Radiation Therapy

42

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Learning Objectives

- Communicate the technical aspects of radiation delivery using SBRT.
- Share the results of SBRT in the clinical setting for colorectal liver metastases.
- Point to future directions for SBRT in the management of patients with metastatic colorectal cancer.

42.1 Introduction

SBRT emerged in the 1990s, due to advances not only in the radiation linear accelerator treatment technology itself, but also due to the addition of onboard linear accelerator imaging, improvements in the quality of the onboard imaging, advancements in the immobilization of patients, and refinements of treatment algorithms (calculations to deliver high doses of radiation accurately) [1]. The past decade has seen increased use of SBRT because it is a well-tolerated and effective treatment in selected patients with early-stage and metastatic cancers, including liver metastases [2–7].

Prior to SBRT, radiation therapy was rarely utilized in the treatment of liver metastases due to the liver being a radiosensitive organ. For example, conventional radiation of the whole liver posed a high risk of radiation-induced liver disease (RILD), which is irreversible liver injury that can lead to organ failure and death [6, 7]. As seen in Fig. 42.1, SBRT differs from whole liver radiation in that SBRT applies fewer fractions (3–5) and higher doses of radiation (8–20 Gy) focally and precisely to the tumour, whereas the antiquated approach of whole liver radiation applied more fractions at conventional doses of radiation (1.5–2 Gy per day) to the entire liver volume. The Radiation Therapy Oncology Group (RTOG) carried out studies in the 1970s and 1980s to evaluate the effect of whole liver radiation on hepatic metastases [8]. In an RTOG Phase I/II dose-escalation trial of whole liver radiation in 1.5 Gy twice-daily fractions, no patient developed classic RILD after treatment with 27–30 Gy, while 10% of patients developed classic RILD after treatment with 33 Gy [9]. When the whole liver was treated with 30 Gy in 2 Gy per fraction, the risk of classic RILD was estimated to be 5% [10, 11].

Important studies from the University of Michigan showed that the use of focal high doses of radiation to the liver could be done safely and effectively [12, 13]. These studies paved the way for more modern radiation trials that showed good rates of local control for liver metastases. Here, we review the role of SBRT for colorectal liver metastases.

In the 1970s, whole liver radiation was tested as a treatment for liver metastases but resulted in unacceptable rates of RILD. In the 1990s, it was demonstrated that focal high doses of radiation using 3D conformal technique was safe and effective. The advents of SBRT and IMRT have resulted in additional treatment options for patients with unresectable liver metastases [10, 11].

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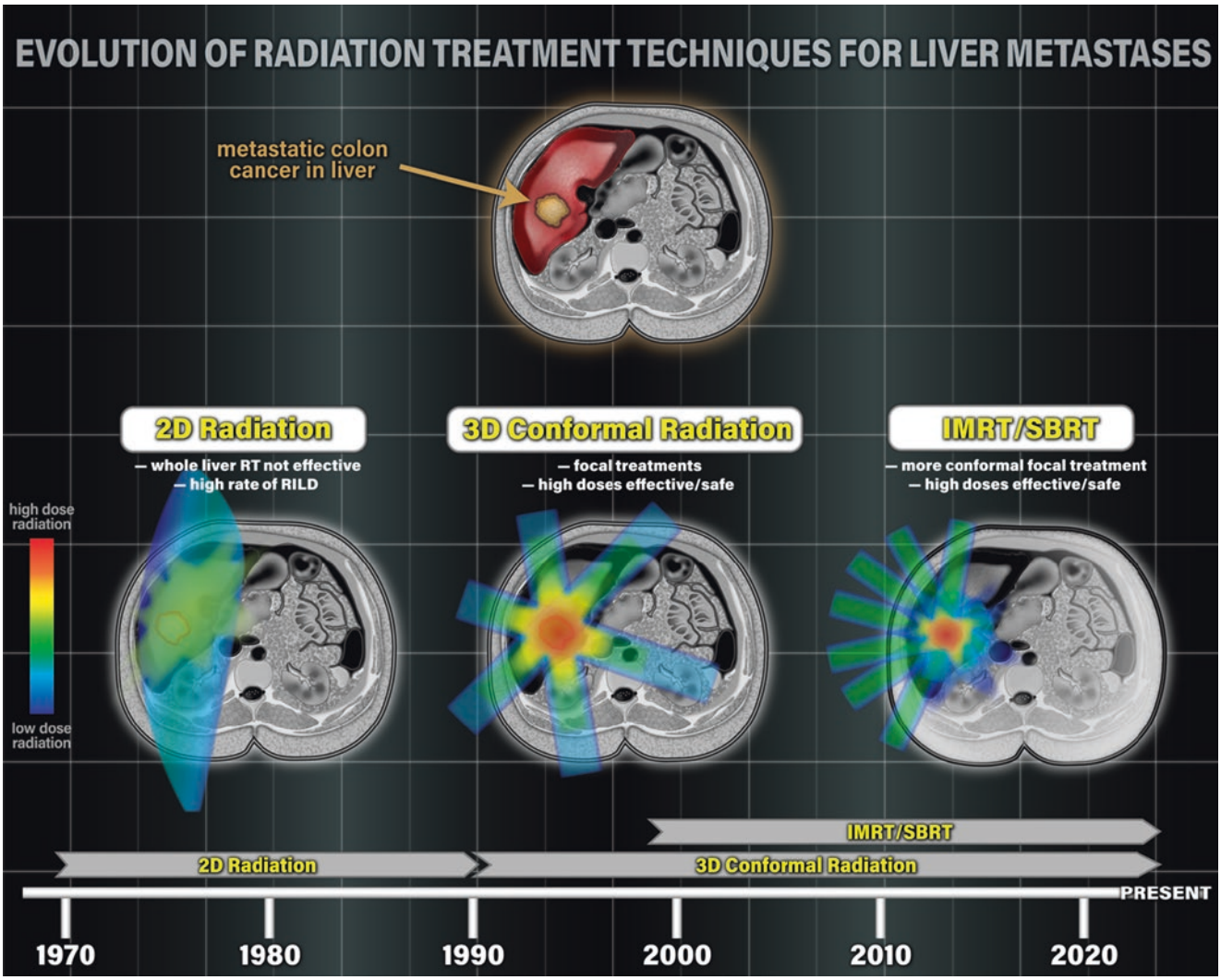

