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TOPIC HIGHLIGHT

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Stereotactic body radiotherapy for oligo-recurrence within the nodal area from colorectal cancer

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Abstract

Recurrence of colorectal cancer (CRC) often presents as solitary metastases, oligometastases or oligo-recurrence. Surgical resection became the preferred treatment for patients with CRC lung and hepatic metastases. However, surgical treatment for oligo-recurrence within nodal area is not a widely accepted treatment due to due to their relative rarity and high postoperative morbidity. Stereotactic body radiotherapy (SBRT) is one of the emerging radiation treatment techniques in which a high radiation dose can be delivered to the tumor. High-dose SBRT can ablate the tumor with an efficacy similar to that achieved with surgery, especially for small tumors. However, there have been very few studies on SBRT for oligo-recurrence within nodal area, although several studies have evaluated the role of SBRT in the treatment of liver and lung metastases from CRC. This article reviews the current clinical status of and treatment methods for oligo-recurrence within nodal area from CRC, with particular emphasis on SBRT.

Key words: Colorectal cancer; Oligo-recurrence; Oligometastases; Stereotactic radiotherapy; Lymph node

Core tip: Surgical treatment for oligo-recurrence of colorectal cancer (CRC) within nodal area is not a widely accepted treatment due to due to their relative rarity and high postoperative morbidity. High-dose stereotactic body radiotherapy (SBRT) can ablate the tumor with an efficacy similar to that achieved with surgery, especially for small tumors. Recently, several investigators successfully treated oligo-recurrence of CRC within nodal area with SBRT. This article reviews the current clinical status of and treatment methods for oligo-recurrence within nodal area from CRC, with particular emphasis on SBRT.

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INTRODUCTION

Colorectal cancer (CRC) remains a major health problem worldwide and is the third most common cause of cancer-related death globally[1]. It is more common in developed than in developing countries. However, in Asia, the incidence of CRC is rising rapidly, and it is now the third most common malignant disease in both men and women[2-4]. Although surgery, chemotherapy, and radiotherapy (RT) for CRC have all developed rapidly in recent decades, approximately 20%-50% of CRC patients still

develop recurrence after definitive treatment[5-7]. This recurrence often presents as solitary metastases or oligometastases, and indeed a study by Tepper *et al*[6] found that approximately 70% of CRC recurrences were solitary.

The term oligometastases, introduced in 1995[8] and expanded upon more recently[9], describes an intermediate state of cancer spread between localized disease and widespread metastases. The implication of this intermediate state is that metastatic disease might be cured using metastasis-directed therapy. As a further conceptual refinement, Niibe *et al*[10] suggested the concept of oligo-recurrence as a disease stage in which there are a limited number of metastases and in which the primary tumor has been controlled. Patients with oligo-recurrence have an improved prognosis compared to those with limited metastasis but uncontrolled primary tumors.

Evidence from a number of clinical studies has suggested that surgical resection of lung and hepatic metastases from CRC prolongs survival[11-15]. As a result, surgical resection, became the preferred treatment for patients with CRC lung and hepatic metastases. However, surgical treatment for oligo-recurrence within the nodal area is not a widely accepted treatment, even when lesions are localized, due to their relative rarity, high postoperative morbidity, and unsatisfied surgical margin etc. If patients with oligo-recurrence do not receive treatment, their median survival is typically only 6-15 mo and the disease is frequently accompanied by refractory pain[16-19].

Stereotactic body radiotherapy (SBRT) is one of the emerging radiation treatment techniques in which a high radiation dose can be delivered to the tumor. It allows for high precision with tight planning margins and a sophisticated treatment plan allowing rapid dose fall-off away from the treatment area. Therefore, this technique provides higher tumor dose description with smaller irradiated volumes of normal tissue. And high-dose SBRT in a single or small number of fractions can ablate the tumor with an efficacy similar to that achieved with surgery, especially for small tumors[16,20-24]. However, SBRT can correspondingly cause more damage to normal tissue if it is included in the radiation field because repair mechanism is not expected in high ablative radiation dose. Therefore, it is important to select the optimal indication for SBRT, and one of these may be nodal metastases as they usually have clearly demarcated margins and allow very little movement. However, there have been very few studies on SBRT for oligo-recurrence within the nodal area, although several studies have evaluated the role of SBRT in the treatment of liver and lung metastases from CRC. This article reviews the current clinical status of and treatment methods for oligo-recurrence within the nodal area from CRC, with particular emphasis on SBRT.

