Stereotactic body radiation therapy for colorectal liver metastases

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ABSTRACT
Multidisciplinary case discussion of patients with colorectal liver metastases (CRLM) has led to improved selection of more complex patients with the oligometastatic disease for treatment with surgical resection, locally ablative therapy or a combination of local modalities to improve the therapeutic ratio in patients with CRLM. Stereotactic body radiation therapy (SBRT) is a noninvasive local therapy with a potential role in the management of oligometastatic CRLM and may be considered as an alternative choice to other locally ablative therapies like radiofrequency ablation, radioembolization, chemoembolization or surgery or after the failure of other local treatment or in combination with surgery. Existing evidence reports for highly selected patients with CRLM, one to five fractions SBRT can be delivered safely, with satisfactory long-term local control, overall survival and quality of life. This review article will present the evidence of SBRT in this setting.

Introduction
Colorectal cancer (CRC) is a leading cause of cancer-related deaths worldwide [1]. The liver is the most common site of metastasis in patients with CRC [2]. Postmortem studies have confirmed that 20% of CRC patients have their disease isolated to the liver [3]. Metastatectomy is recognized as the main potentially curative treatment option in patients with resectable colorectal liver metastases (CRLM) [4]. However, 85% of those patients are considered unresectable at initial presentation or at the time of liver recurrence because of 1) medical conditions, 2) metastatic distribution/location, 3) patient refusal and 4) limited liver reserve [5,6]. Palliative chemotherapy in combination with biological agents may convert unresectable or borderline resectable to resectable disease in about 10–20% of cases, with an increased risk of toxicity [7,8]. Within the setting of oligometastatic disease, stereotactic body radiation therapy (SBRT) presents as an alternative option to other local therapies, to enhance long-term disease control, or possibly cure [9,10].

Current evidence related to the use of SBRT for CRLM has demonstrated encouraging results in terms of safety, local control (LC), overall survival (OS) and quality of life [10–16]. The favorable LC and OS outcomes associated with the use of SBRT for CRLM have been related to appropriate patient selection and reasonable radiotherapy (RT) dose delivered to the targeted lesions. Advances in RT technology, imaging, motion management and RT planning have increased the safety of RT delivery [10–16].

In this review, we provided a summary of a rapid review of existing prospective clinical trials and retrospective series addressing the indications, evidence, toxicity, re-irradiation, and RT delivery systems, with the description of potential future directions for the treatment of CRLM with SBRT.

Clinical rationale for SBRT in CRLM
Innovations in RT technology and techniques over the past two decades include volumetric modulated radiation therapy (VMAT), SBRT, image-guided radiation therapy (IGRT), Cyberknife, MRI-guided radiation therapy and proton beam therapy (PBT) which may all be used to increase the therapeutic benefit of RT for the treatment of patients with CRLM [17–20]. Compared to conformal RT (two dimensional conformal RT (2D CRT), three dimensional conformal RT (3D CRT) and intensity-modulated RT (IMRT)), SBRT permits precise delivery of possibly high ablative doses of external beam RT to liver metastases with steep dose gradients toward the non-involved liver, and surrounding critical structures over single, or few numbers of fractions (ideally one to five fractions) within a few days, decreasing the overall treatment time to prevent treatment delays/interruption on systemic therapy and improve treatment response. Conformal RT is generally delivered in 25–35 fractions, five fractions per week, for approximately 5–7 weeks. SBRT requires experience in target volume delineation, RT planning, image guidance/tracking systems and regular verification of the image sets to prevent geometric misses to the targeted tumor to overcome inter-fraction or intra-fraction movements of the liver,
with strict quality control throughout the whole RT planning and delivery process [11,13,15,17–20]. The liver tolerates high doses to partial volumes, but not to the whole organ (parallel functioning organ) [21–23]. Importance of minimizing the mean dose to the uninvolved liver to <15 Gy in three fractions has been shown to be important to reduce the risk of RT-induced liver disease (RILD) [16]. Moreover, rapid dose falloff at the periphery of the target with SBRT can also facilitate gross tumor dose escalation which is subsequently related to improving LC at 1-year when delivered biological equivalent dose (BED) >117Gy10 [11].

