the Phase I and subsequent Phase II

trials including 60 patients with Child-Pugh score < 7 (though there were nine patients with Child-Pugh score 8–9 included in the Phase 1 trial) who had 1–3 tumors of < 6 cm in cumulative diameter. These were relatively early tumors, as 85 % had a single lesion, the median tumor diameter was 3.1 cm, 60 % were Child-Pugh class A, the median CLIP score was 1, and the median KPS was 90. A stereotactic body frame with abdominal compression was used to immobilize the patient, and margins around the gross tumor were 0.5 cm radial and 1.0 cm superior-inferior. In the Phase II portion of the study, a dose of 48 Gy in 3 fractions (over 5–10 days) was given to patients with Child-Pugh class A, while 40 Gy in 5 fractions (over 3–6 weeks) was given to patients with Child-Pugh class B. Dose-volume constraints were also more rigorous for those patients with Child-Pugh class B (500 cc normal liver was to receive < 12 Gy and one-third of the normal liver was to receive < 18 Gy) than in those patients with Child-Pugh class A (500 cc normal liver was to receive < 7 Gy and one-third of the normal liver was to receive < 10 Gy). At a median follow-up of 26 months, a 70 % complete or partial response rate was observed, with an actuarial 2-year local control (LC) of 90 %. Of note, even though all patients were considered ineligible for transplant at study entry, 40 % of the patients eventually received a liver transplant. Excluding this subgroup from the survival analysis, the median progression-free survival (PFS), overall survival (OS) and time-to-progression (TTP) were 14.1, 20.4, and 36.5 months, respectively. The site of first failure was mostly regional (50 %), meaning elsewhere in the liver. The treatment was well-tolerated overall, with only 12 % of patients with a Child-Pugh score < 7 enduring an increase in hematologic or hepatic dysfunction greater than one grade, and 20 % of patients experiencing an increase in Child-Pugh class within 3 months of treatment. However, the patients from the phase I study with Child-Pugh score 8–9 did have higher rates of toxicity, with 4 of 8 patients developing progressive liver failure (though two of these patients received a higher dose than was later allowed in the phase 2 portion of the trial). Overall, outcomes from this study compare favorably to those of radiofrequency ablation (RFA), TACE, and other locoregional therapies. The median survival to the non-transplant cohort was also comparable to a predicted 22 months for all comers with a CLIP score of 1 [16]. Given these favorable results, the authors report that at their institution, in eligible patients with well-compensated cirrhosis, SBRT is now considered the primary modality for bridging to transplant, and is also strongly considered for first-line definitive therapy in patients who are not transplant candidates.

Similar findings were also reported in a Korean study [17], in which 42 patients (90 % of which were Child-Pugh class A with median tumor size of 15.4 cm^3) underwent 30–39 Gy SBRT in 3 fractions. Of note, unlike in the American series, most of the HCC in this study was HBV-induced, which may have implications in tumor biology or response to radiotherapy. Despite the lower radiation dose, the in-field response rate was 85 %, in-field 3-year PFS was 68 %, median PFS was 15.4 months, and 3-year overall survival was 59 %. Most recurrences were again regional (within the liver but outside the radiation field). One patient had late liver failure, though < 10 % had significant hematologic/hepatic toxicity. In the largest

Table 11.1 SBRT absolute contraindications

Child-Pugh score > 10
< 800 cc of uninvolved liver
Tumor < 0.5 cm from a hollow viscous
Radiation tolerance parameters for uninvolved liver cannot be achieved
Child-Pugh A: 500 cc of normal liver < 7 Gy, $^{1}/_{3}$ of normal liver < 10 Gy
Child-Pugh B: 500 cc of normal liver < 12 Gy, $^{1}/_{3}$ of normal liver < 18 Gy

series, Sanuki et al. reported on the Japanese experience of 185 patients with tumors < 5 cm who were treated in five fractions to a total dose of 40 Gy (for Child-Pugh class A) or 35 Gy (for Child-Pugh class B), with dose reductions as necessary to keep the percentage of liver receiving 20 Gy below 20 % [18]. Outcomes were again excellent, with three year LC 91 % and OS 70 %, both of which were independent of the dose level used. Ten percent of patients had worsening Child-Pugh score by at least two points, though this was reversible in all but 3 patients (two of which with Child-Pugh class B died of liver failure).

