Review and Uses of Stereotactic Body Radiation Therapy for Oligometastases

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Assess stereotactic body radiation therapy (SBRT) as an emerging modality in the treatment of oligometastatic patients.
2. Discuss data on safety and efficacy of SBRT in the oligometastatic setting.
3. Evaluate SBRT as a competitive option in patients with a low burden of disease in the metastatic setting.

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ABSTRACT

In patients with proven distant metastases from solid tumors, it has been a notion that the condition is incurable, warranting palliative care only. The term "oligometastases" was coined to refer to isolated sites of metastasis, whereby the entire burden of disease can be recognized as a finite number of discrete lesions that can be potentially cured with local therapies. Stereotactic body radiation therapy (SBRT) is a novel treatment modality in radiation oncology that delivers a very high dose of radiation to the tumor target with high precision using single or a small number of fractions. SBRT is the result of technological advances in patient and tumor immobilization, image guidance, and treatment planning and delivery. A number of studies, both retrospective and prospective, showed promising results in terms of local tumor control and, in a limited subset of patients, of survival. This article reviews the radiobiologic, technical, and clinical aspects of SBRT for various anatomical sites. *The Oncologist* 2012;17:1100–1107

INTRODUCTION

Improvements in the early detection of distant disease sites now frequently allow the diagnosis of single or limited organ metastases, defined as oligometastases [1]. In this setting, local treatments for oligometastases have been widely investigated and adopted for many cancers with the goal of improving dis-

ease control and survival outcomes. For several anatomical sites, surgical resection of metastases prolongs survival in selected patients [1, 2]. For example, surgical resection became the standard choice for patients with oligometastatic lung cancer, even though the benefits of resection and appropriate selection criteria in patients who develop metastases are poorly defined [1] and the ideal candidates for local therapy are difficult to select. It has been hypothesized that there may be a single target organ for metastases, and the rationale is that when primary cancer and regional nodes are controlled, the solitary or few metastases in that target metastatic organ can be cured [2].

In this scenario, radiotherapy could have a role in the local control of oligometastatic focal disease. Methods of morphological and functional imaging have improved enormously in the past decade and the oligometastatic situation occurs even more frequently during follow-up. As smaller foci of metastases are found, highly conformal radiation therapy, such as stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), may well prove to be less invasive and more effective than surgery because of a lower rate of morbidity, lower costs, and the potential for delivering ablative treatments on an outpatient basis. Radiotherapy is currently in the midst of new developments in technology. High-tech improvements are refining the "ballistic" approach in order to deliver higher radiation doses to target volumes while sparing surrounding normal tissues of critical structures (organs at risk) by means of: (a) intensity-modulated radiation therapy, including volumetric modulation arc therapy and similar rotational approaches; (b) robotic arm delivery of radiation therapy, such as the CyberKnife® Robotic Radiosurgery System (Accuray Inc., Sunnyvale, CA); and (c) high linear energy transfer ionizing radiation delivery as represented by protons and other hadrons [3, 4]. Emerging data show that SBRT in its various treatment modalities is a safe and efficient way to locally control multiple metastatic sites. Preclinical data, clinical experience, and challenges are reviewed here and discussed.

PATIENT SELECTION
Selection criteria for SBRT in treating oligometastatic cancer remain crucial. In general, indications for SBRT are the same as those for metastasectomy, but without the limits regarding feasibility in patients unfit for surgery. In several reports, the eligibility criteria for SBRT for oligometastatic cancer were defined as follows: a limited number of metastases (one to five), a limited tumor diameter (<4 cm), a locally controlled primary tumor, and no other metastatic sites [5]. Other more specific and recently proposed selection criteria to offer SBRT to patients with various oligometastatic tumors include: a controlled primary, favorable histology, limited metastatic disease, the metachronous appearance of metastases, young age, and a good performance status (PS) of the patient [2, 6, 7]. In clinical practice, patients eligible for SBRT are essentially those for whom surgery is not feasible because of their age or PS and because of previous treatment with multiple lines of

systemic therapy, when the toxicity of local treatments should be minimized.

