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Radiation Therapy for Colorectal Liver Metastases

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Abstract
Purpose of Review The purpose of the present study is to review the management of colorectal liver metastases (CLM) with radiation therapy (RT).
Recent Findings Conventional RT is a local-regional modality that may provide symptomatic palliation, local control, and potential for prolongation of survival. Studies of RT to the liver contributed to understanding of the volume effect of liver toxicity and the potential for dose escalation to limited volumes. Stereotactic body radiation therapy (SBRT) delivers highly conformal ablative doses, providing high rates of local control without associated increases in toxicity. Radioembolization can provide local control for chemorefractory patients, but its added value in the first-line setting with modern systemic therapy remains an area of active investigation.
Summary SBRT and radioembolization play key roles in the modern management of patients with CLM who are not eligible for surgery. Patients with limited burden of intrahepatic disease may be ideally suited for SBRT, while those with higher number (≥3) of CLM may be more appropriate for transarterial radioembolization.

Keywords Colorectal liver metastases · Stereotactic body radiation therapy · Radioembolization · External beam radiation therapy

Introduction

In 2016, colorectal cancer (CRC) was diagnosed in over 134,000 people and responsible for over 49,000 deaths [1], ranking as the third most common for both cancer diagnosis and cause of cancer death in the USA. The liver is the most common site of metastatic spread for CRC. Up to a quarter of patients with primary CRC have synchronous liver metastases at time of diagnosis, and up to 50% develop colorectal liver metastases (CLM) during their lifetime [2, 3]. Traditionally, surgery has been the mainstay of curative therapy for patients with metastatic CRC with oligometastatic disease to the liver. National guidelines such as those from the National Comprehensive Care Network recommend surgical resection followed by systemic therapy for patients with resectable liver metastases or upfront systemic therapy in an attempt to convert patients with unresectable disease to resectable [4].

Unfortunately, up to 80% of patients present with unresectable hepatic metastases [5] due to medical comorbidities, extensive extrahepatic disease, significant intrahepatic burden of disease limiting the volume of a functional liver remnant, or unfavorable anatomic location of the tumor [6]. As the prognosis for untreated CLM is very poor [7–10], patients who cannot receive surgery can derive significant benefit from other forms of aggressive liver-directed therapy. Recent advances have provided patients with alternative treatment options including chemoembolization, radiofrequency, alcohol ablation, cryo-ablation, conventional external beam radiation therapy (EBRT), stereotactic body radiation therapy (SBRT), transarterial radioembolization (TARE), and

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brachytherapy. Emerging studies have shown that such modalities can offer promising local control rates and improved survival for select patients. Given the availability and variety of local-regional treatment options, multi-disciplinary tumor board discussion represents the best way to determine optimal treatments for individual patients. A general treatment algorithm is proposed in Fig. 1 but is highly dependent on available resources and institutional practice and expertise. In this article, we will describe key principles of treatment and review existing clinical data related to core modalities of radiation therapy—EBRT, SBRT, TARE, and BT.

External Beam Radiation Therapy

Conventional External Beam Radiation Therapy

EBRT is a local-regional treatment that delivers high-energy photons (X-rays) that, upon interaction with water-based tissue, generate free radicals, which in turn cause DNA damage on a cellular level. Conventionally fractionated EBRT utilizes fraction sizes in the range of 1.8–2 Gy given daily, which allows for normal tissue repair between treatments but requires several fractions to achieve an ablative dose.

Prior to the advent of conformal techniques of radiation delivery, EBRT had a limited role in the definitive management of liver lesions. The doses needed to control solid tumors elsewhere in the body could not be administered in the liver due to concerns of toxicity to the surrounding healthy liver. In 1965, Ingold et al. first described the phenomenon now known as radiation-induced liver disease (RILD) in a group of patients who underwent whole-liver irradiation (WLI) [11]. The classic triad of RILD consists of hepatomegaly, ascites, and alkaline phosphatase elevation, with development of anicteric ascites up to 4 months after treatment [12]. Thus, early studies of liver irradiation with conventional RT for liver metastases were conducted in the palliative setting.

Multiple single institutions have reported outcomes using WLI suggesting that EBRT to 20–30 Gy can result in excellent rates of palliation (55–95%) for pain, jaundice, constitutional symptoms, and tumor shrinkage and improvements in liver function tests [11, 13–17]. Based on these data, the Radiation Therapy Oncology Group (RTOG) conducted a prospective multi-institutional nonrandomized pilot study of 109 patients with metastatic liver lesions treated to 20–30.4 Gy in 7–19 fractions with an optional boost for patients with a single liver metastasis. Symptomatic pain from liver metastases improved in 55% of patients, with no incidence of radiation-induced liver injury, nephritis, or pneumonitis