Fig. 42.1 Evolution of radiation treatment techniques for liver metastases

42.2 Radiation Therapy for Colorectal Liver Metastasis

A limited number of high-dose precision ablative radiation treatments are used for SBRT. The term "stereotactic" refers to the relationship of the tumour target position with known fiducials that provide a series of reference points to designate a coordinate system. This can be used to identify the target tumour, direct the treatment planning process, and guide the treatment toward the target location in the body intended for therapy. Liver metastases are challenging to treat due to the sensitivity of the liver parenchyma to radiation, respiratory motion, and intra- and inter-fraction motions of the surrounding bowel. To overcome these challenges, SBRT fundamentally relies on controlling respiratory motion to avoid variability in treatment delivery, and fractionation to achieve ablative radiation doses [14].

Accounting for internal organ motion during radiotherapy is an inherent challenge since the liver follows the motion of the diaphragm during respiration. Although the general parameters of movement have a degree of predictability [15], this amplitude of motion can vary greatly between patients which necessitates unique attention to each patient's respiratory pattern. The motion also depends on the location of tumour, whether within the liver or biliary tree, as well as near the dome of the liver or more inferiorly [14]. Differences in day-to-day bowel position and shape are other variables that must be monitored and taken into account to ensure safe and consistent treatment. Image-guided radiation therapy (IGRT) has made considerable advancements in recent years. Numerous options for target verification and motion control [14] enable greater certainty in target alignment, which can help reduce dose to normal tissues and escalate dose to tumours. Common IGRT strategies include tracking liver tumour targets using

implanted fiducials [16], CT-on-rails, cone beam CT, and magnetic resonance linear accelerators. Motion management can be achieved with breath hold [17–20], respiratory gating [21, 22], and abdominal compression [23].

Administering SBRT treatment safely to large liver tumours (>6 cm) has been challenging. Use of an SBRT technique with control of organ motion and high-quality image guidance is an essential starting point. Nevertheless, even with the assistance of these technologies, safe delivery of ablative doses in 3–5 fractions without overdosing the liver, GI mucosa, or main bile ducts often proves difficult. An SBRT technique coupled with the time-honored principle of fractionation permits ablative doses to be given (90–100 Gy BED) and leads to a substantial survival benefit for patients with large liver tumours [14]. For most large central tumours (>6 cm), giving 15–25 fractions with an SBRT technique may be necessary to deliver an ablative dose and stay within the tolerance of the OARs (organs at risk). The alternative is to give five fractions and reduce the dose, which may no longer be ablative (Fig. 42.2) [14].