TECHNICAL ASPECTS OF SBRT
Regardless of the treatment delivery unit used, one feature in common is the image-guided therapy capability that enables verification of the location of the tumor or target volume before treatment delivery. This image-guided therapy can be performed using three-dimensional volume imaging, for example, cone beam computed tomography (CT). If two-dimensional imaging is used, invasive fiduciary markers positioned in the tumor or in close proximity to the tumor are required. These image-guidance procedures substantially reduce treatment setup error, using the tumor itself as a fiducial (frameless SBRT), and will in turn enable the planning target volume to be reduced. Currently, several commercially available integrated treatment units that use cone beam CT are on the market [8–10]. None of these treatment delivery units is superior to the others, with each system clearly having its strengths and weaknesses. The training and experience of the SBRT team are much more important than the treatment delivery unit used.

RADIOBIOLOGY OF SBRT
Historically, normal tissue effects are more greatly impacted by fraction sizes than acute effects are, which is why 1.8- to 2.0-Gy fractionation is considered the standard for conventional radiotherapy, resulting in longer treatment times. In fact, small doses per fraction result in a tumoricidal effect by means of mitotic death of cancer cells, allowing recovery of late sublethal damage of normal tissues at the same time. SBRT may add a novel mechanism of radiation-induced damage: at higher doses per fraction, emerging data suggest that, in addition to direct cytotoxicity, a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill [11, 12]. Endothelial apoptosis results in microvascular disruption and death of the tissue supplied by that vasculature [11]. Thus, even if hypofractionated irradiation may heighten the risks of late toxicity from a radiobiologic point of view, SBRT techniques substantially counteract this concern, reducing the volume of normal tissue exposed to high doses as a result of their precision.

SBRT BY SITE
A MEDLINE search was conducted in combination with reference checking for articles on arguments published in indexed journals. Studies excluded by our analysis were: (a) series with small numbers (fewer than seven) of patients, (b) series with a heterogeneous population, and (c) series with a relatively short follow-up duration (<10 months).

Lung Oligometastases
Lung metastases probably represent the paradigm of the potential benefit achievable by SBRT, which is able to produce high rates of tumor control with very limited toxicity (Table 1). For isolated or a few lung metastases (fewer than three or fewer than five, according to different selection criteria), the local control probability at 1 year is in the range of 70%–100%. In

Table 1. Outcomes of stereotactic body radiation therapy for lung metastases from selected trials

Study	*n* of patients	Median dose/*n* of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Onimaru et al. [5]	45	48 Gy/8; 60 Gy/8	18 (2–44)	3-yr, 69.6% for 48 Gy, 100% for 60 Gy	2-yr, 47.1%	Grade 5, 1 (2.2%)
Wulf et al. [32]	27	30 Gy/3; 36 Gy/3	13–17	2-yr, 71%	1-yr, 48%	Grade 3, 1 (3.7%)
					2-yr, 21%	Grade 5, 1 (3.7%)
Yoon et al. [71]	53	30 Gy/3; 40 Gy/4; 48 Gy/4	14 (4–56)	70% for 30 Gy, 77% for 40 Gy, 100% for 48 Gy	1-yr, 89%; 2-yr, 51%	Grade ≥2, 0%
Okunieff et al. [18]	50	50 Gy/10; 48 Gy/6; 57 Gy/3	18.7 (3.7–60.9)	3-yr, 91%	2-yr, 50%	Grade 2, 6.1%
						Grade 3, 2%
Norihisa et al. [6]	34	48 Gy/4; 60 Gy/5	27 (10–80)	2-yr, 90%	2-yr, 84%	Grade 2, 4 (12%)
						Grade 3, 1 (3%)
Brown et al. [72]	35	5 Gy/1 to 60 Gy/4	18 (2–41)	Crude, 77%	2-yr, 72.5%	Grade 3–4, 1 (2.8%)
Rusthoven et al. [14]	38	60 Gy/3	15.4 (6–48)	2-yr, 96%	2-yr, 39%	No grade 4
						Grade 3, 3 (8%)
Ricardi et al. [17]	61	45 Gy/3; 26 Gy/1	20.4 (3–77)	2-yr, 89%	2-yr, 66.5	Grade 3, 1 (1.6%)

