Review Article

Stereotactic body radiation therapy in non-liver colorectal metastases: a scoping review

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Background: In oligometastatic colorectal cancer (CRC), stereotactic body radiation therapy (SBRT) represents a valid non-invasive local ablative treatment with high rates of local control (LC) and a low toxicity profile. This literature review was performed to evaluate the clinical benefit and toxicity of SBRT on non-liver metastases in CRC oligometastatic patients.

Methods: After searching PubMed, Medscape and Embase databases, 18 retrospective studies focused on body oligometastases excluding bone metastases were included in the analysis.

Results: A total of 1,450 patients with 3,227 lung metastases and 53 patients with 66 nodes lesions were analyzed. BED10 ranged from 76 to 180 Gy. In the lung group, the LC rate was 62–91%, 54–81% and 56–77% after 1, 3 and 5 years, respectively. In the nodes group, the 3-year LC rate was 65–75%. The 1-, 3- and 5-year OS rates were 73–100%, 51–64% and 34–43%, respectively for the lung group, and 63–81% at 3 years for the nodes group.

Conclusions: In CRC patients with non-liver oligometastases, the use of SBRT is effective and safe reaching high LC and survival, with few severe side effects. However, prospective randomized studies are needed to validate the results. These studies will also be useful for identifying any predictive factors that allow us to select the subgroup of patients who benefit from SBRT.

Keywords: Colorectal cancer (CRC); stereotactic body radiation therapy (SBRT); oligometastases; metastatic CRC

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Introduction

Colorectal cancer (CRC) is the third most diagnosed cancer worldwide and the second in Europe (1,2). The diagnostic trend is increasing: it is estimated that there will be over two million new cases by 2030 and over the next 10 years there will be one million deaths (3). In approximately 20–25% of cases, CRC patients may have distant metastases at presentation, whereas about 50% will develop a metastatic CRC (mCRC) during the natural history of the disease (4,5). The two most common sites of metastases include the liver and lung (85% of the cases) followed by the lymph nodes and peritoneum (6,7). In particular, the liver represents the first site of metastatic involvement in CRC patients. On the contrary, the main site of extra-abdominal metastatic disease is the lung where approximately 25–40% of distant metastases occur (8). Systemic therapy is the primary treatment for mCRC and survival can be increased by 2–3 years using a multidrug approach (9). On the other hand, surgical resection of CRC metastases is associated with a survival increase (10-13). The hepatic resection can provide a 5-year overall survival (OS) rates of 37–58% (14), as well as the pulmonary resection can provide a 5-year

survival rate of 38–50% (15,16). However, in recent years local ablative treatments (LAT) of unresectable patients have been increasingly used in the presence of limited metastatic cancer, the so-called oligometastatic disease (OMD) (17). The term OMD refers to an intermediate state of cancer between localized and disseminated disease; it is currently defined as a stage of cancer in which up to 5 metastases are present involving up to 3 organs. According to ESMO guidelines, oligometastatic CRC is characterized by the presence of 5 or sometimes more metastases at up to 2 or 3 sites, especially visceral and occasionally lymph nodal (18). Conversely, the presence of metastases in other sites, such as bones and the brain, is often multiple. In this case the tumor disease should not be classified as OMD, linking with a poor prognosis and the use of LAT frequently aims only to avoid short-term complications in this patient setting. However, quantitative characteristics alone cannot define OMD and the complexity of aspects that influence the response to local treatments. Guckenberger *et al.* have recently identified a panel of 17 characteristics to classify OMD (19); the same authors concluded that the Oligocare cohort study results will highlight the validity and therefore the use of these features in clinical practice (11). An alternative noninvasive LAT is stereotactic body radiation therapy (SBRT) that delivers a high dose of radiation accurately and in a small number of fractions (20). In the last two decades, the use of SBRT has progressively increased and several studies report an improvement in local tumor control and therefore long-term survival outcome in oligometastatic patients treated with this method (21-23). The prospective phase II SABR-COMET trial investigated the role of SBRT in oligometastatic patients (<5 lesions) with controlled primary cancer, where colorectal was the most common primary cancer site along with breast and lung (24). The long-term results showed a 5-year OS rate was 42% in the SBRT arm (25). Extra-hepatic metastases occur in 30–40% of patients with mCRC and the aim of this study was to review the literature for survival outcomes and toxicities in this setting of patients with non-liver oligometastases treated with SBRT. We present this article in accordance with the PRISMA-ScR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-832/rc).

