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Treatment Options in Oligometastatic Disease: Stereotactic Body Radiation Therapy – Focus on Colorectal Cancer

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Keywords

Stereotactic body radiation therapy, SBRT · Stereotactic ablative body radiotherapy · Oligometastasis · Colorectal cancer · Gastrointestinal cancer

Summary

Background: Improvements in systemic therapy for metastatic colorectal cancer (CRC) have markedly extended survival, rendering local control of metastases to critical organs of increasing importance, especially in the oligometastatic setting where the disease may not yet have acquired the ability to widely disseminate. While surgical resection remains the gold standard for oligometastases in many organs, stereotactic body radiation therapy (SBRT) presents a non-invasive alternative for achieving local control. **Methods:** A literature review was performed to identify and summarize the findings of key prospective and retrospective studies that have shaped the field of SBRT for oligometastases to the lung, liver, and spine with a focus on oligometastases from CRC in particular. **Results:** Modern dose-escalated SBRT regimens can achieve 1-year local control rates of 77–100%, 90–100%, and 81–95% for oligometastases involving the lung, liver, and spine, respectively. Rates of grade 3 or greater toxicity with contemporary SBRT techniques are consistently low at <10% in the lung, <5% in the liver, and <2%/8% for neurologic/non-neurologic toxicity in the spine, respectively. **Conclusion:** SBRT appears safe and effective for treating oligometastases involving the lung, liver, and spine. Randomized trials comparing SBRT to surgical resection and other local therapeutic modalities for the treatment of CRC oligometastases bear consideration.

Introduction

Up to half of patients with colorectal cancer (CRC) will develop metastatic disease [1], a condition traditionally managed with palliative chemotherapy and best supportive care resulting in dismal 5-year survival rates of less than 5% [2]. However, the emergence of new chemotherapeutic agents and targeted biologics since the late 1990s has produced substantial gains in overall and progression-free survival in patients with metastatic CRC, including extension of median survival to approximately 29 months [3, 4]. In light of these advances, guidelines from the National Comprehensive Cancer Network now recommend aggressive local management with curative intent surgery for resectable oligometastases in candidates with metastatic involvement limited to the lung and liver [5].

In the current article, the role of stereotactic body radiation therapy (SBRT) in the setting of oligometastatic disease will be explored with a focus on CRC. Comparison to other local treatment modalities will be provided where data is available. We will examine the safety and efficacy of SBRT in the three anatomic settings where it is most commonly utilized – namely, the lung, the liver, and the spine. Some historical perspective on the specific associated challenges in regard to normal tissue complications will be offered.

Technical Aspects of Stereotactic Body Radiation Therapy

SBRT can be defined as a technique for delivering high doses of radiation to extracranial lesions in a low number of treatments, typically 1–5 fractions. The crux of what distinguishes SBRT from conventionally fractionated radiation therapy is its capacity for an ablative effect due to the use of very large doses per fraction. While such an effect is desirable in malignant tissue, it can be detrimental to surrounding normal tissue. Safe administration of SBRT therefore requires a high degree of precision.

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Such precision is achieved through several interrelated means. Sophisticated planning software is required to achieve a steep isodose gradient with rapid dose falloff outside the target volume in order to spare surrounding normal tissue. Several static beam angles, i.e. up to 10–12, or movement of the beam in a continuous arc (volumetric modulated arc therapy) can be used to achieve optimal dose distribution, as opposed to conventional three-dimensional conformal radiation therapy (3DCRT) where four or fewer beam angles are employed.

External immobilization devices are important for patients to maintain the correct position in three-dimensional space and to minimize patient and target lesion motion during treatment delivery [6].

High-resolution imaging, fusion of multiple imaging modalities, and methodology are useful to reduce motion and uncertainty in target position during treatment. The latter has historically been a major barrier for using high-dose radiation outside of the brain. However, substantial progress has been made with the advent of on-board image guidance where the linear accelerator generating the radiation beam is equipped with an imaging system that can monitor tumor location. Accurate target localization can be accomplished by three-dimensional volumetric imaging with in-room computed tomography (CT) [7]. Alternatively, the insertion of metal fiducial markers or radiofrequency transponders into the tumor can allow for real-time tracking with on-board planar imaging. Accounting for target movement is critical, especially at anatomic sites in perpetual physiologic motion, such as the lung and liver. This can be accomplished by using infrared chest wall tracking linked either to X-ray images taken during treatment or to predictive algorithms modeling respiratory motion [8]. More simplistically, target motion can be limited using inflatable abdominal compression devices [9] and respiratory gating with breath-hold techniques [10]. This review article will trace the clinical data leading to derivation of modern SBRT regimens used for lesions in the lung, liver, and spine.