most series, the prescribed biologically effective doses are >100 Gy, with several fractionation schedules and different delivery techniques. In most of the studies, SBRT treatment was delivered in a few fractions (3–10), with a limited number of reports employing one single fraction. It is difficult to properly evaluate survival estimates and the real impact on patients' clinical outcomes using SBRT for lung metastases because there is an absence of randomized trials and because most of the phase I–II studies included patients with widely variable clinical characteristics. In a recent review by Siva et al. [13], the 2-year weighted overall survival (OS) rate estimate from the largest studies was 54.5%, ranging from higher rates in selected series such as the study by Norihisa et al. [6], which reported an OS rate at 2 years of 84%, to lower rates, such as the 39% reported from a multi-institutional trial conducted by Rusthoven et al. [14] in a population of nonsurgical unselected patients. In that study, 39.5% of patients presented with two metastases, 28.9% had received more than one previous line of chemotherapy, the median tumor volume was 4.2 cc, and roughly 30% of tumors had a volume >10 cc). Median survival times were not always reported, and ranged from 11.3 months in the pioneering experience of the Swedish group [15, 16] to 42.8 months in a cohort of 61 highly selected patients, the majority of whom were affected by a single metastasis from a primary lung tumor [17]. In most trials, the number of synchronous lung metastases was one to two or one to three, with some experience in patients with one to five lesions [18]. The predominant clinical presentation was a single lung metastasis.

The available data suggest that the best results can probably be achieved in patients with a generally favorable presentation in terms of tumor volume, no or a few previous chemotherapy cycles, and the absence of extrathoracic metastatic disease. Moreover, in some studies, a relatively high percentage of patients received chemotherapy or other local treatments after SBRT, resulting in better disease control after systemic progression. In this setting, SBRT could play a major role in delaying progression, and the progression-free survival (PFS) interval appears to be a crucial endpoint in this patient population for future larger studies. Following early experience, it is natural to compare results using SBRT with results using surgical metastasectomy. Data from the International Registry of Lung Metastases [19] show OS rates of 70% at 2 years and 36% at 5 years in patients affected with a single metastasis. It is difficult to compare OS data using SBRT with data from historical surgical series for several reasons, with the main reason being the different clinical characteristics of the patients (most patients referred for SBRT are judged to be inoperable because of medical comorbidities that are able to significantly affect their OS outcome).

With regard to toxicity, the rates of acute toxicity with SBRT appear to be comparable with or even lower than those with any other alternative therapy. In a systematic review by Siva et al. [13], toxicity rates were very low. There was a 2.6% rate of grade ≥3 toxicity in a single fraction–radiosurgery series and a 4% rate of grade ≥3 toxicity in a hypofractionated radiotherapy series. The lack of grade 1–2 toxicity scores is likely a reflection of the retrospective nature of the majority of reports and incomplete toxicity recording. Generally higher rates of toxicity are reported when treating centrally located lesions (one death secondary to esophageal necrosis in a centrally located tumor). Late toxicity is difficult to evaluate because of the lack of published data. The lung is the major organ at risk, and radiation-induced lung injury (radiation pneumonitis and radiation fibrosis) represents a well-known radiological finding after SBRT, without an exact correlation with clinical or functional respiratory parameters. Currently, although there is still insufficient evidence to confirm the optimal tumor selection parameters, fractionation schedules, and radiation therapy techniques, in patients affected by a single or a few lung metastases (five or fewer), the high local control rates and potential survival benefits without significant side effects justify the use of SBRT as an alternative to surgery.

Table 2. Summary of recent prospective trials with stereotactic body radiation therapy for liver metastases