Highlight box

Key findings

- In metastatic colorectal cancer (mCRC) patients with non-liver oligometastases, the use of Stereotactic Body Radiation Therapy (SBRT) is effective and safe with high survival outcomes and few severe side effects.

What is known and what is new?

- The SBRT represents a valid non-invasive local ablative treatment in oligometastatic patients with mCRC.
- This review of literature summarizes the data of survival outcomes and toxicities in the setting of mCRC patients with non-liver oligometastases treated with SBRT.

What is the implication and what should change now?

- Survival outcomes after SBRT are similar to other local ablative treatment such as surgery, although randomized comparisons between techniques are lacking. Further studies are needed to validate the results, also investigating predictive/prognostic factors that can help tailor local treatment in CRC oligometastatic setting.

Materials and methods

Studies reporting local control rate and survival outcomes for CRC oligometastatic patients treated with SBRT on non-liver lesions were included in the analysis. Case reports, articles not written in English or published only as abstracts were excluded (*Figure 1*). Pubmed, Medscape and Embase were used for the search. Keywords included colorectal cancer, stereotactic body radiotherapy/stereotactic ablative body radiation, SBRT/SABR, oligometastases/oligometastatic disease. Survival outcomes [local control (LC) and OS] and toxicities after SBRT were evaluated.

Results

Lung metastases

In total 17 articles were identified and analyzed, all with retrospective design. There were 1,450 patients with a total of 3,227 lesions. Patients' and treatment characteristics are reported in *Table 1*. After completing SBRT, the median follow-up range for all patients was 14–42.8 months. Median Biologically Effective Dose (BED) (alfa/beta =10) ranged from 76 to 180 Gy. The median lesion diameter ranged from 10 to 16 mm (5–58 mm). All studies used CT for treatment planning, eight of which used additional methods such as PET/CT, which were fused with the planning CT. In three cases this information was not reported. One-year local control rate ranged from 62% to 91%, from 54.2% to 81% after three years and from 56% to 77% after five years of observation.

Among all studies, 14 of them reported information about overall survival (26-29,31-33,36-41,43). Overall

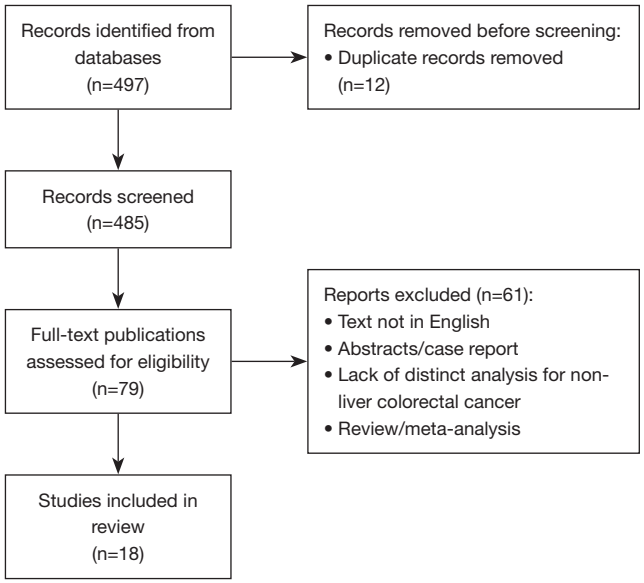

Figure 1 Overview of studies search and selection.

survival rate ranged from 73% to 100% after one year, from 50.8% to 64% after three years and from 34% to 43% after five years.

Regarding potential prognostic factors, in four experiences (26,37,38,41), a lower tumor volume was a predictor for better local control, while two studies (28,31) found a relationship between tumor volume and overall survival. Additionally, a high SBRT dose, referred to as BED (alfa/beta =10), was associated with a higher local control, quantified in values greater than 70 Gy (42), 100 Gy (32,35-37,41), 115 Gy (39) and 125 Gy (43). Sharma *et al.* reported median OS of 30.8 months (range, 17.1–44.5) in patients treated with lower dose (BED10 <100 Gy) versus 48.8 months (range, 34.9–62.7) in subgroup treated with higher doses (BED10 >100 Gy) (36).

We did not find a clear correlation between local response and primary tumor (colon vs rectal cancer). In the series of Jingu *et al.* (32), primary site (rectal cancer being favorable) was selected as prognostic factor for local control (P=0.025) while in the study of Kinj and colleagues (31), rectal primary site was correlated with a lower local control rate (P<0.001).