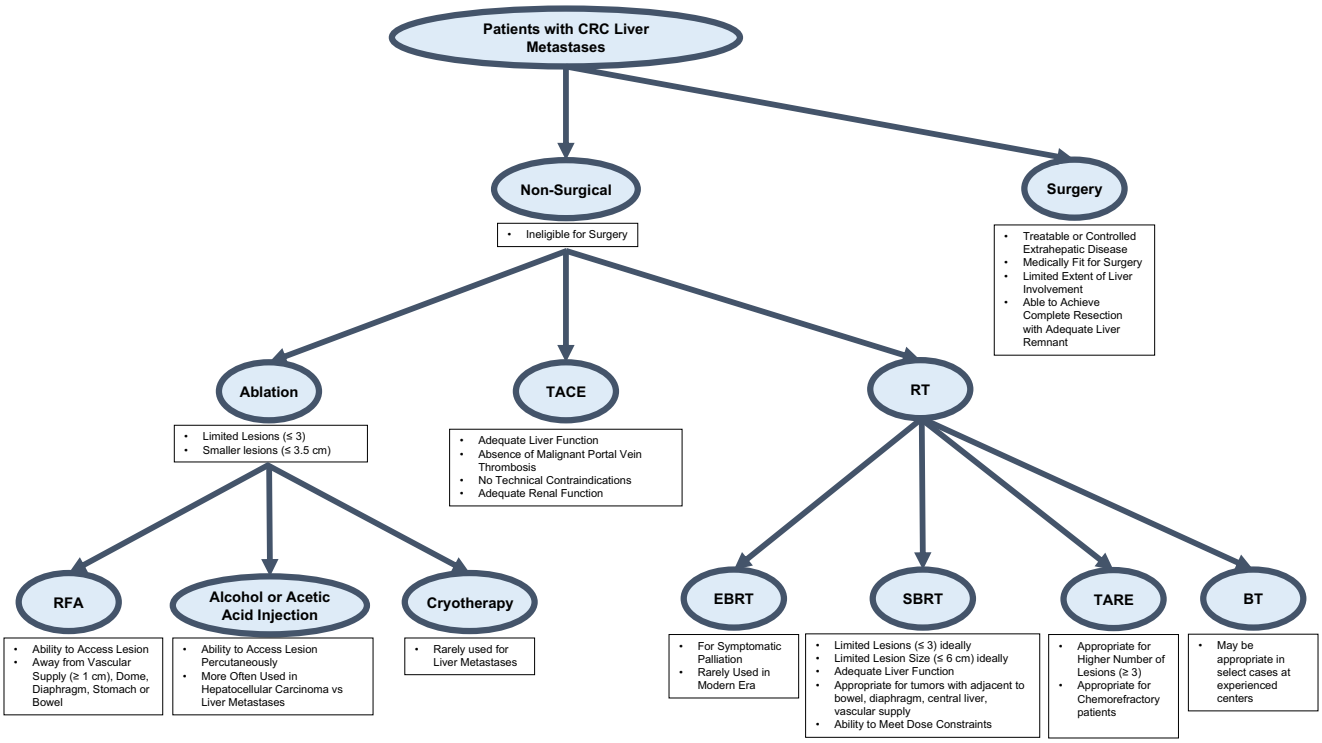

Fig. 1 Proposed treatment algorithm diagram for select loco-regional modalities for patients with colorectal liver metastases. Various treatment modalities and simplified patient selection factors associated with each modality are listed. It should be noted that this algorithm is highly dependent on available resources and institutional practice and expertise. Colorectal cancer (*CRC*), radiofrequency ablation (*RFA*), transarterial chemoembolization (*TACE*), radiation therapy (*RT*), external beam radiotherapy (*EBRT*), stereotactic ablative radiation therapy (*SBRT*), transarterial radioembolization (*TARE*), brachytherapy (*BT*)

[18]. Another prospective RTOG trial studied combining liver RT to 21 Gy in 7 fractions, with the hypoxic cell sensitizer, misonidazole. Although the addition of misonidazole did not significantly improve the therapeutic response to RT, the results further confirmed high rates of pain relief (80% any relief, 54% complete pain relief), with median duration of response of 13 weeks in symptomatic patients. There was no significant morbidity noted, with 22% of patients experiencing radiation-induced nausea and no documented cases RILD [19].

Whereas the historical trend was irradiation to the whole liver, researchers from the University of Michigan demonstrated that development of liver toxicity was volume dependent, describing the risk of RILD as a function of mean liver dose in a normal tissue complication probability (NTCP) model [12, 20, 21]. Thus, there was a renewed interest on dose escalation but in smaller volumes. The University of Michigan reported results of a phase I/II trial of conformal RT combined with concurrent intraarterial hepatic fluorodeoxyuridine (FUDR) for 22 patients with unresectable CLM, with up to 72.6 Gy in 1.5-Gy fractions twice daily (BID). With the exception of the first three enrolled patients who received 30-Gy whole-liver RT, none experienced RILD [22]. Objective response rate was 50%, and median overall survival (OS) was 20 months, representing significant improvements from outcomes of early studies of WLI. The same group then reported results of an expanded phase II series of high-dose conformal RT with concurrent intraarterial hepatic FUDR for 128 patients with unresectable intrahepatic malignancies, of which 47 were CLM. Median RT dose delivered was 60.75 Gy in 1.75-Gy fractions given BID, and OS was 15.8 months for all patients (17.2 months for CLM patients) with the total dose being the only significant predictor of survival. Overall, there was 21 and 9% rate of grade 3 and 4 toxicity, respectively, with 4% chance of grade 3+ RILD including one case of grade 5 RILD [23].

Patients with CLM can suffer significant symptoms from liver metastases including pain, jaundice, and constitutional symptoms. Conventional RT can provide patients excellent rates of symptom palliation. However, a common limitation noted in studies is the duration of response that can be achieved after conventional RT, even to the whole liver. Nevertheless, evidence suggests that dose-escalated conformal RT to partial liver volumes may not only increase local control, but may also potentially increase survival for patients as well. These findings have set the stage for the emergence of SBRT for treatment of unresectable intrahepatic lesions.

Stereotactic Body Radiation Therapy

SBRT represents the modern pinnacle of dose-escalated radiotherapy. With recent advances in conformal techniques such as intensity modulation, advanced image guidance technology with intrafractional tumoral tracking, and extremely high rates of dose delivery, SBRT allows clinicians to precisely and accurately deliver ablative doses of radiation to an intended target with a sharp dose fall-off gradient at the periphery of the target. Liver SBRT involves precisely targeting the intrahepatic lesions while minimizing dose to normal liver and other organs at risk. Consistent with NTCP modeling of liver toxicity as a function of mean dose of whole liver, liver SBRT has not been associated with high rates of RILD despite escalated radiation doses because of such high degree of conformality.