SURGERY FOR OLIGO-RECURRENCE WITHIN THE NODAL AREA FROM CRC

Approximately 50% of local recurrences are restricted to the pelvis or associated with operable oligo-recurrence and are thus potentially amenable to curative re-operation[25-27]. Nevertheless, radical surgery is challenging, not commonly performed, and historically associated with high morbidity and mortality. The most important prognostic factor is whether R0 resection can be achieved. Previous studies have reported 5-year overall survival rate for R0 surgical resection ranging from 19% to 53%, whilst the rate is only between 0% and 32% when complete resection cannot be achieved[28-37]. However, in most cases, recurrence is detected as a fixed mass that invades the pelvic wall or sacrum. Pelvic sidewall recurrence in particular is associated with the worst prognosis and the least likelihood of achieving an R0 resection[38]. The disease often involves key structures such as the ureters, iliac vessels, the sciatic nerve, or the bony pelvis itself, and extensive involvement of the sidewall is a relative contraindication for the surgical treatment of recurrent rectal cancer.

Isolated paraaortic lymph node (PALN) recurrences are rarely encountered from CRC, and consequently its treatment is not well established. Recently, Min *et al*[39] categorized PALN recurrence as a retroperitoneal malignancy, which in turn is a type of locoregional recurrence. Furthermore, several studies[16,40,41] have investigated the therapeutic efficacies of surgery for retroperitoneal, intraabdominal, and PALN recurrences, and several reported outstanding survival rates, which appear to have resulted from the selection of patients with a resectable mass at time of recurrence. In these studies, the reported 5-year survival rates approached a maximum of 56% after complete resection, whereas they ranged from 0% to 7% after incomplete resection. Because radical surgery is rarely feasible for PALN recurrence, they have usually been treated using chemotherapy.

SBRT FOR OLIGO-RECURRENCE WITHIN THE NODAL AREA FROM CRC

Radiobiological aspects of SBRT

SBRT may differ biologically from conventional RT, which is administered in small doses of 1.8-2 Gy per fraction over 6-8 wk. In addition to the direct cell killing within the high-dose region, vascular and stromal effects also likely contribute to tumor control[42]. Experimental models have demonstrated the importance of sphingomyelinase-mediated endothelial apoptosis of tumor cells when high-dose RT is used[43,44]. Another host factor of potential importance after a high single dose (or a few doses) of RT is the activation of the innate and adaptive immune responses against the tumor[45-47]. Lee *et al*[47] reported that a single ablative dose of radiation (20 Gy) to the tumor dramatically increased T-cell priming in the draining lymphatic tissues. This CD8(+) T-cell response was essential for the antitumor effects of irradiation and resulted in a reduction in primary tumor size and an abscopal effect[48,49] on distant metastases. The clearance of