Study	n of patients	Median dose/n of fractions	Median follow-up, mos	Local control rate	Overall survival	Toxicity
Herfarth et al. [37, 38]	33	14–26 Gy/1, prescribed to 80%	18	Crude, 78%; 6-mo, 75%; 12-mo, 71%; 18-mo, 67%	1-yr, 72%	Radiation-induced liver disease: 0%
Hoyer et al. [39]	44	45 Gy/3, prescribed to 95%	4.3 yrs	86%	24-mo, 38%	–
Kavanagh et al. [40]	36	60 Gy/3	19	18-mo, 93%	–	–
Lee et al. [42]	70	27.7–60.0 Gy/6, prescribed to isodose line covering PTV (median, 41.4 Gy)	10.8 for 68 assessable patients	1-yr, 71%	18-mo, 47%	Late grade 4 and 5 toxic effects, 2.9% and 1.5%, respectively
Méndez Romero et al. [43]	14	37.5 Gy/3, prescribed to 65%	12.9	Crude, 94%; 1-yr, 100%; 2-yr, 86%	1-yr, 85%; 2-yr, 62%	Grade ≥4 toxic effects, 0%
Rusthoven et al. [44]	47	12–20 Gy/3, prescribed to isodose line covering PTV	16	1-yr, 95%; 2-yr, 92%	2-yr, 30%	Grade 4 toxic effects, 0%
Goodman et al. [45]	26	18–30 Gy/1, prescribed to 80%	17.3	1-yr, 61.8%; 2-yr, 49.4%	1-yr, 61.8%; 2-yr, 49.4%	Late grade 2 gastrointestinal toxic effects, 2 of 26 patients
Rule et al. [46]	27	30–60 Gy/5	20	2-yr, 56%, 89%, and 100% for the 30-Gy, 50-Gy, and 60-Gy cohorts, respectively	–	Grade ≥3 toxic effects, 0%

Abbreviation: PTV, planning target volume.

Among minimal ablation techniques, radiofrequency ablation (RFA) is the most frequently used method. In a prospective multicenter trial [20], RFA yielded a local control rate of 88% (in both the primary and metastatic lesions) and promising results in terms of OS and cancer-specific survival outcomes, even though the patient cohort was heterogeneous, making direct comparison of survival outcomes difficult. Peripheral and small-sized tumors (3–3.5 cm) are ideal for RFA treatment, and the most common complication is pneumothorax, with a reported incidence of 28%. Other toxicities include pleural effusion (14%) and pain (14%). Globally, RFA is a promising option in selected patients, but trials are needed in order to compare it with other alternative local ablative therapeutic modalities.

Liver Oligometastases

Much clinical experience has accumulated over the past 10–15 years reporting the efficacy and safety of SBRT in various patient populations with metastases localized to sites other than the lung [7, 13, 21–26]. The liver is one of the most common sites of metastatic spread from colorectal cancer (CRC). The data show that surgical resection of limited liver metastases can result in long-term survival in selected patients [27]. Surgery, however, is technically difficult, and only 10%–20% of metastatic CRC patients are candidates for surgical resection. In selected patients with a limited number of hepatic metastases who are not surgical candidates, a variety of ablative techniques have been developed. The most prominent in use are RFA, transarterial chemoembolization, and percutaneous ethanol injection. Although much less invasive than surgery, all

have a certain grade of invasiveness and serious limitations. Retrospective analyses of RFA for liver metastases from CRC have shown broad variability in the 5-year survival rate in the range of 14%–55% [28]. Historically, the liver was thought to be a relatively radiosensitive organ, and it was difficult to achieve the radiation doses necessary to eradicate gross tumors without causing radiation-induced liver disease, which occurs ~4–8 weeks following radiation therapy [29]. SBRT provides a noninvasive means of delivering a local ablative therapy for limited liver metastases, thereby providing optimal local tumor control as well as a limited dose to surrounding healthy tissue, and potentially lower complication rates. The local control rate achievable with SBRT varies in the range of 57%–100% according to several retrospective trials [30–35]. However, the follow-up times of most studies were relatively short, typically <18 months. A number of prospective studies on the use of SBRT for the treatment of liver metastases have been published (Table 2).

Notwithstanding the relatively short follow-up period, ≤18 months in the most series, data from published trials are promising and confirm that a small but significant fraction of oligometastatic patients may benefit from intensification of local therapy with higher radiation doses using SBRT [36–46].

Isolated Metastatic Lymph Nodes

Few published data exist on the local control rate using conventional radiotherapy in the context of isolated or limited lymph node metastases. SBRT does not replace chemotherapy but rather can augment its effects on focal areas of gross disease as well as metastatic lymph nodes. Although the dose and fractionation

Table 3. Summary of published trials of stereotactic body radiation therapy for lymph node metastases