Clinical studies using SBRT to treat CRLM are ongoing. Results of phase I and II studies demonstrated promising local control and occasional long-term survivors [6, 24, 25]. Petrelli F et al. [26] performed a systematic review in 2018 of published trials to evaluate the efficacy of SBRT as a primary modality therapy for CRC liver oligometastases. This review covered a comprehensive search of the Cochrane Central Register of Controlled Trials, Pubmed, and EMBASE for publications regarding SBRT for CRC liver metastases. The results can be seen in Table 42.1, along with updated information to reflect recent advances.

Although SBRT has not been directly compared with other liver-directed treatments in prospective randomized studies, the outcomes from the reported studies to date compare favorably to other types of liver-directed treatments. Local-regional treatment with RT consists of conventional RT, SBRT, TARE, and brachytherapy [27]. Alternative methods of delivering high doses of radiation focally to the target area while limiting dose to surrounding normal liver tissue include TARE and brachytherapy. Early trials on the addition

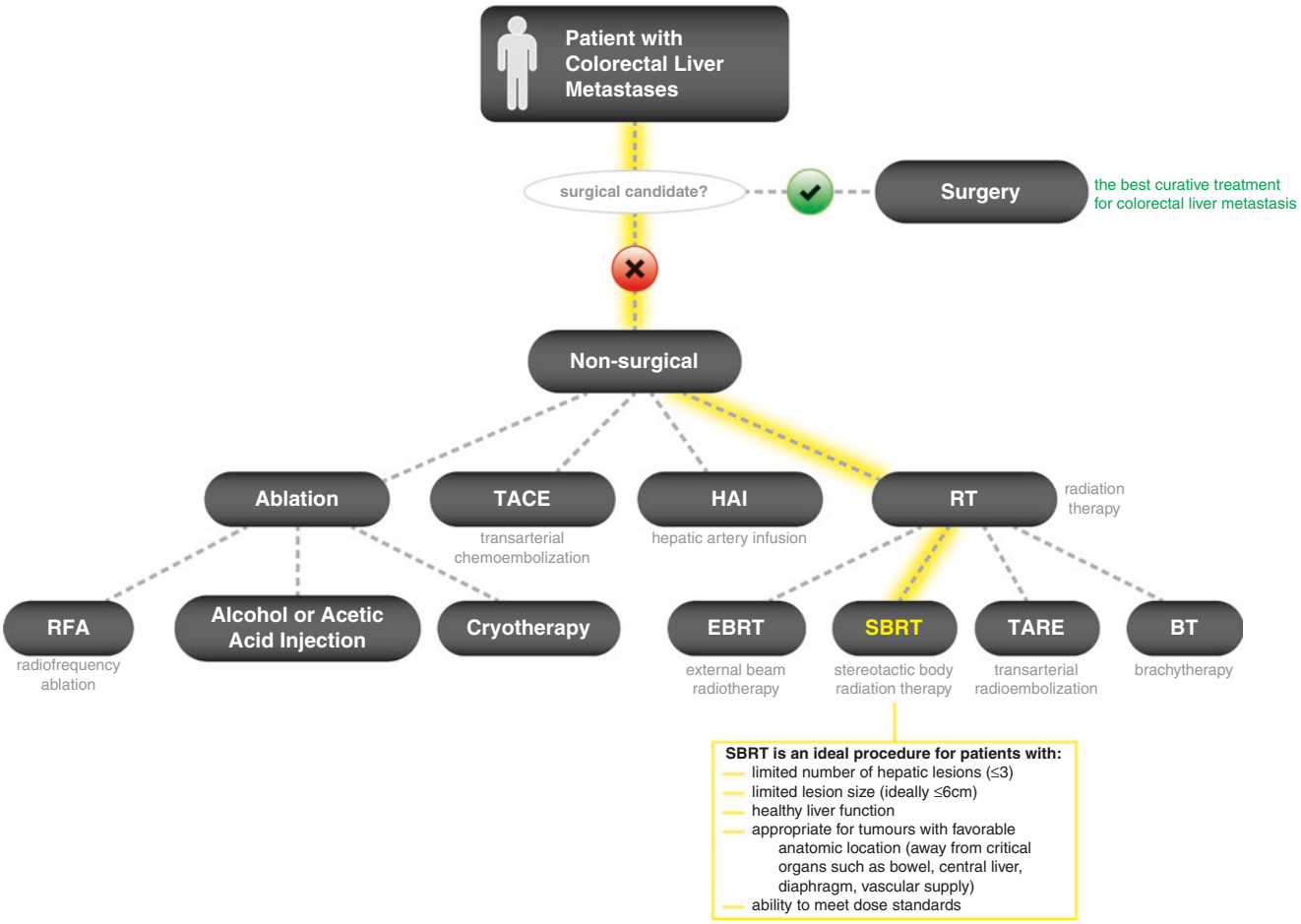

Fig. 42.2 Treatment algorithm for selecting loco-regional modalities for patients with colorectal liver metastases. Please note that this algorithm depends greatly on available resources and institutional practice and expertise. Patients with tumours >6 cm can receive EBRT in ablative doses using 15–25 fractions [14]