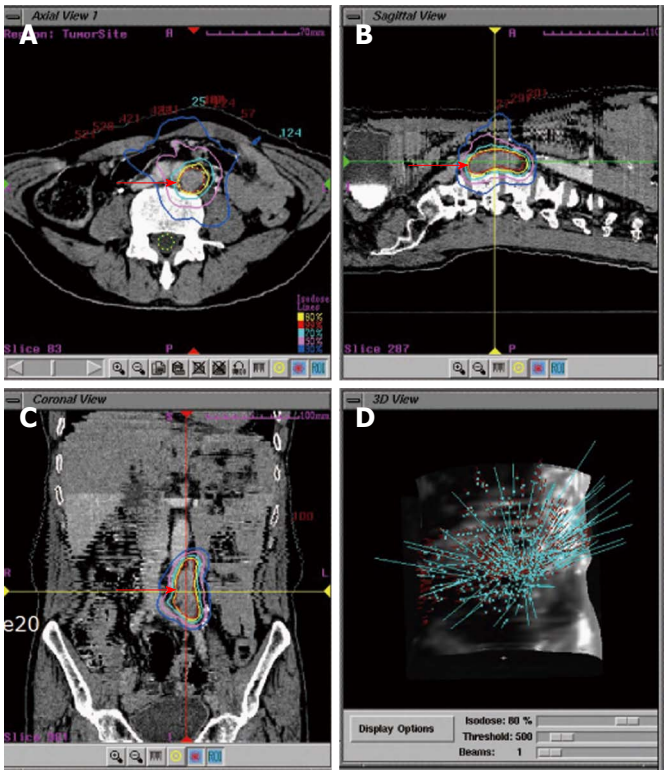

Figure 1 CyberKnife planning of stereotactic body radiotherapy for paraaortic lymph node metastases from colorectal cancer. A: Axial view 1; B: Sagittal view; C: Coronal view; D: 3D view. Gross tumor volume (red arrow) was defined as the visualized lymph node. The radiation dose, 48 Gy in 3 fractions, was prescribed to the 80% isodose line of the maximum dose in order to cover the planning target volume.

nonirradiated tumors after localized radiation therapy is known as the abscopal effect. Activation of an antitumor immune response has been proposed as a mechanism for the abscopal effect. The abscopal effect has been reported in several malignancies[50-52]. Stamell *et al*[52] reported a patient with metastatic melanoma who received palliative radiation to his primary tumor with subsequent clearance of all his nonirradiated in-transit metastases. Anti-MAGEA3 antibodies were found upon serological testing, demonstrating an association between the abscopal effect and a systemic antitumor immune response. While these antitumor effects hardly observed with conventional fractionated RT or with chemotherapy[53,54]. On the basis of these findings, the authors suggested that a new therapeutic strategy may be developed that combines RT with immunotherapy for oligometastasis.

Technical aspects of SBRT

Previously, the delivery of truly ablative doses of radiation has been limited by the risk to normal tissue, and the need for extended fractionation. However, SBRT utilizes stereotactic principles for dose localization and delivers multiple beams to well defined targets in a few fractions. As a result, this technique can deliver higher doses to tumors due to reduced mechanical error margins, and thus cause less normal tissue damage[55] (Figure 1). Regardless of the SBRT treatment delivery unit used, image-guided therapy enables verification of the location of the tumor or target volume before treatment delivery[56]. This image-guided therapy can be performed using three-dimensional volume imaging, using for example cone beam computed tomography (CT). If two-dimensional imaging is used, invasive fiduciary markers positioned in or close to the tumor are required. These image-guidance procedures substantially reduce treatment setup errors, using the tumor itself as a fiducial (frameless SBRT), and will in turn enable the planning target volume to be reduced.

Patient selection

The use of appropriate selection criteria for SBRT in the radical treatment of oligo-recurrence within nodal area remains crucial. In general, indications for SBRT are the same as those for metastasectomy, but without the limits imposed by the need for patients to be fit for surgery. In several reports, the eligibility criteria for SBRT for oligometastatic cancer were described as a limited number of metastases (between 1 and 5), a tumor diameter less than 4 cm, a locally controlled primary tumor, and no additional metastatic sites[57]. Other more specific and recently proposed criteria for the use of SBRT to treat patients with various oligometastatic tumors include a controlled primary tumor, a favorable histology, limited metastatic disease, a metachronous appearance of metastases, young age, and a good performance status[58-60].

As isolated or oligo-recurrence within nodal area is a very rare in CRC cases, clinical trials of SBRT for these recurrences are correspondingly also rare. Kim *et al*[55] published the results of a study in which SBRT was used to treat isolated PALN recurrence from CRC. The patients criteria for this study included a single conglomerate recurrent node or 2-3 recurrent nodes within 1 cm of each other; and excluded a tumor attached to the stomach or intestine (as determined by CT), or more than 3 separate affected LNs affected. This criteria is focusing to preserve normal tissue surrounding lymph node metastasis.

Table 1 Streotactic body radiotherapy for oligo-recurrence within nodal area in colorectal cancer

Ref.	Study year	No. of patients	Proportion of oligo-nodal metastases	SBRTdose (Gy)[1]; range (median)	Outcomes		
					LC	OS	Severe GI toxicity
Bae *et al*[69]	2012	41	44%	45-60 (48)	57% (5 yr)	38% (5 yr)	7%
Kang *et al*[68]	2010	59	53%	36-51 (42)	24% (5 yr)	29% (5 yr)	3%
Kim *et al*[55]	2009	7	100%	36-51 (48)	(-)	71% (3 yr)	14%
Kim *et al*[75]	2008	23	100%	30-51 (39)	74% (4 yr)	25% (4 yr)	4%
Hoyer *et al*[66]	2006	64	5%	45 (45)	63% (2 yr)	38% (2 yr)	5%

[1]Three fractions of streotactic body radiotherapy were used in all studies. LC: Local control; OS: Overall survival; GI: Gastrointestinal.