Clinical indications and evidence for the use of SBRT in CRLM

Currently, no phase III randomized controlled trial data has been published on the use of SBRT for CRLM or comparing SBRT to the standard of care/best supportive care, the prevailing evidence is predominantly limited to some prospective phase I-II clinical trials, and a number of other retrospective case series. Within these studies, there be considerable variability in 1) selection criteria, 2) mixed tumor histologies, 3) metastatic size/volume, 4) number of lesions treated, 5) RT dose and fractionation schedule used, and 6) substantial variability in previous treatment (chemotherapy, surgery or other local ablative therapy) [10–14,16,18,19,24–41] (Table 1).

We have learned from previous studies that LC for CRLM has ranged from 50–100% at 1 year, 32–91% at 2 years and 9–91% at 4 years [10–14,16,18,19,24–41] (Table 2). Although, there are a variety of clinical and biological factors related to improved LC such as baseline tumor size/volume, delivered RT BED and (TPS3 and KRAS) mutation status, predicting LC may help in patient selection for SBRT treatment [14,16,37,42,43]. Rusthoven et al. described a superior LC rate for tumors <3 cm treated with 60 Gy in 3 fractions (100% vs. 77% at 2 years, p = 0.015) [16]. Also, Lee et al. reported a superior LC rate for smaller volume tumors (<75.2 ml; p = 0.001) and a higher delivered dose (p = 0.01) [14]. In contrast, Scorsetti et al. did not find any difference in LC rates for using the cutoff established by Rusthoven et al. when using 75 Gy in three fractions which most likely related to the high BED10 = 262.5 Gy10 that increased LC up to 91% at 2 years even for lesions >3 cm in size [37]. These findings confirm a robust dose-response relationship between delivered BED and LC [14,37]. Furthermore, Chang et al. reported on 65 patients with 106 CRLM and found that BED was an independent prognostic factor for LC and suggested a BED >75Gy10 is required to attain high rates of LC and a BED >117Gy10 needed to achieve 90% LC at 1 year [11]. However, the delivery of high BED is not always achievable due to several factors such as a number of lesions, tumor location or proximity to adjacent organs-at-risk (OAR) [33]. Moreover, McPartlin et al. reported a GTVmin BED 75Gy10 in 6 fractions was associated with LC at 1, 2 and 4 years of 65%, 49% and 49% compared with 44%, 23% and 14% for BED < 75Gy10 [33] confirming the value of dose-response relationship. As experience has grown, the dose-response relationship was further assisted by Joo et al. who reported 2-year LC rates of 52%, 83%, and 89% using a BED ≤80Gy10 (group 1), 100–112Gy10 (group 2), and ≥132Gy10 (group 3), respectively [30]. This means CRLM could also be relatively radioresistant compared with other histological cancer types. Ahmed et al. used a radiosensitivity index that reflected the expressive gene types and confirmed that CRLM was radioresistant compared with other histological cancer types and found 1-year LC rate for colorectal lesions of 59% vs. 100% for non-colorectal lesions (p = 0.019) [24].

The median OS for patients with untreated CRLM is poor and approximately two years when treated with systemic therapies [44]. Incorporation of aggressive local therapy (i.e., SBRT) has been associated with median OS of 16–45 months, and 2 year OS ranges from 26–83% which is higher than might be expected from the best supportive care or systemic therapy alone [10–14,16,19,24–40,42–44]. Several studies have shown a number of factors associated with superior long-term OS after SBRT for CRLM. On multivariable analysis, McPartlin et al. found that performance status 0–1, absence of extrahepatic disease, a smaller volume of liver lesions and LC of disease after SBRT to be associated with improved survival [33]. Although, there was a correlation between the number of factors and OS; patients with all four favorable factors had an OS at 1 and 4 years of 81% and 39%, compared with 3.5% and 0% for those with none [33].