Stereotactic Body Radiation Therapy for Lung Oligometastases

Lung metastases develop in 5–15% of CRC patients [11]. Although prospective data regarding the benefit of pulmonary metastasectomy are lacking, a meta-analysis of 25 studies involving 2,925 patients demonstrated 5-year overall survival rates of 27–68% [12]. While most patients progress distantly, local recurrence following pulmonary metastasectomy occurs at a rate of 19.5–28% [13–15], often in spite of negative margins [16].

Most early data were derived from heterogeneous series including metastases from diverse primary histologies as well as primary lung tumors. More recent series provide a focus on lung oligometastases specifically from CRC. As summarized in table 1, these studies consistently demonstrate SBRT for pulmonary oligometastases to have a high degree of safety with grade 3 toxicity rates of less than 10% and in most series less than 5%; grade 4 or greater toxicity is rare with no cases documented in the reports described in table 1 [17–27]. Efficacy in providing long-term control of irradiated pulmonary metastases from CRC appears to vary from 67–94%, in part based on dose and fractionation. These findings appear similar to historical rates of local recurrence for pulmonary oligometastases from CRC following surgical metastasectomy, which range from 19.5–28% [13–15]. Some of the earlier studies delineated above demonstrate decreased local control for pulmonary oligometastases from CRC as opposed to other primary tumors. Possible reasons for these observations include the common presence of satellite tumor cells around CRC metastases as well as a higher ratio of hypoxic cells in CRC metastases as opposed to other tumor types with consequent reduction in radiosensitivity [28]. Nonetheless, studies published within the past 3 years employing modern thoracic SBRT techniques and escalated doses with a biological effective dose (BED) of at least 94 Gy consistently report excellent local control rates of greater than 90% specifically for colorectal oligometastases.

Survival outcomes following SBRT for pulmonary oligometastases from CRC are encouraging. In the studies listed in table 1 where the relevant data were available, overall survival at 1, 2, and 5 years ranged from 83–100%, 43–76%, and 39–49%, respectively. Despite the fact that SBRT patients are typically older, unfit for surgery, and have greater medical comorbidity, these outcomes are within range of those for surgical metastasectomy, which is associated with 5-year overall survival rates of 27–68% [12]. A group from the Netherlands compared 68 patients treated with pulmonary metastasectomy to 42 patients treated with SBRT for up to 5 pulmonary oligometastases [29]. SBRT consisted of 60 Gy in 3–8 fractions (BED 105–180 Gy). A large number of patients in both the metastasectomy and SBRT groups (57 and 74%, respectively) had CRC as their primary tumor. The SBRT group had worse baseline prognostic factors, including significantly older age and a shorter metastasis-free interval. Despite these biases, rates of overall survival at 1, 3, and 5 years were similar for metastasectomy and SBRT at 87, 62, and 41% versus 98, 60, and 49%, respectively. At 2 years, local control rates were similar at 90% for metastasectomy and 94% for SBRT. While prospective head-to-head studies are needed, these retrospective data suggest that survival is no worse after SBRT compared to metastasectomy.

Moreover, local control has not yet been shown to increase survival in any surgical or SBRT series [30]. This highlights the need for additional prospective data with standardized patient inclusion criteria for both pulmonary metastasectomy and SBRT. The PulMICC trial (NCT01106261), which is currently recruiting in the UK, will provide data on the feasibility of enrolling adequate numbers of CRC patients for a phase III randomized trial with power to identify survival differences between pulmonary metastasectomy and active surveillance.