A further important consideration is the identification of patients with truly oligo-recurrence. Most published surgical oligo-recurrence series describe patients managed in an era before modern imaging techniques such as Positron emission tomography (PET)/computerized tomography (CT) became widely available. Thus, many patients were probably understaged, potentially leading to an underestimation of the effect of aggressive management on truly oligo-recurrence, since some of those patients treated aggressively would have had more extensive disease than was visible on CT or magnetic resonance imaging. Improved imaging will enable better selection of patients. Indeed, these advanced imaging methods (PET/CT scan) and molecular diagnostic techniques were used in some of the most recent studies[14] and are likely to have contributed to better patient selection and improved 5-year survival in this study compared with previous trials[15,61,62].

Clinical outcome

There is only a little published data on the treatment outcome of using SBRT for CRC oligo-recurrence within nodal area. An overview of published case series and phase 2 trials are presented in Table 1. However, several studies included cohorts that were too heterogeneous to evaluate the effect of SBRTs on these lesions. Greco *et al*[63] and Milano *et al*[64,65] studied heterogeneous in terms of the treated site or primary tumor histology. Hoyer *et al*[66] and Kim *et al*[55] studied including only a very small number of cases of nodal metastases although all enrolled patients had oligometastases from CRC.

In review of SBRT for oligometastases in all primary and all treated sites, Tree *et al*[67] indicated that generally around 20% of patients remain disease-free 2-4 years after treatment. Kang *et al*[68] reported the results of a study including 59 CRC patients with LN (31), lung (13), liver (10), and other (5) metastases, which were confined to 1 organ and treated by SBRT (median 42 Gy in 3 fractions). The 3-year overall survival, disease progression free survival, and local control rates were 49%, 25% and 66%, respectively, and the 5-year overall survival, disease progression free survival, and local control rates were to 29% and 19% and 24%, respectively. Focusing to the 31 patients with oligo-recurrence within nodal area, progression-free survival was 25% at 3 years and 19% at 5 years. In further study using high dose SBRT (median 48 Gy in 3 fractions) in same institute, Bae *et al*[69] reported better survival in the cohort of 41 CRC patients with LN (18), lung (12), and liver (11) metastases confined to a single organ. The 5-year overall survival, disease progression free survival, and local control rates were to 38%, 40% and 57%, respectively. The difference of outcomes between these studies may come from different dose of SBRT. These will be discussed further in the section of "SBRT dose".

Despite the heterogeneous nature of these studies with respect to the methods used to categorize oligometastatic disease from CRC, the findings indicate that a substantial proportion of patients, generally over 20%, remain disease-free 4-5 years after SBRT (Figure 2). These findings support the idea of an oligometastatic state in which aggressive local therapy could improve cause-specific survival.

SBRT dose

The efficacy of SBRT had primarily been investigated in the context of the treatment of early stage non-small cell lung cancer (NSCLC), in which disease a dose-control relationship has been established. Onishi *et al*[70] reported that the local control and survival rates for patients with stage I NSCLC were significantly better using a biologically effective dose larger than 100 Gy (α/β = 10 Gy). On the basis of this result, dose escalation was performed in a number of primary and metastatic cancer patients, and there were also efforts to escalate the SBRT dose to abdominal LN metastases from CRC. In the study conducted by Kim *et al*[55], the SBRT dose was escalated in a stepwise manner by 3 Gy from 36 Gy in 3 fractions. During escalation of dose, however, the 2 severe complication resulted in when 48 or 51 Gy was delivered in 3 fractions. They therefore did not escalate the radiation dose over 51 Gy during the treatment of paraaortic LN or pelvic LN. They also found that the radiation dose to tumor was a significant prognostic factor of overall survival. The median survival time was 32 and 72 mo with a SBRT dose of $\leqslant$ 42 Gy and > 42 Gy in 3 fractions, respectively. Bae *et al*[69] also found that SBRT dose was a significant prognostic factor for local control in multivariate analysis and that a dose of $\geqslant$ 48 Gy in 3 fractions resulted in a 5-year local control rate of 69%.