Finally, hypofractionated radiation therapy has also been shown to be feasible in patients with larger tumors and more advanced disease, as has been reported in a large Canadian series of 102 patients [19]. In this study, the median tumor volume was 173 cm^3, 55 % of patients had a vascular tumor thrombus, and 61 % had multifocal disease. The dose prescribed was determined according to the estimated risk of RILD, with median dose 36 Gy (range 24–54 Gy) in 6 fractions over 2 weeks. Given the more advanced tumors in this study, along with the fact that the larger tumors received lesser doses due to a higher risk of RILD with larger treatment volumes, it is not surprising that the median PFS was only 5.4 months, considerably lower than the other SBRT studies. However, LC at 1 year was 87 %, and median survival was 17 months, both of which are better than expected for this group of patients. The most frequent site of progression was again outside the treatment volume. Of note, there were 7 deaths that may have been treatment related, and Child-Pugh score progression was observed in 30 % of patients within 3 months of RT, some of which was reversible. The higher toxicity can again probably be accounted for by the large volumes treated, but tumor progression certainly also contributed.

The absolute and relative contraindications of SBRT are shown in Tables 11.1 and 11.2, respectively. Child-Pugh class is an important predictor of morbidity, and while there is sufficient safety data in class A, SBRT should be used with caution (or not at all) in classes B and C. The presence of portal vein thrombosis does not impact the safety or efficacy of SBRT. Other procedural considerations to prevent toxicity, which are not contraindications per se, include keeping an interval of 14 days between SBRT and chemotherapy, and 6 months between SBRT and any local embolization procedure. There may also be some situations in which SBRT is technically feasible, but systemic therapy or best supportive care is more appropriate than any local therapy, including patients with life expectancy < 12 weeks, or patients with progressive or untreated gross extrahepatic disease.

Table 11.2 SBRT relative contraindications

Child-Pugh Score 8–9 (especially if not on the liver transplant list)
ECOG > 2 or KPS < 70
> 3 lesions, or total size of lesions > 6 cm
History of right upper abdomen radiation therapy
Active hepatitis (viral or nonviral)
Significant ascites
Renal insufficiency (Cr > 1.8 or CrCl < 50)
Liver function abnormalities:
Bilirubin > 3 mg/dL
Albumin < 2.5
AST/ALT > 3 × upper limit of normal
PT/PTT > 1.5 × upper limit of normal (and not correctable with Vitamin K)
CBC Abnormalities:
ANC < 1000
Platelets < 50,000
Hemoglobin < 9

In summary, SBRT appears most applicable to relatively small, inoperable tumors, though it could be considered for larger lesions if there is at least 800 cm^3 of uninvolved liver and the liver radiation tolerance is respected. Child-Pugh class is an important predictor of morbidity, and while there is sufficient safety data in Child-Pugh class A, SBRT should be used with caution (or not at all) in Child-Pugh class B and C. Although there is no randomized data comparing SBRT to RFA or TACE, Phase I/II trials suggest comparable, if not superior outcomes with SBRT. At this time, we suggest that the decision for the most appropriate modality be as individualized as possible to the patient, making use of a multidisciplinary tumor board or clinic whenever feasible. With a lack of randomized data to support one modality over another, much of the decision-making at this time will be institution specific.

11.1.3 Radioembolization

The technique of radioembolization is similar in many ways to any other embolization procedure (e.g. TACE), in that it involves catheter-based infusion of particles targeted at the arterial branch of the hepatic artery feeding the portion of the liver where the tumor is located. However, unlike chemoembolization, in which the mechanism of action of tumor necrosis is ischemia secondary to reduced blood flow, the mechanism of action in radioembolization is primarily due to radiation induced necrosis. Since radioembolization has minimal embolic effect, and won't

obstruct the blood supply to the functional liver, it is often considered the safer alternative to TACE for tumors with portal vein thrombosis.

There are two different radioisotopes used for radioembolization worldwide, Iodine-131[I-131]-labeled Lipiodol and Yttrium-90[Y90]-labeled microspheres. The former is not used in the USA due to lack of availability. The latter is available either as the glass Theraspheres or resin SIR-Spheres, with Theraspheres being the more common alternative in North America. Y90 is a β-emitter, with a half-life of 64 h, and maximum penetration of 11 mm in tissue. Typical prescription doses are in the range of 120–150 Gy, significantly higher than those possible with EBRT. According to the Radioembolization Brachytherapy Oncology Consortium Consensus Guidelines, Therasphere may be used in patients with unresectable primary HCC with liver-dominant tumor burden and life expectancy >3 months [20]. Prior to treating a patient, it is important to do a 99^{m}-Tc macroaggregated albumin (MAA) scan to demonstrate that there is no shunting of blood flow to the lung or gastrointestinal tract that cannot be corrected by catheter techniques. The potential for ≥30 Gy radiation exposure to the lung is considered an absolute contraindication to radioembolization. Relative contraindications include a limited hepatic reserve, irreversibly elevated bilirubin and prior RT involving the liver.