Not all patients with liver tumors are appropriate candidates for liver SBRT; thus, patient selection is key. Tumors should be clearly defined on imaging. SBRT is an ideal procedure for patients with unresectable lesions who are ineligible for other local-regional therapies either due to concerns of insufficient efficacy, excessive toxicity, technical limitations, or other factors such as medical comorbidities. Although highly localized and precise, SBRT involves scatter RT dose to the healthy liver volume, so patients should ideally have healthy liver function (CTP class A) as well as sufficient volume to meet dose standards. Ideal patients should also have limited extent or controlled extrahepatic disease, favorable anatomic location of the tumor (away from critical organs such as bowel, central liver, and others), and limited size (ideally ≤6 cm) and number of hepatic lesions (ideally ≤3). In general, patients with CTP class C liver function, significant or uncontrolled extrahepatic disease, or insufficient liver volume spared should not be offered SBRT.

Published literature contains various retrospective and prospective reports with moderate heterogeneity between studies, especially in the patient population, as many studies are not specific to CLM, and variability in fractionation schemes of SBRT exists. For the purposes of this review, we will focus on prospective studies (Table 1).

Herfarth et al. studied single-dose SBRT for solitary unresectable liver metastases in a prospective phase I/II trial of 37 patients with 60 liver tumors (of which 30 were CLM) treated with 14–26 Gy in one fraction. Local control was 81% at 18 months, and median survival was 25 months, with no major side effects [24]. Tumor histology did not affect local control rates [25]. Goodman et al. also studied the feasibility of single-fraction SBRT for liver malignancies in phase I dose escalation study. Patients with primary or metastatic (73%) tumors, with maximum 5 tumors and maximum tumor diameter 5 cm, were treated with liver SBRT to 18–30 Gy in a single fraction. Cumulative risk of local failure at 1 year was 23% with median survival 28.6 months and 2-year OS of 50.4%, suggesting that single fraction liver SBRT can deliver promising local tumor control with minimal acute and long-term toxicity [31].

Reports using multi-fraction SBRT have also shown similarly promising local control rates with acceptable toxicity

Table 1 Outcomes of select prospective trials of liver SBRT for liver metastases

Reference	Phase	Patients with CLM	Median age (years)	No. of CLM tumors	Number and size of tumors in eligibility criteria	Mean/median tumor volume (cm^3)	Dose	Median follow up (months)	Grade 3 or higher toxicity	Grade 3 or higher classic RILD	Local control	Overall survival
Herfarth et al. [24, 25]	I/II	18 of 37 (49%)	61	30 of 60 (50%)	≤ 3 tumors (4 if tumors are close), max diameter ≤6 cm	10	14–26 Gy in 1 fraction	15.1	0%	0%	68% (18 months)	25 months (median)
Hoyer et al. [26]	II	64 of 64 (100%)	67	41 of 141 (28%)	≤4 tumors, max diameter ≤6 cm	22.4	45 Gy in 3 fractions	51.6	16.3% chest wall, GI	1.6 or 0% (unclear etiology of hepatic failure)	86% (2 years)	38% (2 years), 19.2 months (median)
Lee et al. [27]	I	40 of 68 (59%)	63	143 (N/A)	None	75.2	27.7–60 Gy in 6 fractions	10.8	9% Liver enzyme elevation, GI	0%	71% (1 year)	47% (18 month), 17.6 months (median)
Rusthoven et al. [28]	I/II	15 of 47 (32%)	58	63 (N/A)	≤3 tumors, max diameter ≤6 cm	14.9	36–60 Gy in 3 fractions	16	2% Chest wall	0%	92% (2 years)	30% (2 years), 20.5 months (median)
van der Pool et al. [29]	I/II	20 of 20 (100%)	72	31 of 31 (100%)	≤3 tumors, max diameter ≤6 cm	6.4	37.5–45 Gy in 3 fractions	26	10% Liver enzyme elevation	0%	74% (2 years)	83% (2 years), 34 months (median)
Mendez-Romero et al. [30]	I/II	15 of 25 (60%)	63	28 of 45 (62%)	≤3 tumors, max diameter ≤7 cm	22.2	25 Gy in 5 fractions or 30–37.5 Gy in 3 fractions	12.9	16% Liver enzyme elevation, hepatic failure	0%	82% (2 years)	54% (2 years)
Goodman et al. [31]	I	6 of 26 (23%)	63	40 (N/A)	≤5 tumors, max diameter ≤5 cm	32.6	18–30 Gy in 1 fraction	17	0%	0%	77% (1 year)	50.4% (2 years)
Scorsetti et al. [32••]	II	42 of 42 (100%)	67	52 of 52 (100%)	≤3 tumors, max diameter ≤6 cm	18.6	75 Gy in 3 fractions	24	0%	0%	91% (2 years)	83.5% (1 year) 29.2 months (median)

Colorectal liver metastases (CLM), radiation-induced liver disease (RILD), not available (N/A)

results. Mendez-Romero et al. reported prospective data on SBRT to 37.5 Gy in three fractions for patients with primary and metastatic liver lesions, with 94 and 82% rates of local control, respectively. Rates of toxicity were acceptable, with 5.9% rate of grade 3 or higher hepatotoxicity with serum GGT increase [30]. Rusthoven et al. reported results of a multi-institutional prospective phase I/II trial of three-fraction liver SBRT to 36–60 Gy for patients with one to three liver metastases, of whom 31% of patients had primary CRC. In-field local control rates were 95 and 92% at 1 and 2 years after SBRT, with 100% 2-year local control rate for tumors 3 cm or less in maximum diameter. Median survival was 20.5 months [28]. Grade 3 or higher toxicity was rare (2%). The authors concluded that high-dose three-fraction liver SBRT is a safe and effective treatment.