Information about toxicity of the treatment was reported in 13 papers (26-33,36-39,41). Regarding toxicity greater than or equal to G3, nine series reported 0 toxicities and three series reported a toxicity rate of 1.5–6%. One experience described a rate of late G3 toxicity (radiologic pulmonitis) of 10.8% (27).

Nodes metastases

In our analysis we found two series concerning SBRT on lymph node metastases by colorectal cancer (26,34). In these retrospective experiences 53 patients were treated on a total of 66 nodes metastases. The main characteristics of patients, radiation therapy and outcome are summarized in *Table 1*.

In the study of Bae *et al.* (26), it was reported a median BED (alfa/beta =10) of 124.8 Gy and MRI and PET/CT scans were used to delineate gross tumor volume (GTV) accurately.

Three-year local control rate ranged from 65% to 75%, while overall survival rate ranged from 63% to 81% after three years. In the series of Franzese *et al.* (34), according to RECIST criteria, more than half of patients had a complete remission (20 cases, 53%), while partial response was observed in 14 patients (37%), stable disease in 3 patients and one case was progressing at the first evaluation after SBRT.

Bae *et al.* (26) reported that in 18 patients treated with SBRT, three (16.7%) experienced severe gastrointestinal adverse events (AEs): two G3 AEs and one G4 AEs. The other series (34) did not register any toxicity.

Discussion

In this review we evaluate the efficacy of SBRT in non-liver oligometastases in CRC patients from the analysis of 18 retrospective studies.

This report showed that SBRT correlated with high survival outcomes and was overall well tolerated. The LC had a 1-year rate ranging from 62% and 91% and a 3-year rate of 65% to 81%. Only one study reported no LC data (37). The wide range of LC could be explained by retrospective design of studies included in the analysis. Specifically, doses and fractionation regimen used as well as size and number of lesions were heterogeneous. After SBRT, grade >3 adverse effects occurred in 1–11% of cases (26,27,32,36,39). Nine articles reported low (grade 1–2) or no toxicity (28-31,33.34,37.38,41), while tolerance to SBRT was not assessed in 4 studies (35,39,42,43).

Most available data derive from heterogeneous series including metastases from different primary histologies. Some of these studies demonstrated a decreased local control for lung oligometastases from CRC as opposed to other primary tumors. This can be partly explained by the presence of satellite tumor cells around CRC metastases as

Table 1 Summary of non-liver oligometastases in CRC treated with SBRT

Author, year	Study design	N patients/ lesions	Median age (years)	Site of metastases	Size of metastases	Median dose/fractions	Median BED (Gy)	Median follow-up, (months)	LC	OS	Toxicity (Grade 3 or higher)	Adjuvant chemotherapy (n patients)
Bae, 2012 (26)	Retrospective	30/35	56	Lung: 12/16	Median GTV: 6 cc (2–29 cc)	48 Gy/3 fr	124.8	28	66% (3 yrs) 66% (5 yrs)	57% (3 yrs) 34% (5 yrs)	0	33
				Nodes: 18/19	Median GTV: 18 cc (2–40 cc)				65% (3 yrs) 54% (5 yrs)	63% (3 yrs) 43% (5 yrs)	16.7% (gastrointestinal)	
Filippi, 2015 (27)	Retrospective	40/59	70	Lung	Median diameter: 15 mm (20–40 mm)	26–48 Gy/1–8 fr	93.6 (93.6–151.2)	20	NA	84% (1 y) 73% (2 yrs) 39% (5 yrs) 26 mo (median)	10.8% (late toxicity)	4
Jung, 2015 (28)	Retrospective	50/79	65	Lung	Median GTV: 1.5 cc (0.2–34.8 cc)	48 Gy/3–4 fr	N.A.	42.8	88.7% (1 y) 70.6% (3 yrs)	64% (3 yrs)	0	22
Agolli, 2016 (29)	Retrospective	44/69	70	Lung	Median diameter: 14 mm (3–46 mm) Median PTV: 9.8 cc (2–78.5 cc)	23–45 Gy/1–3 fr	76–120	36	68.8% (1 y) 60.2% (2 yrs) 54.2% (3 yrs)	38 mos (median) 67.7% (2 yrs) 50.8% (3 yrs)	0	NA
Pasqualetti, 2017 (30)	Retrospective	33/56	67	Lung	Median GTV: 2.3 cc	24–42 Gy/1–3 fr	NA	23	6 mos: 87.8% 1y: 62% 18 mos: 30%	NA	0	NA
R. Kinj, 2017 (31)	Retrospective	53/87	69	Lung	Median diameter: 16 mm (3–70 mm) Median GTV: 3.2 cc (0.2–16 cc) Median PTV: 12.1 (0.4–189)	60 Gy/3 fr	180	33	79.8% (1 y) 78.2% (2 yrs)	79.8% (1 y) 78.2% (2 yrs)	0	NA
Jingu, 2017 (32)	Retrospective	93/104	69	Lung	Median diameter: 15 mm	50 Gy/3–15 fr	105.6	28	65% (3 yrs) 56% (5 yrs)	56% (3 yrs) 43% (5 yrs)	Grade 3 pneumonitis (2%) Grade 5 pneumonitis (1%)	47
Mazzola, 2018 (33)	Retrospective	23/40	70	Lung	Median diameter 23 mm	No Bevacizumab group: 55 Gy/6 fr Bevacizumab group: 51 Gy/5 fr	No Bevacizumab group: 110 Bevacizumab group: 103	18	89% (1 y)	100% (1 y)	0	NA
Franzese, 2017 (34)	Retrospective	35/47	66	Nodes	Median CTV 8 cc	30–45 Gy/5–13 fr	N.A.	15	85% (1 y) 75% (2 yrs) 75% (3 yrs)	100% (1 y) 81% (2 yrs) 81% (3 yrs)	0	NA