The largest prospective trial evaluating Therasphere comes from Northwestern University [21]. 291 patients with HCC were treated, with response rates of 42% using WHO criteria and 57% using EASL criteria. The median TTP was 7.9 months for the entire cohort, and outcomes were strongly correlated with Child-Pugh score and the presence or absence of portal vein tumor thrombosis (PVTT). While Child-Pugh class A patients without PVTT could expect a median TTP of 15.5 months, Child-Pugh class B patients without PVTT had a median TTP of only 13 months. Median TTP was only 5.6–5.9 months for all patients with PVTT, regardless of Child-Pugh score. Complications of treatment most commonly involved a mild postembolization syndrome of fatigue, constitutional symptoms, and abdominal pain (20–55%). Grade 3 or 4 elevation in bilirubin was seen in 19% of patients, while the 30-day mortality was 3% of patients.

Given the significant overlap in patient eligibility for radioembolization and chemoembolization, a randomized trial comparing the two was carried out in France, in which 142 patients with unresectable HCC were randomized to I-131-labeled Lipiodol or TACE [22]. In this study, the response rate and survival were similar in both arms at 1 and 3 years follow-up, however, there was significantly less toxicity in the radioembolization arm, with only 3 patients having severe side effects (as compared to 29 patients after chemoembolization). There are no randomized trials to date involving Therasphere, however, a recent comparative analysis published again by the group at Northwestern by Salem et al. suggests that radioembolization results in a better median TTP than TACE (13 vs. 8 months, respectively), again with less toxicity. There was no difference in median survival in the two groups [23]. It is important to note that in these studies, the chemoembolization groups were treated with the lipiodol technique (70 mg cisplatinum diluted in 140 mL of saline solution and 10 mL Lipiodol [22] and 30 mg mitomycin, 30 mg adriamycin and 100 mg

cisplatin mixed with lipiodol [23]). The more recently introduced technique with drug-eluting beads has been shown to have lower toxicity, as discussed in Chap. 7c.

In summary, radioembolization is an emerging technology in the USA that may be better tolerated than TACE, with similar (if not somewhat improved) efficacy. It is also thought to be a safer alternative than TACE in patients with PVTT, but given the short median survival of these patients, it is unclear if they would benefit more from it than they would from systemic therapy alone. The expense of radioembolization also remains an issue, though may become less so if randomized data were to further clarify the optimal indications for, and benefit from its use. With respect to toxicity, trials comparing radioembolization with TACE with drug-eluting beads will be helpful.

Conclusion

Considering the various forms of treatment for HCC, including radiotherapy, it is necessary to consider patient-specific factors in selecting the optimal treatment. Personalized management of HCC requires the selection of individual and/or combined treatment modalities, provided by different clinicians. For example, there are several types of local therapy for HCC that may be applicable either as a bridging therapy in those patients awaiting transplant, or as a means of attempting to downstage a tumor in a patient with liver-confined disease. While the choice of a therapeutic regimen relies heavily upon the local expertise at a given institution, there are several patient- and tumor-specific characteristics that can guide management.

The indications for SBRT and RFA are somewhat overlapping, in the sense that the optimal candidate for both procedures is a patient with up to 3 lesions, with a total size (of the lesions combined) <6 cm. There is some data to suggest that SBRT can be done for any size lesion assuming that a patient has >800 cc of uninvolved liver and radiation tolerance limits for that normal liver are respected, however, this data comes from a single institution only, and should be further studied to confirm its safety. Although there are no RCTs comparing SBRT to RFA, prospective data suggests that SBRT has approximately equivalent local control rates to RFA for lesions <3 cm, and better local control than RFA for lesions >3 cm. SBRT may be favored for lesions located on the liver capsule due to the risk of tumor rupture and seeding with RFA. SBRT may also be favored for lesions close to major blood vessels, as RFA may be less effective in this situation due to the heat sink phenomenon. Conversely, RFA should be favored, with caution, when the tumor is in close proximity (<0.5 cm) to a hollow viscous (duodenum, stomach, colon) due to the risk of perforation after SBRT.