Colorectal liver metastasis has been shown to be one of the most resistant primary histologies for liver SBRT. A study conducted by Rusthoven et al. showed median survival for favorable primary sites of 32 months compared to 12 months for unfavorable primaries (p < 0.001) [16]. Lee et al. reported a one-year survival rate for colorectal, breast, and other liver metastases of 63%, 79%, and 38%, respectively (not statistically significant on the univariate analysis) [14]. Moreover, Chang et al. confirmed the strong correlation between a prescribed RT dose higher than 48 Gy in three fractions and OS [11]. Also, Hoyer et al. found a positive correlation between OS and lesions <3 cm diameters and metastatic presentation in CRLM [13]. These findings confirm that optimal candidates for liver SBRT are those with favorable biological behavior. Therefore, full staging prior to liver SBRT is recommended [33].

Recommendation

Based on the available literature, we recommend that liver SBRT is considered for oligometastatic CRC, which is unsuitable for surgical resection (for technical, or medical reasons), after the failure of other local therapies, and in combination with surgical resection [11–16,37,45]. Oligometastatic CRC patients who may be candidates for liver SBRT ideally should have an eastern cooperative oncology group (ECOG) performance status of ≤2, expected survival of >3 months, >700 cc of the uninvolved liver, up to five metastases, and with the potentially treatable extrahepatic disease, adequate organ function and no chemotherapy within 2 weeks of SBRT [41]. Whenever feasible (considering safety to OAR), an excellent LC rate (>80%) can be achieved with SBRT dose prescription equivalent to ≥100Gy10; however, a higher SBRT
Table 1. Characteristics of included studies.