Table 1 (*continued*)

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Author, year	Study design	N patients/ lesions	Median age (years)	Site of metastases	Size of metastases	Median dose/fractions	Median BED (Gy)	Median follow-up, (months)	LC	OS	Toxicity (Grade 3 or higher)	Adjuvant chemotherapy (n patients)
Wang, 2018 (35)	Retrospective	15/24	62	Lung	Median diameter 10 mm	48–60 Gy/4–5 fr	105.6–132	30	81% (1 y)	NA	NA	NA
									69% (3 yrs)			
									69% (5 yrs)			
Sharma, 2019 (36)	Retrospective	118/202	<70 (73%) >70 (37%)	Lung	<3 cm (71%), >3 cm (29%)	Peripheral mts: 51–60 Gy/3 fr or 30 Gy/1 fr	>100 (70%)	31	83% (2 yrs)	69% (2 yrs)	6%	NA
						Central mts: 50–60 Gy/5 fr	<100 (30%)		81% (3 yrs)	55% (3 yrs)		
						Ultracentral mts: 48–56 Gy/6–7 fr			77% (5 yrs)	36% (5 yrs)		
Li, 2019 (37)	Retrospective	53/105	61	Lung	Median diameter 11 mm	48–75 Gy/4–10 fr	100	14	90% (1 y)	95% (1 y)	0	15
										74% (2 yrs)		
Kobayashi, 2020 (38)	Retrospective	20/26	69	Lung	Median diameter 7 mm	54–60 Gy/3 fr	151–180	19	66% (2 yrs)	89% (2 yrs)	0	3
Yamamoto, 2020 (39)	Retrospective	330/371	73	Lung	Median diameter 15 mm	NA	115.3	25	86% (1 y)	94% (1 y)	1.5 %	196
									65% (3 yrs)	63% (3 yrs)		
Nicosia, 2020 (40)	Retrospective	38/107	75	Lung	Median diameter 14 mm	30–70 Gy/3–10 fr	105	28	91% (1 y)	76% (1 y)	NA	10
									80% (2 yrs)	71% (2 yrs)		
Li, 2021 (41)	Retrospective	17/38	61	Lung	Median GTV 1.8 cc	50–63 Gy/5–12 fr	100	10	78% (1 y)	73% (1 y)	0	14
Benson, 2021 (42)	Retrospective	18/28	58	Lung	1 cc	50 Gy/4 fr	113	26	86% (1 y)	N.A.	NA	0
Nicosia, 2022 (43)	Retrospective	529/1033	70	Lung	Median diameter 13 mm	48 Gy/1–10 fr	105	26	75% (2 yrs)	42.6 mos (median)	NA	178

CRC, colorectal cancer; SBRT, stereotactic body radiotherapy; LC, local control; OS, overall survival; BED, biologically effective dose; GTV, gross tumor volume; PTV, planning target volume; FR, fractions; y, year; yrs, years; NA, not available; mos, months; mts, metastases.

well as a higher ratio of hypoxic cells in CRC metastases as opposed to other tumor types with consequent reduction in radiosensitivity (44).