In several studies to evaluate SBRT result for oligometastases from heterogeneous primary cancers[71-75], all reports did not suggest that the SBRT dose was a prognostic factor of survival or local control. The SBRT

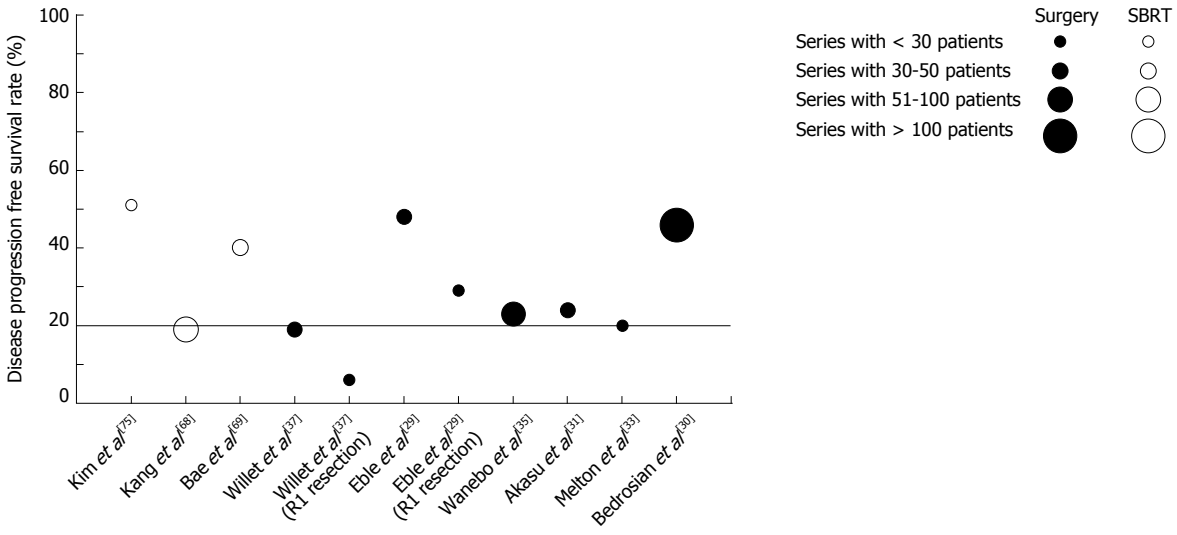

Figure 2 Disease progression free survival in patients with oligo-recurrence within nodal area from colorectal cancer treated with streotactic body radiotherapy or surgical resection. The cohort of Kang and Bae's studies are mostly composed of nodal metastases but additionally include lung and liver metastases. The cohort of surgical series include not only oligo-recurrence within nodal area but also central recurrence at anastomosis site. Dot size was weighted for number of patients in each cohort. SBRT: Streotactic body radiotherapy.

dose ranged from 30 to 51 Gy delivered in 3-6 fractions, and the highest dose was 51 Gy in 3 fractions[76]. Lower doses, such as those used successfully in the study by Bignardi *et al*[72], might be sufficient to eradicate viable tumor cells. Interestingly, Herfarth *et al*[77] performed a separate analysis of patients with metastatic disease and found that CRC metastasis had worse local control than metastases from other histological tumor types (45% *vs* 95%, respectively). In particular, in patients who had previously undergone systemic chemotherapy, tumors may have been radioresistant. Our data[55] support the radiocurative dose for metastases from CRC may be higher than those from other primary tumors as a result of induced cross-resistance from prolonged chemotherapy (discussed above)[77-79]. One hypothesis to explain these phenomenon may be Epidermal growth factor receptor (EGFR), which is reported to be overexpressed in approximately 70%-75% of CRCs[80]. A recent study using CRC-derived cell lines showed that cells with high constitutive EGFR-positive cells within a colorectal adenocarcinoma may have an intrinsic susceptibility to chemotherapy like oxaliplatin and 5-fluorouracil[81] as well as anti-EGFR agents. While, Khalifa *et al*[78] reported that recurrences following postoperative chemotherapy were approximately 5 times more likely to have lower levels of EGFR expression. In similar pattern, several studies have shown that an absence of EGFR expression is associated with radioresistance[82,83]. Furthermore, in a study of CRC treated with preoperative RT, Zlobec *et al*[79] reported that a complete pathological response was nearly 6 times more likely in EGFR-positive tumors than in EGFR-negative cases. In this point, the lower EGFR status of recurrent CRC after intensive chemotherapy may induce radio-resistance, requiring higher SBRT dose to achieve local control.