For patients with larger lesions, options for local therapy include TACE, radioembolization, and conventionally fractionated EBRT. Retrospective data suggests that radioembolization is better tolerated than TACE (with lipiodol techniques), with similar (if not somewhat improved) efficacy. Whereas portal vein thrombosis is a relative contraindication to TACE, it is not a concern for patients receiving

radioembolization or EBRT. Absolute and relative contraindications for radioembolization and EBRT are similar to those for SBRT, though with some variation in radiation dose constraints to the liver and other organs at risk. Prior to radioembolization, a ^{99m}Tc macroaggregated albumin (MAA) scan must be obtained, and if there is a potential for ≥ 30 Gy radiation exposure to the lung (via a "lung shunt"), or if there is flow to the GI tract that cannot be corrected by catheter techniques, radioembolization is contraindicated. EBRT requires sparing of at least 20% of the total liver volume ($V_{effective} < 0.8$), and that strict dose-volume constrains be used for the uninvolved liver to keep the risk of radiation-induced liver disease < 10%. Given the low dose per fraction used in EBRT, the proximity of a tumor to a hollow viscous is of no concern for toxicity. Assuming that the above criteria are met, radioembolization or EBRT are considered safe for all patients with Child-Pugh class A or B (though not class C). Though clinically useful in patients with larger tumors, neither of these therapies would be used for smaller tumors amenable to SBRT.

References

1. Dawson LA, McGinn CJ, Normolle D et al (2000) Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol 18:2210–2218
2. Mornex F, Girard N, Beziat C, et al (2006) 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 66:1152
3. Dawson LA, Normolle D, Balter JM et al (2002) Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 53(4):810–821
4. Seong J, Park HC, Han KH, Chon CY (2003) Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: a retrospective study of 158 patients. Int J Radiat Oncol Biol Phys 55:329
5. Zeng ZC, Tang ZY, Fan J et al (2004) A comparison of chemoembolization combination with and without radiotherapy for unresectable hepatocellular carcinoma. Cancer J 10(5):307–316
6. Oh D, Lim do H, Park HC et al (2010) Early three-dimensional conformal radiotherapy for patients with unresectable hepatocellular carcinoma after incomplete transcatheter arterial chemoembolization: a prospective evaluation of efficacy and toxicity. Am J Clin Oncol 33:370
7. Tazawa J, Maeda M, Sakai Y et al (2001) Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. J Gastroenterol Hepatol 16:660–665
8. Nakagawa K, Yamashita H, Shiraishi K et al (2005) Radiation therapy for portal venous invasion by hepatocellular carcinoma. World J Gastroenterol 11:7237–7241
9. Choi BO, Choi IB, Jang HS et al (2008) Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. BMC Cancer 8:351
10. Kim JY, Chung SM, Choi BO, Kay CS (2011) Hepatocellular carcinoma with portal vein tumor thrombosis: improved treatment outcomes with external beam radiation therapy. Hepatol Res 41:813–24. doi:10.1111/j.1872-034X.2011.00826.x
11. Hawkins MA, Dawson LA (2006) Radiation therapy for hepatocellular carcinoma: from palliation to cure. Cancer 106:1653–1663

12. Rusthoven KE, Kavanagh BD, Cardenes H et al (2009) Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 27:1572–1578
13. Herfarth KK, Debus J, Lohr F et al (2001) Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol 19:164–170
14. Cárdenes HR, Price TR, Perkins SM et al (2010) Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol 12: 218–225
15. Andolino DL, Johnson CS, Maluccio M et al (2011) Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 81:e447–453
16. Llovet JM, Bruix J (2000) Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 32:679–680
17. Kwon JH, Bae SH, Kim JY et al (2010) 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 10:475
18. Sanuki N, Takeda A, Oku Y et al (2013) Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. Acta Oncol 53:399–404
19. Bujold A, Massey CA, Kim JJ et al (2013) Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31:1631–1639
20. Kennedy A, Nag S, Salem R et al (2007) Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 68:13
21. Salem R, Lewandowski RJ, Mulcahy MF et al (2010) Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 138:52–64
22. Raoul JL, Guyader D, Bretagne JF et al (1997) Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology 26:1156–1161
23. Salem R, Lewandowski RJ, Kulik L et al (2011) Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 140:497–507.e2