For more extended fractionation, a prospective pilot study from University of Rochester of SBRT for patients with five or less oligometastatic lesions (45% were liver metastases) to 50 Gy in ten fractions showed 2-year local control and OS rates of 67 and 50%, respectively. Lee et al. conducted a phase I study of six-fraction SBRT to median dose 41.8 Gy (range 27.7–60 Gy) for patients with unresectable liver metastases, of whom 61% had CLM. Local control at 1 year was 71% with median survival of 17.6 months. Other than a 5% incidence of grade 3 liver enzyme elevation, there was no RILD or other forms of grade 3+ hepatotoxicity noted [27].

Some recent prospective protocols using SBRT have limited patients strictly to CLM. Scorsetti et al. conducted a phase II study of SBRT for CRC metastases in the liver as well as other sites of metastatic spread such as the lung. Patients were treated to 45 Gy in three fractions with 2-year local control, progression-free survival, and OS of 86, 19, and 38%, respectively [32••]. One patient died of hepatic failure, though it was unknown whether it was due to radiation injury or thrombosis, and treatment was otherwise well tolerated. Similarly, favorable results were noted in another series of 20 consecutive patients with CLM treated with 37.5 or 45 Gy in three fractions with 2-year local control of 74 and 10% rate of grade 3 treatment-related hepatic injury (liver enzyme elevation) [29].

Limitations with many of the published data are the fact that they include a mix of histologies and do not report specifically on CLM. There is evidence that CRC metastases may be more radioresistant with lower control rates, compared to other histologies [33•], suggesting the need for higher doses of radiation. Chang et al. reported in a pooled analysis that the optimal dose to achieve a 90% local control rate at 1 year was 48 Gy in three fractions, which corresponds to a biologically effective dose of 125 Gy using the standard linear quadratic model with $\alpha/\beta = 10$ [34•]. This dose is similar to what was subsequently reported by Stinauer et al. to be the optimal dose to achieve a 90% 1-year local control for melanoma and renal cell carcinoma, histologies that have traditionally been considered to be radioresistant [35]. Regardless, taken together, these data show by and large the efficacy of SBRT for liver metastases. Future investigation on SBRT for liver metastases should focus on specific histologies.

Transarterial Radioembolization

TARE, also known as selective internal radiation therapy, is an alternative means of delivering focal radiation via hepatic artery injection of yttrium-90 (Y-90) tagged to glass or resin microspheres into the tumor. The selectivity of Y-90 radiomicrospheres for the tumor is due to the fact that the vascular supply to tumor preferentially derives from the hepatic artery, whereas the portal vein is responsible for the majority of blood flow to the normal liver parenchyma. As Y-90 is a high-energy beta particle (energy maximum, 2.27 MeV; mean, 0.9367 MeV) with an average penetration range of 2.5 mm (max 11 mm), it is capable of limiting radiation injury to normal liver tissue while delivering high doses of radiation to the target [36]. There are two Y-90 containing commercially available products: glass spheres (TheraSphere™, MDS Nordion, Ottowa, ON, Canada) and resin spheres (SIR-Spheres ®, TAREex Medical, Sydney Cove, Australia) approved by the Food and Drug Administration (FDA) in 1999 and 2002, respectively. These microspheres are on average 25–32 μm in diameter–small enough to penetrate through tumor vasculature but too large to pass through capillaries, thus avoiding migration into the cardiopulmonary system [37]. Overall, TARE has been shown to be a safe and effective modality for the treatment of unresectable primary [38] and metastatic hepatic tumors [39–45].

Early Randomized Clinical Trials

The first phase III comparative trial of TARE randomized 74 patients with isolated unresectable CLM to a single intrahepatic artery administration of SIR-Spheres and regional hepatic arterial infusion (HAI) chemotherapy with FUDR vs. regional HAI chemotherapy with FUDR alone [46]. The objective response rate (ORR) (44 vs. 17.6%, $p = 0.01$) and median time to disease progression in the liver (15.9 vs. 9.8 months, $p = 0.001$) were significantly greater for patients receiving SIR-spheres, but there was no difference in OS. Cox regression analysis did suggest a survival benefit for combined modality patients who lived longer than 15 months ($p = 0.06$). Grade 3–4 treatment-related toxicity and quality of life were similar. Eleven of the 74 patients received prior first-line therapy, and when these patients were excluded, the ORR was 37 vs. 14%, ($p = 0.051$) and median progression-free survival (PFS) was 17.6 vs. 15.9 months ($p = 0.07$) [47].

Subsequently, a small phase II trial [48] randomized 21 patients with previously untreated CLM, with or without

extrahepatic metastases, to systemic fluorouracil/leucovorin (5FU/LV) chemotherapy vs. 5FU/LV preceded by a single injection of SIR-Spheres. There was a significant improvement in ORR (50 vs. 0%, $p < 0.001$), time to disease progression (18.6 vs. 3.6 months, $p < 0.001$), and median survival (29.4 vs. 12.8 months, $p = 0.02$) in the group receiving SIR-Spheres. Three years after randomization, 36% of patients in the group receiving SIR-Spheres were alive compared with 0% in the group receiving chemotherapy alone. Although the trial closed prematurely due to a paradigm shift in the systemic therapy for metastatic CRC, this is the only trial showing an improvement in survival with the addition of TARE to first-line systemic treatment. There was more grade 3–4 toxicity in the group who received combined treatment, but no difference in quality of life over a 3-month period when rated by patients ($p = 0.96$) or physicians ($p = 0.98$).