Stereotactic Body Radiation Therapy for Liver Oligometastases

The liver represents the most common site of CRC metastasis. The survival of patients with untreated hepatic metastases from

Table 1. Summary of studies investigating the use of SBRT for pulmonary oligometastases; all BED calculations are based on an assumed α/β = 10 for the metastatic tumor

Author, year	Study design	No. patients *No. with CRC*	No. lung metastases *No. from CRC*	SBRT dose and fractionation	BED, Gy	Local control outcomes	Survival outcomes, %	Grade 3 or greater toxicity, %	Grade 2 toxicity, %
Wulf et al. [17], 2004	retrospective	61 (20 NSCLC) *4*	51 *NR*	10–12.5 Gy × 3	60–94	80 (1 yr); 80 (3 yrs)	85 (1 yr); 33 (2 yrs)	0	3.3
Fritz et al. [18], 2006	retrospective	58 (33 NSCLC) *NR*	31 *NR*	30 Gy × 1	120	80 (5 yrs)	97 (1 yr); 73 (2 yrs); 42 (5 yrs)	0	0
Guckenberger et al. [19], 2007	retrospective	70 (38 NSCLC) *NR*	48 *NR*	26 Gy × 1 (n = 23); 10–12.5 Gy × 3 (n = 19); 6–7 Gy × 4–8 (n = 5)	48–94	88% (2 yrs)	NR	1.4	5.7
Norihisa et al. [20], 2008	retrospective	34 *9*	43 *NR*	12–15 Gy × 4–5	106–132	90 (2 yrs)	84 (3 yrs)	3	12
Rusthoven et al. [21], 2009	phase I/II	38 *9*	63 *NR*	16–20 Gy × 3	125–180	100 (1 yr); 96 (2 yrs)	39 (1 yr)	7.9	NR
Kim et al. [22], 2009	retrospective	13 *13*	13 *13*	13–17 Gy × 3	90–138	77 (1 yr); 53 (2 yrs); 53 (3 yrs)	100 (1 yr); 76 (2 yrs) 65 (3 yrs)	0	NR
Takeda et al. [23], 2011	retrospective	34 *15*	44 *21*	10 Gy × 5	100	94 (1 yr; all); 80 (1 yr; CRC); 94 (2 yrs; all); 73 (2 yrs; CRC)	NR	3	6
Qiu et al. [24], 2015	retrospective	65 *65*	144 *144*	5 Gy × 10 (55%); 10 Gy × 5 (38%); other (6%)	75–100	NR	43 (2 yrs)	NR	NR
Filippi et al. [25], 2015	retrospective	40 *40*	59 *59*	26 Gy × 1 (68%); 15 Gy × 3 (19%); 11 Gy × 5 (9%); 12 Gy × 4 (1%); 7.5 Gy × 8 (3%)	94–151	93 (20 months)	88 (1 yr); 73 (2 yrs); 39 (5 yrs)	0	7.5
Carvajal et al. [26], 2015	retrospective	13 *13*	13 *13*	34 Gy × 1 (31%); 18 Gy × 3 (31%); 12.5 Gy × 4 (23%); 7.5 Gy × 8 (15%)	105–151	92 (1 yr) 92 (2 yrs)	92 (2 yrs)	0	NR
Agolli et al. [27], 2016	retrospective	44 *44*	69 *69*	23–30 Gy × 1 15 Gy × 3	76–120	67 (3 yrs)	83 (1 yr); 68 (2 yrs); 51 (3 yrs)	0	25

SBRT = Stereotactic body radiation therapy; BED = biological effective dose; Gy = Gray; NSCLC = non-small cell lung cancer; yr = year; yrs = years; NR = not reported; CRC = colorectal cancer.

Table 2. Summary of studies investigating the use of SBRT for hepatic oligometastases; all BED calculations are based on an assumed $\alpha/\beta = 10$ for the metastatic tumor