| Author/year         | Design | N: pts. | N: liver lesions | Lesion’s size (range) cm/ml | Primary site/previous CT (%) | Dose: range Gy/n fx (BED10/Gy) | Median follow-up (months) |
|---------------------|--------|---------|------------------|----------------------------|----------------------------|--------------------------------|---------------------------|
| Herfath/2004 [12]   | Phase 1–2 | 18      | 1–3              | ≤6 cm/10 (1 to 132) ml      | Colorectal (53%)/NR         | 14–26 Gy/1fr (33.6–93.6 Gy) | 5.7                       |
| Mendez Romero/2006 [36] | Phase 1–2 | 14      | 1–4              | 3.2(0.5–7.2) cm/22.2(11.3–322) ml | Colorectal (82.3%)/NR       | 30–37.5 Gy/3fr (60–84.4 Gy) | 52                        |
| Hoyer/2006 [13]     | Phase 2  | 44      | 1–6              | 3.5(1–8.8) cm              | Colon (59%), rectum (41%)/ | 45 Gy/3 fr (112.5 Gy)       | 16                        |
| Rusthoven/2009 [16] | Phase 1–2 | 15      | 1–3              | 2.7(0.4 to 5.8) cm/14.9(0.75–98) ml | Colorectal (31.9%)/≥1 (85%) | 36–60 Gy/3fr (79.2–180 Gy) | 10.8                      |
| Lee/2009 [14]       | Phase 1  | 40      | 1–8              | 13.4(5–7–3,090) ml         | Colorectal (58.8%)/≥1 (85%) | 27.7–60 Gy/5–6 fr (40.44–120 Gy) | 12                        |
| Kim/2009 [31]       | Prospective | 10      | 1–4              | 3.4–271 ml                 | Colon (50%), rectum (40%)/≥1 line 100% | 36–51 Gy/3 fr (79.2–137.7 Gy) | 26                        |
| van der Pool/2010 [18] | Prospective | 20      | 1–3              | 0.7–6.2 cm                 | Colon (75%), rectum (25%)/NR | 37.5–45 Gy/3fr (91.6–112.5 Gy) | 14                        |
| Chang/2011 [11]     | Retrospective | 65      | 1–4              | 30.1(0.6–3088) ml          | Colorectal/≥1 (72%)         | 22–60 Gy/1–6 fr (40.5–180 Gy) | 14                        |
| Vautravers–Dewas/2011 [40] | Retrospective | 30      | 1–4              | 0.7–10 cm                  | –                            | 40 Gy/4 fr (112.5 Gy)       | 14.3                      |
| Stintzing/2013 [38] | Prospective | 30      | 1                | 0.7–5.3 cm                 | Colorectal/67%              | 24–26 Gy/1fr (81.6–93.6 Gy) | 23.3                      |
| Liu/2013 [32]       | Retrospective | 24      | 1–4              | 8.8(0.2–222.4) ml          | Colorectal (23%)/NR         | 24–60 Gy/1–5 fr (81.6–132 Gy) | 18                        |
| Berber/2013 [26]    | Retrospective | 53      | 1.6 (median)     | 182(60–581) ml             | Colorectal/ NR              | 41 Gy/3 fr (96.76 Gy)       | 17                        |
| Scorsetti/2015, 2018 [10,37] | Phase 2 | 42      | 1–3              | 1.1–5.4 cm/(1.8–134.3) ml  | Colorectal (71%), rectum (29%)/(100%) | 75 Gy/3fr (262.5 Gy)       | 24                        |
| van de Voorde/2015 [39] | Retrospective | 17      | 1–3              | –                          | Colorectal (51.5%)/NR       | EQD2 62–150 Gy /3–10fr      | 21                        |
| Goodman/2015 [29]   | Retrospective | 54      | 1–3              | 2.7(0.9–10.2) cm/29.7(3.4–149.8) ml | Colorectal (67%)/NR         | 32–60 Gy/3–5 fr (52.48–180 Gy) | 33                        |
| Mendez Romero/2017 [25] | Retrospective | 40      | 1–3              | 2.5(0.7–6.2) cm            | Colorectal/ NR              | 50.25 Gy/3 fr (134.42 Gy)   | 25 & 26                   |
| Ahmed/2016 [24]     | Retrospective | 22      | 1–5              | 2(0.6–6.7) cm              | Colorectal (67%)/NR         | 37.5 Gy/3 fr (84.38 Gy)      | 20.5                      |
| Dori/2017 [28]      | Retrospective | 24      | 1–3              | 3.5(7–11.6) cm/8.7(0.4–134.7) ml | Colon (75%), rectum (25%)/(87.5) | 45–72 Gy/8 fr (71.7–115.5 Gy) | 16.5                      |
| McFarlin/2016 [33]  | Phase 1 & 2 | 60      | 1–6              | 40.8(0.6–3089) ml          | Colorectal/≥1 (82%)         | 22.7–62.1/5–6 fr (31.38–126.37 Gy) | 28.1                      |
| Joo/2017 [30]       | Retrospective | 70      | 1–3              | 41% ≥3 cm                  | Colorectal/3≥ (31%)         | 45–60 Gy/3–4 fr (58–180 Gy) | 34.2                      |
| Andratschke/2018 [25] | Retrospective | 213     | 1–4              | 0.6–699 ml                 | Colorectal (48.1%)/NR       | Several doses/1–13 fr (102.5–134.3 Gy) | 15                        |
| Vernaleone/2019 [19] | Retrospective | 38      | 1–4              | 1–5 cm                     | Colorectal (71%), rectum (29%)/NR | 25–45 Gy/3–5 fr (37.5–112.5 Gy) | 11.8                      |
| Clerici/2019 [27]   | Retrospective | 104     | 1–3              | –                          | Colorectal (51.5%)/NR       | 75 Gy/3fr (262.5 Gy)         | 33                        |
| Palma/2020/41       | Phase 2    | 9       | 1–5              | –                          | Colorectal (14%)/NR         | 35–54 Gy/3–5fr (59.5–151.2) | 51                        |
| Mendez Romero/2020 [35] | Prospective | 359     | 1–2              | 27(8–88) ml                | Colorectal (80%)/NR         | 11–12 Gy/5 fr (115.5–132 Gy) | 13.2                      |