Transarterial radioembolization with Modern Systemic Chemotherapy

Even though early trials showed a benefit to TARE, the application of these results in the setting of modern systemic chemotherapy is less clear. Successful completion of a phase I trial examining first-line treatment with SIR-Spheres with modified FOLFOX4 systemic [49] and a phase II trial examining SIR-Spheres with irinotecan in patients refractory to 5FU [50] led to the development of three modern phase III randomized controlled trials (RCTs) to further characterize the benefit TARE in the setting of modern systemic therapy.

The SIRFLOX study was an international, multi-center, open-label RCT that enrolled 530 patients between 2006 and 2013 with chemotherapy-naïve liver metastatic CRC with no or limited extrahepatic metastases [51••]. Patients were randomized to receive first-line modified FOLFOX (mFOLFOX6) or mFOLFOX6 plus TARE with or without bevacizumab at the discretion of the investigator. At a median follow-up of 3 years, median PFS and ORR at any site were similar in TARE vs. control, 10.7 vs. 10.2 months ($p = 0.43$), and 76.4 vs. 68.1% ($p = 0.113$), respectively. However, the median PFS in the liver by competing risk analysis was significantly improved in the TARE arm, 20.5 vs. 12.6 months ($p = 0.002$), as was the ORR in the liver, 78.7 vs. 68.8% ($p = 0.042$), and the CR rate, 6 vs. 2%. Planned subgroup analysis of patients with liver only metastatic disease did not show any improvement in PFS ($n = 318$, HR 0.9 (0.70–1.15)). There was a significant increase in overall grade 3–4 toxicity in the TARE arm vs. control, 85.4 vs. 73.4%. Overall, TARE did not improve PFS at any site but did significantly delay disease progression in the liver, at the cost of increased toxicity. Thus, it is unclear whether this modest benefit justifies the increase in toxicity and resources required for TARE.

Two ongoing trials hope to further characterize the value of TARE in the setting of modern systemic chemotherapy. FOXFIRE is an open-label, randomized, phase III trial of radiosensitizing chemotherapy—5-fluorouracil, oxaliplatin, and folinic acid (oxMdG)—with or without TARE as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic CRC [52]. FOXFIRE Global is a randomized, multi-center study assessing OS in similar patients treated with first-line FOLFOX6m alone vs. FOLFOX6m plus TARE, with bevacizumab given at the discretion of the investigator (NCT01721954). OS data from SIRFLOX are expected to be combined with FOXFIRE and FOXFIRE Global studies for analysis and presentation in 2017, with the hope that the combination will have sufficient statistical power to conclude whether or not TARE improves survival [47].

Chemotherapy Refractory Disease

TARE has an emerging role in the management of patients with unresectable CRC liver metastases who have failed multiple systemic chemotherapy regimens. A systemic review of clinical studies before November 2012 found 20 studies comprising 979 patients who failed a median of three lines (range 2–5) of chemotherapy [53]. After TARE, the average rate of complete radiographic response, partial response, and stable disease was 0% (range 0–6%), 31% (range 0–73%), and 40.5% (range 17–76%), respectively. The median time to intrahepatic progression was 9 months (range 6–16), and median OS was 12 months (range 8.3–36 months). Subsequently, Saxena et al. [54••] published the largest single-center experience of 302 similar patients treated with TARE, reporting similar median survival of 10.5 months (2-year survival 21%), compared to a typical median survival of 4–6 months with best supportive care [55]. Independent poor prognostic factors of survival included extensive tumor volume, number of previous lines of chemotherapy, poor radiological response to treatment, and low preoperative hemoglobin. Toxicity was minimal and generally considered acceptable.

The only comparative oncological study of TARE for chemotherapy refractory disease was a phase III trial that randomized 46 patients with CLM to infusional 5FU (300 mg/m^2 days 1–14 every 3 weeks) vs. the same chemotherapy preceded by a single injection of SIR-Spheres and found improved time to liver progression (5.5 vs. 2.1 months, $p = 0.003$) and overall disease control rate (86 vs. 35%), with no significant increase in grade 3–4 toxicities [56].

Overall, these results demonstrate the benefit of TARE in the treatment of chemorefractory CLM, but the optimal sequencing of TARE remains unknown. The currently accruing EPOCH trial is a multi-institutional phase III clinical trial in the USA evaluating TheraSphere plus standard-of-care chemotherapy (oxaliplatin or irinotecan) vs. standard-of-care chemotherapy alone in patients with CLM who have failed first-line chemotherapy (NCT01483027) [57].

Table 2 summarizes the data available from randomized controlled trials of TARE in the treatment of isolated or predominantly liver metastatic CRC, either as part of first-line therapy or in chemorefractory cases.

The consensus panel from the Radioembolization Brachytherapy Oncology Consortium suggests that TARE be limited to patients who have unresectable metastatic hepatic disease with liver-dominant tumor burden and life expectancy greater than 3 months [58]. Prior to TARE, a pretreatment ^{99m}TC macroaggregated albumin scan is conducted, and TARE is contraindicated if the scan suggests that there is potential for 30 Gy or more of radiation exposure to the lung or flow to the GI tract that cannot be corrected by catheter technique. Relative contraindications to TARE include limited hepatic reserve, irreversibly elevated serum bilirubin, prior radiation therapy involving the liver, and a compromised portal vein (unless selective or super-selective RE can be performed) [59].