Author, year	Study design	No. patients *No. with CRC*	No. liver metastases *No. from CRC*	SBRT dose and fractionation	BED, Gy	Local control outcomes, %	Survival outcomes, %	Grade 3 or greater toxicity, %
Herfarth et al. [43], 2001	phase I/II	37 (4 PLC) *NR*	56 *30*	14–26 Gy × 1	34–94	67 (18 mos; 45 for CRC, 91 for all others)	72 (1 yr)	0
Wulf et al. [44], 2006	retrospective	39 *NR*	51 *23*	(1) 26 Gy × 1; (2) 12–12.5 × 3; (3) 7–10 Gy × 3–4	(1) 94; (2) 79–84; (3) 48–60	(1) 100 (1 yr); 86 (2 yrs); (2) 100 (1 yr); 86 (2 yrs); (3) 86 (1 yr); 58 (2 yrs)	72 (1 yr); 32 (2 yrs)	0
Méndez Romero et al. [45], 2006	phase I/II	25 (8 PLC) *15*	34 *28*	12.5 Gy × 3	84	100 (1 yr); 86 (2 yrs)	85 (1 yr); 62 (2 yrs)	24
Katz et al. [46], 2007	retrospective	69 *20*	174 *NR*	5 Gy × 10; other (30–55 Gy in fraction sizes of 2–6 Gy)	75 (variable)	76 (10 mos); 57 (20 mos)	78 (10 mos); 37 (20 mos)	0
Lee et al. [47], 2009	phase I	68 *40*	143 *NR*	4.7–10 Gy × 6	41–120	71 (1 yr)	63 (1 yr)	13
Rusthoven et al. [48], 2009	phase I/II	47 *15*	63 *20*	12–20 Gy × 3	79–180	95 (1 yr); 92 (2 yrs)	30 (2 yrs; all); 60 (2 yrs; for favorable histology including CRC)	2
Vautravers-Dewas et al. [49], 2011	retrospective	42 *NR*	62 *30*	15 Gy × 3 10 Gy × 4	80–113	90 (1 yr); 86 (2 yrs)	94 (1 yr); 48 (2 yrs; note 58% for CRC)	2.4
Rule et al. [50], 2011	phase I	27 *NR*	37 *16*	(1) 12 Gy × 5; (2) 10 Gy × 5; (3) 10 Gy × 3	60–132	(1) 100 (2 yrs); (2) 89 (2 yrs); (3) 56 (2 yrs)	50–67 (2 yr)	0
Scorsetti et al. [51], 2015	phase II	42 *42*	52 *52*	25 Gy × 3	263	91 (2 yrs)	65 (2 yrs)	0
Goodman et al. [52], 2016	retrospective	81 *NR*	106 *71*	10.8–18 × 3–5	112–151	96 (1 yr); 91 (4 yrs)	90 (1 yr); 69 (2 yrs); 44 (3 yrs); 28 (4 yrs)	4.9

SBRT = Stereotactic body radiation therapy; BED = biological effective dose; Gy = Gray; PLC = primary liver cancer; yr = year; yrs = years; mos = months; NR = not reported; CRC = colorectal cancer.

CRC is dismal at approximately 20–30% at 1 year, 8–10% at 2 years, and 0–5% at 5 years [31, 32]. In three large series, overall survival for patients with resectable liver-limited metastases was approximately 30–40% at 5 years and 22–24% at 10 years [33–35]. The efficacy of liver metastasectomy in CRC is now well established with more modern series reporting 5-year survival rates as high as 58% [36, 37] and – in cases of a solitary liver metastasis – up to 71% [38] with some cures.

The findings above provide a strong rationale for pursuing aggressive local management of liver-only metastases in well selected CRC patients. Unfortunately, liver metastases from CRC prove to be unresectable in 40–90% of patients [39, 40]. Radiofrequency ablation (RFA) represents one alternative, though it is limited by tumor size and anatomic location, including contraindication for metastases located nearby large vessels or the diaphragm.

Historically, there has been a bias against radiotherapy for malignant disease of the liver because of low tolerance of the whole liver to radiation. The most serious complication of external beam radiation therapy (EBRT) to the liver is radiation-induced liver disease (RILD). RILD is a clinical syndrome of hepatomegaly, ascites, elevated liver enzymes (most notably alkaline phosphatase), and eventually jaundice that can occur 2 weeks to 4 months following EBRT. The pathophysiology resembles Budd-Chiari syndrome and veno-occlusive disease.