BED: biologic equivalent dose; NR: not reported.
Table 2. Outcomes with SBRT for colorectal liver metastases.

| Author/year                  | Median OS (months) | 1y OS (%) | 2y OS (%) | 3–5y OS (%) | 1y LC (%) | 2y LC (%) | 3–5y LC (%) | Median PFS (months) | Liver or GI toxicity (%) |
|------------------------------|-------------------|-----------|-----------|-------------|-----------|-----------|-------------|---------------------|--------------------------|
| Herfath/2004 [12]            | 25                | 72        | NR        | –           | 71        | –         | –           | –                   | No significant toxicity  |
| Mendez Romero/2006 [36]      | –                 | 85        | 62        | –           | 100       | 86        | –           | –                   | G3 elevation of gamma glutamyl transferase (8) and ashenia (4) |
| Hoyer/2006 [13]              | 19.2              | 67        | 38        | –           | –         | 78        | –           | 6.5 (TTP)           | G3 intestinal toxicity (5), liver failure (2), nausea & diarrhea G1–2 (34 & 23), G3 (3); death n = 1 |
| Rusthoven/2009 [16]          | 32                | –         | 30        | –           | 95        | 92        | –           | 6.1                 | No RILD                  |
| Lee/2009 [14]                | 17.6              | 63        | –         | –           | 71        | –         | –           | 3.9                 | G3 gastritis (2), nausea (2), lethargy, and thrombocytopenia, G4 thrombocytopenia (1), G1 nontraumatic rib fractures (3) |
| Kim/2009 [31]                | 25                | 53        | 40        | –           | 80        | 60        | –           | –                   | G1 nausea and musculoskeletal discomfort (40) |
| van der Poel/2010 [18]       | 34                | 100       | 83        | –           | 100       | 74        | –           | 11                  | Liver toxicity: G3 (10), G2 (90) |
| Rusthoven/2009 [16]          | 34                | 100       | 83        | –           | 100       | 74        | –           | 11                  | Liver toxicity: G3 (10), G2 (90) |
| Mendez Romero/2020 [35]      | 50                | –         | 42%       | –           | –         | 88        | –           | –                   | G2 abdominal pain (0.005), bile duct stenosis (0.008), colecystitis (0.005), gallbladder perforation (0.002) |

OS: overall survival; LC: local control; GI: gastrointestinal; G: grade; TTP: time to progression; DFS: disease free survival; RILD: radiation induced liver disease.

*It represents two different dose levels.
dose is required for the larger tumor to achieve similar outcomes.

**Effect of biomarkers on outcomes of SBRT to CRLM**

Within the contrast of biomarkers, Hong et al. verified available tumor genomic data on a cohort of 89 patients, of the 34 patients had CRLM, and found an inferior LC for lesions with KRAS mutation (1-year LC of 43% vs. 72%, \( p = 0.02 \)), and particularly poor LC for those with combined KRAS and TP53 mutation (1-year LC of 20% vs. 69%, \( p = 0.001 \)) [42].

Additionally, Jethwa et al. has shown an increased local failure for CRLM which harbor TP53 mutation (HR: 3.1, 95% CI: 0.9–10.6, \( p = 0.06 \)) and an even stronger connotation for lesions with both TP53 and KRAS mutation (HR: 4.5, 95% CI: 1.1–18.7, \( p = 0.04 \)) with a 1-year cumulative incidence of local failure (LF) of 44% (95% CI: 0–71%) compared with 11% (95% CI: 2–18%) for patients without combined KRAS and TP53 mutation [43]. Jethwa et al. has shown that KRAS mutation (HR: 2.4, 95% CI: 1.3–4.6, \( p < 0.01 \)) and combined KRAS and TP53 mutation (HR: 5.7, 95% CI: 1.9–16.6, \( p < 0.01 \)) were associated with worse survival in patients treated with SBRT [43].