Table 42.1 Studies on SBRT for colorectal liver metastases

	Characteristics of studies on SBRT for colorectal liver metastases					Outcomes					
Author/year	Type of study	Total number of treated liver metastases	Lesion sizes (range) (cm)	Dose: range Gy/n° fxs (BED 10 Gy)	Median follow up (months)	Median OS (months)	1 year LC (%)	1 year OS (%)	2 years LC (%)	2 years OS (%)	Median PFS (months)
Chang/2011	Retrospective cohort (pooled analysis)	65	1–2 (80%)	22–60 Gy/1–6 fxs (40.5–180 Gy)	14	–	62	72	45	38	–
Vautravers-Dewas/2011	Retrospective	30	–	40 Gy/4 fxs (80 Gy) 45 Gy/3 fxs (112.5 Gy)	14.3	–	79	–	86	58	–
Liu/2013	Retrospective	24	1–4	24–60 Gy/1–5 fxs (81.6–132 Gy)	18	25.2	86	–	67	–	–
Berber/2013	Retrospective	53	1.6	41 Gy/3 fxs (96.76 Gy)	17	–	60	56	–	–	–
van de Voorde/2015	Retrospective	17	–	EQ2 62–150 Gy/3–10 fxs (NR)	21	25	–	–	–	–	–
Goodman/2016	Retrospective	54	–	32–60 Gy/3–5 fxs (52.48–180 Gy)	33	38	93	95	88	78	10
Ahmed/2016	Retrospective	22	2 (0–5)	50–60 Gy/5 fxs (100–132 Gy)	20.5	–	–	100	59	73	–
Mendez Romero/2016	Retrospective	40	1–2 (95%)	50.25 Gy/3 fxs (134.42 Gy) 37.5 Gy/3 fxs (84.38 Gy)	25 and 26[a]	43 and 35[a]	90 and 96[a]	94 and 95[a]	90 and 74[a]	81 and 69[a]	–
Doi/2017	Retrospective	24	1 (75%)	45–72 Gy/8 fxs (71.7–115.5 Gy)	16	45	67.2	82.3	35.9	67.1	16 (LC time)
Joo/2017	Retrospective	70	1–2 (86%)	45–60 Gy/3–4 fxs (58–180 Gy)	34.2	–	–	–	92 (BED ≥ 112) 61 (BED < 112)	75	–
Ambrosino/2009	Prospective series	11	1.8	25–60 Gy/3 fxs (45.83–180 Gy)	13	–	–	–	–	–	–
Kim/2009	Prospective series	10	14	36–51 Gy/3 fxs 79.2–137.7 Gy)	12	25	80	53	60	40	–
van der Pool/2010	Prospective series	20	2.3	37.5–45 Gy/3 fxs (93.6–112.5 Gy)	26	34	–	100	74	83	11
Stintzing/2013	Prospective series	30	1 (86%)	24–26 Gy/1 fxs (81.6–93.6 Gy)	23.3	34.4	85	–	80	–	–
Lee/2009	Phase I	40	2 (1–8)	27.7–60 Gy/6 fxs (40.44–120 Gy)	10.8	15	71	63	–	–	3.9
McPartlin/2017	Phase I & II	60	1 (1–6)	22.7–62.1/6 fxs (31.28–126.37 Gy)	28.1	16	50	63	32	26	–
Hoyer/2006	Phase II	44	3.5	45 Gy/3 fxs (112.5 Gy)	52	19.2	–	–	78	38	6.5 (TTP)
Scorsetti/2015/2018	Phase II	42	1 (81%)	75 Gy/3 fxs (262.5 Gy)	73	27.6	95	85.2	91	65	12
Hong/2017	Phase II	89	2.5 (0.5–11.9)	30, 40, 50 GyE/5 fxs (48, 72, 100 GyE)	30.1	18.1	71.9	66.3	–	35.9	3.7

SBRT stereotactic body radiotherapy; *LINAC* linear accelerator; *pts* patients; *BED* biologically equivalent dose; *M+* metastases; *CT* chemotherapy; *Gy* gray; *GyE* gray equivalent; *fxs* fractions; *NR* not reported; *OS* overall survival; *LC* local control; *PFS* progression-free survival; *G* grade