In the pilot study for whole-liver EBRT, i.e. RTOG 76-05, 103 patients with solid tumor hepatic metastases were treated with a variety of dose regimens ranging from 21 Gy in 3 fractions to 30.4 Gy in 19 fractions [41]. No hepatic toxicity was observed, leading to a subsequent dose escalation study, RTOG 84-05 [42]. 173 patients with liver metastases from a gastrointestinal primary cancer (75% CRC) were treated with whole-liver EBRT. The dose was escalated from 27 to 30 to 33 Gy in 1.5-Gy twice daily fractions. RILD was observed in 5 of 51 patients at the 33-Gy dose level, while no liver injury was observed at the 27- or 30-Gy dose levels. Median survival was not significantly different between the 3 groups at 4.2, 4.2, and 4.3 months, respectively. The authors concluded that 33 Gy was an unsafe dose to the whole liver without any associated benefit in clinical outcomes.

Efficacy of SBRT appears, at the least, quite promising for liver metastases from CRC. Multiple studies in table 2 [43–52] show the importance of dose escalation in using SBRT to treat liver metastases [43, 44, 48, 50, 51]. High doses appear to be particularly important in treating CRC metastases; a recent study using a 10-gene assay to assess radiosensitivity of hepatic metastases from different primary histologies demonstrated CRC metastases to be more radioresistent than breast adenocarcinoma, lung adenocarcinoma, and anal squamous cell cancer [53]. The excellent local control observed in recent series, however, suggests that modern SBRT doses have surpassed the threshold needed to control liver metastases from CRC.

Surgery remains the gold standard for hepatic oligometastases. The lesions treated in the studies of SBRT included in table 2 were considered unresectable, suggesting that they generally tended to be larger, multiple in number, or in critical anatomic regions; alternatively, patients may have been unfavorable candidates for surgery due to medical comorbidity, insufficient hepatic reserve, or presence of extrahepatic metastases. In spite of these baseline disadvantages compared to lesions undergoing hepatic resection, local control outcomes for SBRT approach those of surgery at most available time points. Local control ranges from 71–100% at 1 year and 57–100% at 2 years in the data are presented in table 2; however, these data include suboptimal doses used in the early portions of dose escalation trials. When one considers only dose-escalated regimens [45, 48–52], 1-year and 2-year local control range from 90–100% and 81–100%, respectively. A major limitation of the current outcomes data for SBRT is the lack of long-term prospective follow-up; however, a large retrospective review shows durable local control of 91% at 4 years [52]. In general, these local control outcomes are comparable to reported surgical local control rates of 88–95% at 3 years [38, 54] and appear substantially better than local control rates of 32–76% at 2 years with RFA [55, 56]. Overall survival rates for patients undergoing SBRT range from 63–94% at 1 year and 32–83% at 2 years in the studies presented, with 4-year overall survival available in one retrospective study at 28%.

Stereotactic Body Radiation Therapy for Spine Oligometastases

Bone metastases are rare in patients with CRC with an overall incidence of only 5–11% [57, 58]. In series of patients presenting with metastatic epidural spinal cord compression (MESCC), metastases from CRC account for only 1.5–4.7% of cases [59, 60].

The majority of patients with MESCC have historically been treated with palliative conventional EBRT alone. Given the inherent radioresistance of certain malignancies, including CRC [53], renal cell carcinoma, and melanoma [61, 62], this BED is unlikely to provide durable long-term local control. Retrospective series suggest that the median time to recurrence following conventionally fractionated EBRT to the spine is approximately 6 months [63]. Attempts to increase the dose of conventionally fractionated EBRT for relatively radioresistant histologies are limited by the dose tolerance of the spinal cord and have not shown significant improvements in local control [64].

SBRT is a particularly attractive option for metastatic lesions in close proximity to the spinal cord as it can achieve precise delivery of high dose radiation to the target with sharp dose gradients to avoid exceeding dose tolerance of the nearby spinal cord. Selected studies that helped to establish the safety and efficacy of both hypofractionated and single-fraction SBRT for spine oligometastases are summarized in table 3 [65–69]. Of note, only the study performed by Yamada et al. [66] included patients with MESCC (although patients with high-grade MESCC were excluded) while the other 4 studies excluded patients with any degree of MESCC.