In conclusion, TARE is an effective local treatment for patients with unresectable CLM, capable of providing high rates of local control. As a first-line treatment, TARE with systemic chemotherapy may improve objective hepatic response and PFS in the liver with acceptable additional toxicity. Whether this translates to improvements in survival is under active investigation and hopefully will be clearer with the completion of the FOXFIRE and FOXFIRE Global trials. For patients who have failed first-line systemic therapy, emerging evidence suggests benefit from TARE.

Brachytherapy

Hepatic brachytherapy represents another form of dose-escalated radiation therapy in the liver, with insertion of radioactive sources directly into the tumor [60]. Brachytherapy has been used in limited circumstances due to its ability to deliver a tumoricidal dose of radiation while sparing surrounding normal liver parenchyma, with dose fall-off gradients often superior that of SBRT. Like other local-regional modalities, brachytherapy has been reserved for unresectable lesions or residual disease after resection. Experience exists with both ^{125}I and ^{192}Ir isotopes, as well as with both forms of interstitial brachytherapy techniques: low-dose rate (LDR) using implanted seeds and high-dose rate (HDR) delivered intraoperatively via afterloader. Largely of academic interest, brachytherapy for liver metastases is rarely performed at select institutions.

An older case series from MSKCC investigated the use of ^{125}I LDR brachytherapy in six patients with either unresectable liver metastases or positive margins after surgery. Doses of 120 Gy to 185 Gy were used, and all patients experienced a clinically significant drop in CEA levels. All but one patient experienced durable local control lasting from 5 to

Table 2 Randomized trials using radioembolization for the treatment of CRC liver metastases

Reference	Randomization	Number of lesions	Response rate	Progression	Survival	≥G3 toxicity
Gray et al. [46]	HAC + RE vs. HAC alone (first-line 63, refractory 11)	74	44 vs. 18% (p = 0.01)	Liver median PFS 16 vs. 10 months (p = 0.001)	1-, 2-, and 3-year OS 72 vs. 68%, 39 vs. 29%, and 17 vs. 6% (NS)	62 vs. 62% (NS)
Van Hazel et al. [48]	5FU/LV + RE vs. 5FU/LV alone (first-line)	21 (N = 6 extrahepatic disease)	50 vs. 0% (p < 0.001)	Time to PD 18.6 vs. 3.6 months (p < 0.001)	Median OS 29.4 vs. 12.8 months (p = 0.02)	N = 13 vs. N = 5
Van Hazel et al. [51••]	mFOLFOX6 ± bev + RE vs. mFOLFOX6 alone (first-line)	530 (40% extrahepatic disease)	Any site 76 vs. 68% (p = 0.11); liver 79 vs. 69% (p = 0.04)	Median PFS any site 10.7 vs. 10.2 months (p = 0.43); liver 20.5 vs. 12.6 months (p = 0.002)	Data not yet published	85 vs. 73% (p = 0.516)
Hendlisz et al. [56]	5FU + RE vs. 5FU alone (refractory)	46	Disease control 86 vs. 35% (p = 0.001)	Time to liver PD 5.5 vs. 2.1 months (p = 0.003)	Median OS 10.0 vs. 7.3 months (p = 0.80)	N = 1 vs. N = 6 (p = 0.10)

RE radioembolization, *HAC* hepatic arterial chemotherapy, *PFS* progression-free survival, *OS* overall survival, *NS* not significant, *G3* grade 3, *5FU* fluorouracil, *LV* leucovorin, *PD* progression of disease, *mFOLFOX6* modified FOLFOX fluorouracil, leucovorin, and oxaliplatin, *bev* bevacizumab

14 months [61]. The analysis was later expanded to 12 patients, and investigators reported on outcomes of patients who underwent resection of hepatic metastases but were found to have either unresectable disease or residual disease at the time of surgery. Brachytherapy was performed for gross residual disease in ten implants and positive margins in seven implants; all implants utilized ^{125}I with the exception of a single ^{192}Ir implant. Local control was 67% at 2 years and 44% at 4 years. No local recurrences occurred in implants performed for microscopic residual disease [62]. Another series of LDR brachytherapy treated 56 patients with either unresectable or residual disease at the time of surgery treated with LDR; 1-, 3-, and 5-year liver control rates were 41, 23, and 23%, respectively, with the only apparent treatment-related toxicity of a single case of a liver abscess, likely due to seed implantation [63]. Although the authors observed an additional complication of wound abscess related to seed implantation, no long-term radiation toxicity was seen in any of the patients [64]. Finally, a series of 33 patients treated with intraoperative HDR brachytherapy using ^{192}Ir to 15–30 Gy showed a local control of 25% at 26 months and no significant radiation-related toxicities were observed [65].