Scorsetti [7, 30], Stintzing [31], van de Voorde [32], van der Pool [33], Vautravers-Dewas [34], Ahmed [35], Ambrosino [36], Berber [37], Chang [38], Mendez Romero [39], Doi [40], Goodman [41], Hoyer [42], Joo [43], Kim [44], Lee [25], Liu [45], McPartlin [46], Hong [47]

[a] Two different dose levels

of TARE to first-line systemic therapy suggested a role in selected patients, but additional data is needed to clearly define the role of TARE in different settings (surgically resectable, unresectable, salvage treatment [28]). Although infrequently used, brachytherapy represents an additional method of conformal radiotherapy that can offer patients with CLM moderate rates of liver control [27].

More broadly, aggressive local treatment of liver oligometastases may be an effective option with encouraging survival rates. In a 2017 randomized phase II trial [29], 119 patients with unresectable colorectal liver metastases ($n < 10$ and no extrahepatic disease) received systemic treatment alone or systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection. The long-term overall survival (OS) results showed that there was a statistically significant difference in OS in favor of the combined modality arm compared to systemic treatment alone. Median OS was 45.6 months (95% CI = 30.3–67.8 months) in the combined modality arm vs 40.5 months (95% CI = 27.5–47.7 months) in the systemic treatment arm.

This was the first randomized study to demonstrate that aggressive local treatment can prolong OS in patients with unresectable CLM. This trial had limitations. However, most notably the small sample size and selection of patients are considerations for wider applicability. Although the study's results show promising impacts on LC and OS, definitive validation in larger randomized studies is warranted. The extension of this concept to SBRT in patients with oligometastatic disease.

In addition to aggressive liver-directed therapies that may include SBRT, future prospective trials will test the impact of molecular characteristics, radiation dose, and novel systemic and immune-based therapies [48]. A 2017 phase II single-arm study evaluated the efficacy and safety of risk-adapted, proton-based SBRT for liver metastases from solid tumours [47]. This is the largest prospective study of liver SBRT for hepatic metastases to date with protons. Proton beam therapy utilizes charged particles as opposed to high-energy photons. Protons can offer a clinical advantage over photon-based radiation in certain patients, particularly those with tumours on the right side of the liver [49, 50].

Protons were well tolerated and proved effective even for metastases that were greater than or equal to 6 cm. Radioresistant subgroups were identified based on genotype. Mutation in the KRAS oncogene was found to be a strong predictor of poor LC ($P = 0.02$). Tumour with both mutant KRAS and TP53 were particularly radioresistant, with a 1-year LC rate of only 20.0%, compared with 69.2% for all others ($P = 0.001$). This stresses the need for tumour genotyping prior to SBRT and treatment intensification in this patient subset. Future efforts will investigate how to achieve more durable local control in KRAS- and TP53-mutant tumours [47]. Future studies may select patients for proton radiation based on molecular characteristics or in combination with other novel therapies to overcome resistance.

There is also potential for future investigation into the role of liquid biopsies to guide the field of radiation oncology. Liquid biopsies are characterized by the isolation of cancer-derived components and provide a rich source of non-invasive tumour-specific biomarkers. These biomarkers could have a substantial impact on cancer treatment by categorizing patients into risk groups, tracking radiation therapy impacts before, during, and after treatment, and identifying patients with radioresistant tumours. The liquid biopsy is a minimally invasive, inexpensive, and easily repeatable technique that can enable efficient screening and early diagnosis [51]. The concept of this type of personalized medicine is becoming more readily incorporated into clinical practice and research studies and could serve as a solution to the much-needed predictive biomarkers to guide therapeutic management [52].

Patients should be considered for participation in randomized clinical trials when possible because the efficacy of liver metastasis SBRT has not yet been fully established. SBRT can treat liver metastases safely; studies have shown that radiation doses >47 Gy (3–6 fxs) can improve local control. The optimal fractionation has yet to be clearly defined [25, 53, 54].

42.3 Conclusion

Currently, the best curative treatment for colorectal liver metastasis is surgical resection. However, many patients are not viable surgical candidates. Stereotactic body radiotherapy (SBRT) is a well-established alternative treatment option for patients with liver metastases that are unsuitable candidates for surgical resection. Advancements in technology have allowed SBRT to deliver high dose radiation precisely to the tumour, sparing surrounding normal liver tissue. Numerous recent studies have shown evidence of encouraging local control and OS rates after treatment with SBRT, without increased rates of RILD. The safety and success of liver SBRT rely heavily on ensuring appropriate patient selection and attention to normal tissue dose tolerances.

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