Results from a study of patients with oligo-recurrence within abdominopelvic nodal area suggested that a SBRT dose of more than 42 Gy in 3 fractions is a favorable prognostic factor for overall survival and local control, and dose escalation was recommended. However, there is as yet no consensus on the optimal dose and number of fractions, and further study with larger patient numbers is therefore required[55,69].

Toxicity

When oligo-recurrence within nodal area in the abdominopelvic area is treated with SBRT, the gastrointestinal tract is one of the most important dose-limiting organs. Since Timmerman *et al*[84] complied unvalidated normal tissue dose constraints for SBRT, most published studies have considered this recommendation or individual empiric data to be the permitted dose constraints for gastrointestinal toxicity. Surely, dosimetric parameters such as maximal point dose (D_{max}) and absolute volume of gastrointestine to receive some radiation dose, or fraction number affect complication. Unfortunately, because prospective study to control these variable factors were not available till now, there was no definite conclusion for gastrointestinal tolerance dose. Based on extensive experience to give SBRT to tumor located in abdominopelvic site, using 3 fraction, we suggested the dose constraint for gastroduodenum and intestine[85,86]. For severe gastroduodenal toxicity, D_{max} was found to be the best dosimetric predictor. A D_{max} of 35 Gy and 38 Gy were respectively associated with a 5% and 10% probability of the development of severe gastroduodenal toxicity. For intestinal toxicity, absolute volume to receive 20 Gy, 25 Gy, 30 Gy, or 35 Gy and D_{max} of the intestine were all the valuable predictor of severe toxicity. At D_{max} below 37 Gy, no severe intestinal toxicity was not detected. These tolerance dose are higher than expected for SBRT to some extent. Based on limited individualized clinical data, Kavanagh *et al*[87] and Rusthoven *et al*[88] suggested D_{max}

below 30 Gy in 3 fractions for stomach and intestine as the constraint. Timmerman *et al*[84] suggested D_{max} < 27 Gy in 3 fractions for the intestine and < 30 Gy for the colon, which based on the data of the biological effective dose using universal model, not validated by clinical data. One reason to cause discrepancy from these data based on dosimetric uncertainty. Intrafractional and interfractional gastrointestinal movement make it difficult to define accurate radiation dose of gastrointestine. In addition, as the volume of gastrointestine may vary according to the food consumed and respiration, the dose-volume histogram endpoint for pretreatment planning might not accurately reflect the actual dose distribution. In spite of these uncertainties, about D_{max} of 30 Gy in 3 fractions in gastroduodenum is supposed to be safe dose constraint

CONCLUSION

Oligo-recurrence within nodal area from CRC are rarely lethal in themselves. However, aggressive local treatment such as SBRT could prevent further extensive widespread metastatic disease. Several investigators have suggested that higher SBRT doses are associated with a better prognosis with respect to local control and survival. However, there is still no consensus on the optimal dose, number of fractions, or planning constraints. Given the radioresistant nature of CRC oligo-recurrence, increasing the SBRT dose may be a necessity, although because LNs are usually surrounded by radiosensitive normal tissue, the possibility of complications, especially gastrointestinal toxicity, should be carefully considered in treatment planning with SBRT for oligo-recurrence within nodal area in the abdominopelvic area. The constraints for the gastrointestinal tract and colon, a D_{max} of 30 Gy could prevent severe gastrointestinal toxicity during SBRT for tumors located in this area.

The outcomes of SBRT for oligo-recurrence within nodal area from CRC appear to be similar to those obtained after surgery despite the fact most studies have only included a small number of patients with a heterogeneous clinical profile. A substantial proportion of patients, generally over 20%, remain disease free 4-5 years after SBRT. This finding supports the idea of an oligo-recurrence state in which aggressive local therapy could improve the cure rate in appropriately selected patients. However, the general aim of oncological interventions for metastatic disease is not cure, but improvement in the quality of life and prolongation of overall survival. To this end, the use of SBRT, which is less invasive, better tolerated, and of a shorter duration than conventional radiation therapy, could have a number of advantages. These include the preservation of the quality of life through delaying further systemic treatment or preventing pain and prolonging survival through reducing subsequent metastatic spread to important organs.

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