Conclusion

Patients with CLM often are not eligible for surgical resection due to limiting tumor and/or patient factors. Local-regional treatment with radiation therapy consists of conventional RT, SBRT, TARE, and brachytherapy. Early studies of conventional RT demonstrated its feasibility for palliating symptoms from metastatic disease, while later studies contributed to understanding of the volume effect of RILD, spurring interest in higher-dose irradiation to smaller volumes of liver. Technological advances allow SBRT to deliver ablative doses of RT to the tumor while sparing normal liver tissue. Careful patient selection and consideration of normal tissue dose tolerances are critical to the safety and effectiveness of liver SBRT. Through multiple studies, SBRT has demonstrated excellent rates of local control and the potential to prolong survival, without increased rates of hepatotoxicity. TARE and brachytherapy represent alternative methods of delivering high doses of radiation focally to the target area while limiting dose to surrounding normal liver tissue. Early trials on the addition of TARE to first-line systemic therapy suggested improvements in PFS and OS rates, and TARE is being actively investigated in the setting of modern systemic therapies. Although rarely utilized, brachytherapy represents another form of conformal radiotherapy that can offer patients with CLM moderate rates of liver control.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30.
2. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006;55(Suppl 3):iii1–8.
3. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg. 2006;93(4):465–74.
4. NCCN Clinical Practice Guidelines in Oncology [Internet]. [cited 2016 Dec 14]. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
5. Folprecht G, Grothey A, Alberts S, Raab H-R, Köhne C-H. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol Off J Eur Soc Med Oncol. 2005;16(8):1311–9.
6. Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. World J Gastroenterol. 2014;20(15):4220–9.
7. Bengmark S, Hafström L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer. 1969;23(1):198–202.
8. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet Lond Engl. 1994;343(8910):1405–10.
9. Jaffe BM, Donegan WL, Watson F, Spratt JS. Factors influencing survival in patients with untreated hepatic metastases. Surg Gynecol Obstet. 1968;127(1):1–11.
10. Bengtsson G, Carlsson G, Hafström L, Jönsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg. 1981;141(5):586–9.
11. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. Am J Roentgenol Radium Therapy, Nucl Med. 1965;93:200–8.
12. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys. 1995;31(5):1237–48.
13. Stearns MW, Leaming RH. Irradiation in inoperable cancer. JAMA. 1975;231(13):1388.
14. Turek-Maischeider M, Kazem I. Palliative irradiation for liver metastases. JAMA. 1975;232(6):625–8.
15. Sherman DM, Weichselbaum R, Order SE, Cloud L, Trey C, Piro AJ. Palliation of hepatic metastasis. Cancer. 1978;41(5):2013–7.
16. Whiteley HW, Stearns MW, Leaming RH, Deddish MR. Palliative radiation therapy in patients with cancer of the colon and rectum. Cancer. 1970;25(2):343–6.

17. Prasad B, Lee MS, Hendrickson FR. Irradiation of hepatic metastases. Int J Radiat Oncol Biol Phys. 1977;2(1–2):129–32.
18. Borgelt BB, Gelber R, Brady LW, Griffin T, Hendrickson FR. The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. Int J Radiat Oncol Biol Phys. 1981;7(5):587–91.
19. Leibel SA, Pajak TF, Massullo V, Order SE, Komaki RU, Chang CH, et al. A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: results of a Radiation Therapy Oncology Group randomized prospective trial. Int J Radiat Oncol Biol Phys. 1987;13(7):1057–64.
20. Cheng JC-H, Wu J-K, Huang C-M, Liu H-S, Huang DY, Cheng SH, et al. Radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: dosimetric analysis and implication. Int J Radiat Oncol Biol Phys. 2002;54(1):156–62.
21. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys. 2002;53(4):810–21.
22. Robertson JM, Lawrence TS, Walker S, Kessler ML, Andrews JC, Ensminger WD. The treatment of colorectal liver metastases with conformal radiation therapy and regional chemotherapy. Int J Radiat Oncol Biol Phys. 1995;32(2):445–50.
23. Ben-Josef E, Normolle D, Ensminger WD, Walker S, Tatro D, Ten Haken RK, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(34):8739–47.
24. Herfarth KK, Debus J, Lohr F, Bahner ML, Rhein B, Fritz P, et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol Off J Am Soc Clin Oncol. 2001;19(1):164–70.
25. Herfarth KK, Debus J, Wannenmacher M. Stereotactic radiation therapy of liver metastases: update of the initial phase-I/II trial. Front Radiat Ther Oncol. 2004;38:100–5.
26. Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol Stockh Swed. 2006;45(7):823–30.
27. Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(10):1585–91.
28. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol. 2009;27(10):1572–8.
29. van der Pool AEM, Méndez Romero A, Wunderink W, Heijmen BJ, Levendag PC, Verhoef C, et al. Stereotactic body radiation therapy for colorectal liver metastases. Br J Surg. 2010;97(3):377–82.
30. Méndez Romero A, Wunderink W, Hussain SM, De Pooter JA, Heijmen BJM, Nowak PCJM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase i-ii study. Acta Oncol Stockh Swed. 2006;45(7):831–7.
31. Goodman KA, Wiegner EA, Maturen KE, Zhang Z, Mo Q, Yang G, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. Int J Radiat Oncol Biol Phys. 2010;78(2):486–93.
32.•• Scorsetti M, Comito T, Tozzi A, Navarria P, Fogliata A, Clerici E, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. J Cancer Res Clin Oncol. 2015;141(3):543–53. **Prospective Phase II trial demonstrating high LC and promising OS rates with SBRT for unresectable CLM.**
33.• Ahmed KA, Caudell JJ, El-Haddad G, Berglund AE, Welsh EA, Yue B, et al. Radiosensitivity differences between liver metastases based on primary histology suggest implications for clinical outcomes after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2016;95(5):1399–404. **Study showing inherent biological differences in radiosensitivity and that colorectal metastases may be more radioresistant than other histologies.**
34.• Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer. 2011;117(17):4060–9. **First study suggesting an optimal dose using SBRT for colorectal liver metastases.**
35. Stinauer MA, Kavanagh BD, Schefter TE, Gonzalez R, Flaig T, Lewis K, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. Radiat Oncol Lond Engl. 2011;6:34.
36. Gulec SA. Y-90 Radiomicrosphere therapy for colorectal cancer liver metastases. Semin Nucl Med. 2016;46(2):126–34.
37. Dominello M, Bowers J, Zaki M, Konski A. Radiotherapy and radioembolization for liver metastases. Ann Palliat Med. 2014;3(2):104–13.
38. Kennedy AS, McNeillie P, Dezarn WA, Nutting C, Sangro B, Wertman D, et al. Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors. Int J Radiat Oncol Biol Phys. 2009;74(5):1494–500.
39. Wong CO, Salem R, Qing F, Wong KT, Barker D, Gates V, et al. Metabolic response after intraarterial 90Y-glass microsphere treatment for colorectal liver metastases: comparison of quantitative and visual analyses by 18F-FDG PET. J Nucl Med Off Publ Soc Nucl Med. 2004;45(11):1892–7.
40. Lewandowski RJ, Thurston KG, Goin JE, Wong C-YO, Gates VL, Van Buskirk M, et al. 90Y microsphere (TheraSphere) treatment for unresectable colorectal cancer metastases of the liver: response to treatment at targeted doses of 135-150 Gy as measured by [18F]fluorodeoxyglucose positron emission tomography and computed tomographic imaging. J Vasc Interv Radiol JVIR. 2005;16(12):1641–51.
41. Stubbs RS, O'Brien I, Correia MM. Selective internal radiation therapy with 90Y microspheres for colorectal liver metastases: single-centre experience with 100 patients. ANZ J Surg. 2006;76(8):696–703.
42. Kennedy AS, Coldwell D, Nutting C, Murthy R, Wertman DE, Loehr SP, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Phys. 2006;65(2):412–25.
43. Vente MA, Wondergem M, van der Tweel I, van den Bosch MA, Zonnenberg BA, Lam MG, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Eur Radiol. 2009;19(4):951–9.
44. Mulcahy MF, Lewandowski RJ, Ibrahim SM, Sato KT, Ryu RK, Atassi B, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer. 2009;115(9):1849–58.
45. Benson AB, Geschwind J-F, Mulcahy MF, Rilling W, Siskin G, Wiseman G, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. Eur J Cancer Oxf Engl. 1990;49(15):3122–30.
46. Gray B, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, et al. Randomised trial of SIR-spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol Off J Eur Soc Med Oncol. 2001;12(12):1711–20.