**Recommendation**

Based on previous data, we recommend a review of genomic testing prior to SBRT for CRLM, as it can dictate treatment-associated prognosis, and help with the treatment decision. CRLM patients with KRAS and/or TP53 mutation who had large lesions close to critical OAR preventing higher RT dose prescription, may not be the best candidate to benefit from SBRT, and a discussion with the patient should take place understanding that the local control benefit of such local therapy may be as low as only 20%. However, future prospective studies are warranted to validate these statements and incorporate them into the standard practice.

**SBRT-associated toxicity**

Toxicity is generally limited by achieving the recommended dose constraints for the liver and other surrounding normal tissue [12–14,16,23,26,29,33,34,36,37,46–49] (Table 3).

**Hepatic toxicity**

Prospective and retrospective studies have demonstrated <10% acute grade 3 toxicity related to liver SBRT [10–14,16,19,24–34,38–40]. Most prospective studies have reported no or rare incidence of RILD [12,13,16,36,37], and an uncommon rise in hepatic transaminases after SBRT. Van der Pool et al. reported acute grade 3 liver toxicity in 2 of 20 patients who developed liver enzyme elevation after 3 fractions of 12.5 to 15 Gy per fraction [18]. Hoyer et al. reported 2% incidence of liver failure after 45 Gy in 3 fractions SBRT schedule [13]. Overall, RILD and liver failure may be preventable with appropriate selection of candidate patients and prescribed RT dose for liver SBRT.

**Extrahepatic toxicity**

Extrahepatic complications are generally a result of the location of the treated lesion, e.g., near the bowel, stomach and chest wall. Hoyer et al. reported that 5/44 patients with CRLM developed grade 3 intestinal toxicity within 6 months.
after SBRT [13]. Lee et al. reported acute G3 gastritis/esophagitis in 2/40 patients, late grade 4 duodenal bleeding and grade 5 malignant small bowel obstruction and late grade 1 non-traumatic rib fractures in 2/40 patients treated for liver metastases after SBRT related to a maximum dose to 0.5 cc of the rib of 51.8 and 66.2 Gy in six fractions [14]. Rusthoven et al. reported late grade 3 soft tissue breakdowns requiring surgical debridement to area received 48 Gy in a patient treated with 60 Gy in 3 fractions [16]. Cardiac, kidney and heart toxicity has been poorly described in the liver SBRT literature [11,13,14,16,18,19,24–34,37,38,40]. These toxicities emphasize the importance of careful dose selection prescribed to tumor with respect to normal tissue dose constraints.

### Recommendation

To prevent acute and late radiation-induced liver disease (RILD) after SBRT, we recommend selecting patients with adequate liver function and sufficient uninvolved hepatic reserve ($\geq$700 cc) [13,14,16]. We also recommend having a reasonably safe distance (e.g., $\geq$5 mm) from luminal organs to prevent gastrointestinal complications, otherwise, a lower radiation dose in a larger number of fractions (i.e., 30 Gy in 5 fractions), with each-other-day SBRT schedule can be used. Recommended dose constraints for the liver and other surrounding normal tissue are summarized in Table 3 (these constraints were recommended from a wide variety of sources, arguably none of which are high-level evidence).

### Re-irradiation for liver metastases

In- and outside of the RT volume, recurrence within the liver presents a challenge for consideration of retreatment with SBRT because of anatomical and functional concerns of the abdominal organs [50]. Overall, re-irradiation with SBRT is an efficient ablative treatment option in highly selected patients (when the priority of sparing normal liver and gastrointestinal luminal structures are given over aggressive re-irradiation of new recurrence) [51]. In the setting of re-irradiation with SBRT, there is limited data on dose constraints for normal liver tolerance. McDuff et al. have shown that re-irradiation is safe with $<5\%$ risk of radiation-induced liver toxicity when normal liver parenchyma (<800 cc) received $<15$ Gy and gastrointestinal luminal structures did not exceed cumulative tolerance from two radiation courses in 49 patients of mixed primary and metastatic cases [52]. For gastrointestinal organs, unfortunately, there is no sharp data on dose constraints and repair to predict complications after re-irradiation with SBRT. To date, the best available re-irradiation data is limited to retrospective case series from a single institution reporting cumulative dose from two standard radiation techniques (external beam and SBRT) [53]. Abusaris et al. has reported grade 2 or 3 gastrointestinal toxicity ranging from 26% to 28% after re-irradiation with SBRT in recurrent pancreatic cancer. In this study, the cumulative bowel dose from both courses of RT was 90–98 Gy with no reported grade 3–5 toxicities [54]. With a median follow-up of 10.5 months, McDuff et al. have reported 1-year local failure rate of 61.0% for liver metastases (52% of them had colorectal liver metastases) [52].