These reports provide strong support for the use of SBRT for the challenging clinical situation of oligometastases involving the spine. The technique appears safe with rare grade 3 or greater neurologic toxicity at 0–1.6% and grade 3 non-neurologic toxicity rates of 8% or less. Efficacy appears high with local control rates of 81–

Table 3. Summary of studies investigating the use of SBRT for spine oligometastases; all BED calculations are based on an assumed α/β = 10 for the metastatic tumor

Author, year	Study design	No. patients *No. with CRC*	No. spine metastases *No. from CRC*	SBRT dose and fractionation	BED, Gy	Local control outcomes, %	Survival outcomes, %	Grade 3 or greater toxicity, %
Chang et al. [65], 2004	phase I/II	63 *1*	74 *1*	9 Gy × 3; 6 Gy × 5	48–51	84 (1 yr); 77 (2 yrs)	70 (1 yr)	4.8
Yamada et al. [66], 2008	retrospective	93 *11*	103 *NR*	18–24 Gy × 1	50–81	90 (15 mos; 95 for 24 Gy vs. 81 for 18–23 Gy)	36 (45 mos)	0
Amdur et al. [67], 2009	phase II	21 *1*	25 *1*	15 Gy × 1	38	95 (8 mos)	25 (1 yr)	0
Wang et al. [68], 2012	phase I/II	149 *6*	166 *NR*	9-10 Gy × 3	51–60	81 (1 yr); 73 (2 yrs)	72 (1yr); 49 (2 yrs)	8
Garg et al. [69], 2012	phase I/II	61 *NR*	63 *NR*	16–24 Gy × 1	42–81	88 (18 mos)	64 (18 mos)	3.3

SBRT = Stereotactic body radiation therapy; BED = biological effective dose; Gy = Gray; yr = year; yrs = years; mos = months; NR = not reported; CRC = colorectal cancer.

90% at 1 year despite the fact that multiple series included spine metastases that had progressed after prior conventional EBRT [65–68]. When dose can be escalated to 24 Gy in a single fraction, local control rates at 1 year can reach 95% [66]. Moreover, the length of survival following spinal SBRT was substantial in many of the prospective trials in table 3 at median 23–30 months. The observed longevity following SBRT suggests that effective local therapy to achieve long-term local control is worthwhile for spine metastases, where progression could drastically reduce mobility, neurologic function, and quality of life.

In cases of high-grade MESCC, upfront spinal cord decompression surgery is often needed to remove epidural disease in near or direct contact with the cord [70, 71]. The use of postoperative SBRT to the region at risk and any residual osseous or epidural disease can allow for safer, less radical surgery and achieve high rates of local control. Laufer et al. [72] reported a series of 186 patients (8% CRC) with MESCC treated with surgical decompression followed by SBRT given at 3 dose levels: 24 Gy in a single fraction (BED 81.6 Gy), 24–30 Gy in 3 fractions (BED 43.2–60 Gy), or 18–36 Gy in 5 or 6 fractions (BED 24.5–57.6 Gy). Local control for all patients was 83.6% at 1 year. Patients receiving higher BED regimens of 24 Gy in a single fraction or 24–30 Gy in 3 fractions demonstrated local control of 91 and 95.9% at 1 year, respectively, versus 77% in patients receiving 18–36 Gy in 5 or 6 fractions. Local control was not found to be associated with primary tumor histology. No neurologic toxicity occurred due to SBRT; 4 patients underwent reoperation due to hardware failure.

The durability of local control and symptom palliation with SBRT appears markedly superior to conventional EBRT when comparison is made to historical controls. RTOG 06-31 (NCT00922974) is an ongoing randomized trial that will seek to address this question in a standardized fashion. Patients with significant pain from spine metastases and no history of prior radiation or surgery to the region of interest will be randomized to 16 Gy in a single fraction using SBRT versus delivery of 8 Gy in a single fraction with conventional radiation.

Conclusion and Future Directions

Advances in systemic therapy for CRC have markedly extended the survival of patients with metastatic disease, rendering effective local therapy of increasing importance. This is especially true in the oligometastatic setting where malignant cells may not yet have acquired widespread metastatic potential. Despite the traditional radioresistance associated with CRC, modern dose-escalated SBRT regimens are able to overcome this and achieve high rates of local control. While surgery remains the gold standard for resectable oligometastases from CRC, the local control outcomes in recent reports of SBRT closely approach those of surgery. These results in combination with the low morbidity associated with SBRT are compelling for consideration of randomized trials comparing SBRT to resection.

Disclosure Statement

No conflicts of interest.

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