From these biological features derives the need to deliver a multidrug therapeutic scheme and a high doses of radiation to achieve a therapeutic effectiveness.

Nevertheless, the appropriate total dose and appropriate dose per fraction in SBRT for pulmonary oligometastases from CRC have still not been determined.

A systematic review and a meta-analysis conducted in 2018 by Jingu *et al.* (45) recommends a prescription dose >100 Gy of BED10 to the periphery of the planning target volume (PTV) in SBRT for pulmonary oligometastases from CRC. In line with these literature data, our review shows how dose escalation is important in terms of LC of lung metastases from CRC. Indeed, a high BED10 was associated with a higher LC, in most works quantified in values greater than 100 Gy (32,35-37,41) and in some studies reached values like 115 Gy (39) and 125 Gy (43). In the series of Sharma (39), BED >100 Gy was also associated with better OS (P=0.017). Comparing, instead, the different sites of metastasis by CRC, Ahmed *et al.* showed that liver metastases was more difficult to control than of lung (46) and together with Fode *et al.* (47,48) have documented that lung metastases could be controlled more easily than metastases in other sites.

Another crucial aspect in the management of metastatic CRC is represented by systemic therapy. Thibault *et al.* in 2014 reported the outcomes of a large lung SBRT programme for primary non-small cell lung cancer (NSCLC) and lung metastases. Among the 45 CRC metastases, a previous chemotherapy was associated to a better local control (49).

According to these data, a retrospective study included in our review and conducted by the Japanese Radiation Oncology Study Group (32) showed that chemotherapy administered after SBRT in adjuvant setting was a favorable prognostic factor for LC in patients with pulmonary oligometastases from CRC (HR =0.246, 95% CI: 0.097–0.625, P=0.003). Another study which investigated this factor was performed by Mazzola *et al.* (33). In this retrospective study, patients with lung oligometastases by CRC treated with SBRT, received previous chemotherapy (CT) alone or in combination with bevacizumab and the results were compared with those of a similar cohort of patients in whom bevacizumab was not previously administered. In the bevacizumab group, a higher rate of post-SBRT complete response was observed in case of oligopersistent versus oligorecurrent metastases (P=0.001). Also a Chinese experience (41), analyzing the prognostic factors derived by SBRT in patients with lung oligometastases or oligoprogression from CRC, demonstrated that targeted therapy before SBRT was a beneficial prognostic indicator for 6-month progression-free survival (PFS) (P=0.026).

Among the factors that can influence the outcome in this setting of patients, metastatic burden is included. The study published by Agolli and colleagues (39), in which a series of 44 oligometastatic CRC patients were treated with SBRT in all active lung metastases (69 lesions), reported that multiple metastases were significantly associated with worse PFS (P<0.04) and worse metastases free survival (MFS) (P<0.04). Also in the series of Kinj (31), patients with >2 lung metastases from CRC treated with SBRT have been proven to have a lower local control of disease (P<0.02). Moreover, in the series of 118 patients with inoperable lung colorectal oligometastases treated with SBRT analyzed by Sharma *et al.* (36), the presence of single metastasis was associated with a better OS (P=0.04).

While we have well established, albeit retrospective, evidence on SBRT in lung metastases from CRC, the treatment of lymph nodes from the same primary cancer is nowadays not clear and the literature is still poor. Node metastases, especially in the abdomen or pelvis are rarely considered amenable to surgery, so traditionally patients are directed to chemotherapy. By using SBRT, many patients can delay the demand to begin or change systemic therapy. In our review, two studies were identified (26,34), in which we observed a 3y-LC rate ranging from 65% to 75% and a 3y-OS rate ranging from 63% to 81%.

All patients well tolerated radiation therapy, confirming that SBRT can be considered an effective therapeutic chance with minimal adverse effect on life quality of patients.

With the limits of a review of retrospective studies, this work provides evidence on the efficacy and safety of SBRT as a local ablative therapeutic option in patients affected by oligometastatic CRC. We identified favorable prognostic factors including a BED (alfa/beta =10) >100 Gy, a low tumor size/volume and a low metastatic burden which results in a limited number of metastases.

Conclusions

In CRC patients with non-liver oligometastases, SBRT is effective and safe reaching high LC and survival, with few

severe side effects. Survival outcomes are similar to other LAT such as surgery, although randomized comparisons between techniques are lacking. Further studies are needed to validate the results, also investigating predictive/prognostic factors that can help tailor local treatment in CRC oligometastatic setting. This could allow the physician to choose which approach is most suitable for obtaining the best outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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