### Advances in SBRT technology

#### Proton therapy for liver metastases

Proton beam therapy (PBT) provides a unique advantage of limited radiation range with little exit dose beyond the target over photon beam utilized in other RT delivery systems [17]. In comparison with photon-based SBRT, dosimetric analysis of PBT resulted in a major reduction in the irradiated normal liver volume by an average of 176 cc and 4 Gy mean liver dose for lesions $>3$ cm and/or located at the dome of the liver [42]. Hong et al. enrolled 89 patients in a phase I/II study of proton-based SBRT for liver metastases from different primaries, mainly colorectal (38.2%) with 29.4% of CRLM patients treated for 2–4 lesions and 17.6% of them had tumor size $>6$ cm, median tumor size was 2.5 cm (range, 0.5–11.9 cm). The radiation dose was 30–50 GyE (BED$_{10}$ 48–100 Gy) delivered in 5 sessions. For the total cohort, 1 and 3 years LC was 71.9% and 61.2%, respectively. Even for lesions $\geq$ 6 cm, authors reported satisfactory 1-year LC of 73.9% and median OS of 18.1 months, with no grade 3–5 toxicities had been reported [42]. A large retrospective series of 133 patients with liver metastases from different primaries was published by Fukumitsu et al. (43% of patients had CRLM), lesions were 1–18 cm (median, 4 cm). With RT dose of 72.6 GyE in 22 fractions (BED$_{10}$=96.56 Gy) for relatively large median tumor size, 2- and 5-years LC were 66% and 46%, and 2- and 5-years OS rates were 53% and 25%, respectively. Seven of 8 patients with lesions $>10$ cm had no evidence of local recurrence or significant treatment-related toxicity [55].

Furthermore, PBT could also be used as a salvage therapy for CRLM not amenable to second-stage hepatectomy. In small retrospective series limited to 5 patients with CRLM, right hemiliver ablative PBT was delivered with 67.5 GyE in 15 fractions (BED$_{10}$=97.9 Gy), 70 GyE in 28 fractions (BED$_{10}$=89.6 Gy) or 100 GyE in 25 fractions (BED$_{10}$=140 Gy). LC was achieved in 4 patients who were treated with BED$_{10}$ $>$89.6 Gy$_{10}$ [56]. Another attractive indication for PBT is re-irradiation of recurrent CRLM, McDuff et al. published a retrospective series of 49 patients who received re-irradiation for recurrent primary or oligometastatic liver metastases. In this study, five patients (10%) received re-irradiation using PBT [52].
**MR-guided liver stereotactic body radiation therapy**