47. Townsend AR, Chong LC, Karapetis C, Price TJ. Selective internal radiation therapy for liver metastases from colorectal cancer. Cancer Treat Rev. 2016;50:148–54.
48. Van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol. 2004;88(2):78–85.
49. Sharma RA, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25(9):1099–106.
50. van Hazel GA, Pavlakis N, Goldstein D, Olver IN, Tapner MJ, Price D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(25):4089–95.
51.•• van Hazel GA, Heinemann V, Sharma NK, MPN F, Ricke J, Peeters M, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(15):1723–31. **Phase III RCT of patients with chemonaïve liver metastatic CRC demonstrating benefit in median liver PFS, but not any site median PFS or ORR, with the addition of TARE to first-line mFOLFOX6 +/- bevacizumab.**
52. Dutton SJ, Kenealy N, Love SB, Wasan HS, Sharma RA. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional selective internal radiation therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. BMC Cancer [Internet]. 2014;14(1):497. doi:10.1186/1471-2407-14-497.
53. Saxena A, Bester L, Shan L, Perera M, Gibbs P, Meteling B, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol. 2014;140(4):537–47.
54.•• Saxena A, Meteling B, Kapoor J, Golani S, Morris DL, Bester L. Is yttrium-90 radioembolization a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases? A large single-center experience of 302 patients. Ann Surg Oncol. 2015;22(3):794–802. **Large single-center experience of patients with chemorefractory unresectable CLM treated with TARE resulting in a high median survival of 10.5 months (2-year survival 21%).**
55. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(10):1626–34.
56. Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(23):3687–94.
57. Efficacy evaluation of therasphere following failed first line chemotherapy in metastatic colorectal cancer—full text view—ClinicalTrials.gov [Internet]. [cited 2017 Jan 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT01483027.
58. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, et al. 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. 2007;68(1):13–23.
59. Lam MGEH, Abdelmaksoud MHK, Chang DT, Eclov NC, Chung MP, Koong AC, et al. Safety of 90Y radioembolization in patients who have undergone previous external beam radiation therapy. Int J Radiat Oncol Biol Phys. 2013;87(2):323–9.
60. Denecke T, Lopez HE. Brachytherapy of liver metastases. Recent Results Cancer Res Fortschritte Krebsforsch Progres Dans Rech Sur Cancer. 2008;177:95–104.
61. Donath D, Nori D, Turnbull A, Kaufman N, Fortner JG. Brachytherapy in the treatment of solitary colorectal metastases to the liver. J Surg Oncol. 1990;44(1):55–61.
62. Armstrong JG, Anderson LL, Harrison LB. Treatment of liver metastases from colorectal cancer with radioactive implants. Cancer. 1994;73(7):1800–4.
63. Martinez-Monge R, Nag S, Nieroda CA, Martin EW. Iodine-125 brachytherapy in the treatment of colorectal adenocarcinoma metastatic to the liver. Cancer. 1999;85(6):1218–25.
64. Nag S, DeHaan M, Scruggs G, Mayr N, Martin EW. Long-term follow-up of patients of intrahepatic malignancies treated with iodine-125 brachytherapy. Int J Radiat Oncol Biol Phys. 2006;64(3):736–44.
65. Thomas DS, Dritschilo A. Interstitial high dose rate irradiation for hepatic tumors. In: Nag S, editor. High dose rate brachytherapy: a textbook. New York: Futura; 1994. p. 339–46.