MRI-guided radiotherapy (MRgRT) is a novel, attractive and rapidly evolving technology that allows for a higher visualization of the tumor and adjacent normal tissues. The feasibility and patient’s tolerability of MRgRT were evaluated in a prospective study that assessed 8/43 patients with liver lesions. In this study, 65% of patients reported some MR-related complaints (e.g., paraesthesia, uncomfortable positioning), however, with high levels of satisfaction related to their active participation in treatment, overall, MRgRT was defined as a tolerable treatment option [57]. CRLM appears to be ideal for MRgRT applications, especially in the setting of better tumor visualization and changing anatomy. Each fraction is customized to the daily tumor and normal tissue anatomy which potentially afford dose escalation that is subsequently associated with better LC rates >90% at 1 year when doses of 60–75Gy are delivered in 3 fractions using traditional RT delivery systems [10,37]. MRgRT applications allow for adaptive dose adjustment when the tumor is close to adjacent critical structures and yields a capability to customize the dose to the OAR that could constrain the daily SBRT dose to ensure higher degrees of safety (e.g., common bile duct that can be seen on T2 weighted MR images) [20]. This might be of particular importance for biliary structures related side effects after SBRT for centrally located tumors, or luminal structures-related side effects after SBRT for peripherally located tumors [58]. Unfortunately, there is limited data on CRLM treated with MRgRT (SBRT). Rosenberg et al. has reported freedom from local progression of 75% at a median follow up of 21.2 months for 18 metastatic liver lesions (44% colorectal metastasis) and 2 year OS of 60% of primary and metastatic liver tumors treated with MR-guided treatment with 7.7% grade 3 GI toxicities [58]. These findings are in keeping with those previously reported within the literature [59].

The challenge with MRgRT is that it requires additional time, personnel, and resources to adapt a treatment plan for each fraction has increased the complexity MRgRT [60]. Despite the numerous explored applications with MRgRT, the available evidence is still limited and the actual quantification of the advantages of using such an advanced technology requires further evaluation in the radiation oncology community [61].

**Recommendation:**

In the context of available resources, we suggest the use of PBT or MR-guided SBRT for CRLM when adequate therapeutic ratio cannot be achieved with traditional SBRT delivery systems due to large lesions, proximity to critical structures, or in the setting of re-irradiation.

**Future directions**

Future work is necessary to extend our knowledge and utilization of existing radiation delivery systems that appear effective in the treatment of CRLM with a satisfactory toxicity profile [20,42,55,57–61]. The role of SBRT using PBT and MR-linac as a radiation delivery option for liver metastases is being investigated in ongoing clinical trials that currently accruing patients ((NCT01239381, NCT04020276, NCT01697371, NCT02683200, NCT02722395, and NCT04242342). Future analyses of ongoing clinical trials will determine whether SBRT is superior to microwave ablation (NCT02820194, NCT01233544, NCT03963726, NCT03654131, and NCT04081168). In addition, we will learn from studies exploring the mechanisms underlying the efficacy of SBRT, which may engage the immune system (NCT03101475, NCT02239900, and NCT02837263), biomarkers and chemotherapy (NCT01569984, NCT01220063, and NCT01847495). Moreover, the potential for improved tumor control from selective boosting of tumor subvolumes could also be explored, particularly in conjunction with fluorodeoxyglucose, fluoromisonidazole, or other positron emission tomography radiotracers to overcome tumor metabolic activity or hypoxia. Also, further work is warranted to extend the knowledge about the tolerance of the liver and gastrointestinal organs to re-irradiation. Though repeated SBRT has been reported to be safe and effective to treat CRLM, however, no clear dose-volume parameters are available to guide re-irradiation which present a challenge for radiation oncologist during decision-making and discussion with patients.

**Conclusions**

Based on a review summary of relevant data, SBRT appears to be potentially successful in achieving local tumor control for patients with CRLM who are unsuitable for surgical resection, after the failure of other local therapies, and in combination with surgical resection.

Whenever feasible (considering safety to OAR), an excellent LC rate can be achieved with SBRT dose prescription equivalent to ≥ 100Gy10; however, a higher SBRT dose is required for the larger tumor to achieve similar outcomes. SBRT for CRLM patients with KRAS and/or TP53 mutation is associated with a relatively low rate of local control (as low as 20%), which should be considered during treatment decision for CRLM with SBRT RT dose reconstruction along with the use of advanced RT technology (e.g., MR linac-based or proton-based SBRT) is required when re-irradiation with SBRT is clinically indicated to ensure the safety of SBRT. Phase III randomized controlled trials incorporating SBRT into the treatment of CRLM are warranted to define widely accepted international standards of SBRT.

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