Study	Primary	*n* of patients	Median dose/ *n* fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Choy et al. [47]	Cervix	30	33–45 Gy/3 (*n* = 24); 4 patients also received 27–45 Gy external beam radiotherapy	15 (2–65)	4-yr, 67.4%	4-yr, 50.1 mos	Late grade 3 or 4 toxicity, 3%
Jereczek-Fossa et al. [48]	Prostate	34	30 Gy/4.5	16.9	17-mo, 91%	–	Late genitourinary grade 3, 5%
Kim et al. [49]	Stomach	7	45–51 Gy (median, 48 Gy)/3	26 (19–33)	–	3-yr, 43%	Late grade 3 or 4 toxicity, 0%
Kim et al. [50]	Colorectum	7	36–51 Gy/3	26 (15–70)	86 %	3-yr, 71.4%	Late grade 4 toxicity, 14%
Bignardi et al. [51]	Miscellaneous	19	45 Gy/6	12	12-mo, 77.8%	–	Late grade 3 or 4 toxicity, 0%

Table 4. Summary of published trials of stereotactic body radiation therapy for adrenal metastases

Study	*n* of patients	Median dose/*n* of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Casamassima et al. [26]	48	36 Gy/3	16.2 (3–63)	1–2 yrs, 90%	1-yr, 39.7%; 2-yr, 14.5%	1 case of grade II adrenal insufficiency
Chawla et al. [24]	30	40 Gy/10	9.8 (3.2–28.3)	1-yr, 55%	1-yr, 44%; 2-yr, 25%	Mild grade 1 fatigue and nausea, "common"
Oshiro et al. [25]	19	45 Gy/10	11.5 (5.4–87.8)	Objective response rate, 68%	1-yr, 56%; 2-yr, 33%; 3-yr, 22%	1 grade 2 duodenal ulcer
Holy et al. [54]	18	20 Gy/5 or 40 Gy/8	21	Objective response rate, 77%	Median, 23 mos	–
Torok et al. [55]	7	16 Gy/1 or 27/3	14 (1–60)	1-yr, 63%	Median, 8 mos	–

schedules have been extremely heterogeneous, early data from some recent series (Table 3) seem to be promising in terms of the local control rate [47–51]. Because small volumes are irradiated for metastatic lymph nodes, dose escalation might result in better efficacy without prohibitive toxicity.

The poorer disease-free survival rates observed in several series may be explained by the substantial differences in the patient populations in several aspects, mainly concerning the primary tumor behavior and the burden of microscopic systemic disease outside the irradiated target [22, 51].

In summary, even though most patients treated locally using SBRT for lymph nodes metastases eventually fail at other sites, the local control provided by this initial experience may be potentially significant for preserving quality of life and delaying further systemic treatments [47–50]. Evaluation of tolerance doses to the vascular wall close to the lymph node target, especially with ablative doses, remains an interesting issue and will certainly involve long-term surviving patients.

Metastases in Adrenal Glands

Adrenal gland metastases can occur as a result of various types of extra-adrenal primary cancers, although the most frequent primary tumor is non-small cell lung cancer (NSCLC) [52]. In general, longer median survival and OS times have been

demonstrated with resection of clinically isolated adrenal metastases when compared with nonsurgical therapy, including RFA, external beam radiotherapy, arterial embolization, radioembolization, blend embolization, chemical ablation, and cryoablation [53]. Table 4 depicts and compares the characteristics of the published studies on SBRT for adrenal metastases.

In summary, as of now, few studies have been published regarding the role of SBRT in treating patients with adrenal glands metastases, and several criticisms could arise regarding the lack of clear data on local control and on dose fractionation [24–26, 52–55]. Nevertheless, the good tolerability and the promising clinical results should stimulate the scientific community to further design clinical studies with the aim of optimizing local control and evaluating a potential PFS benefit.

Spinal Metastases

Spinal radiosurgery has been proven to be an option in the treatment of spinal metastases in properly selected patients, even though only retrospective and phase I–II studies are available. Local control based on imaging and/or pain control is achieved in ~80% of presentations (given the follow-up of each study). As noted by Sahgal et al. [56] in a recent review,

Table 5. Summary of published trials of stereotactic body radiation therapy for spinal metastases

Study	n of patients	Median dose/ n of fractions	Median follow-up, mos	Local control rate	Pain response
Yamada et al. [73]	93	24 Gy/1	15	15-mo, 90% (imaging)	NS
Ryu et al. [74]	49	10–16 Gy/1	6.4	93% (imaging and pain)	85%
Sahgal et al. [56]	14	24 Gy/3	9	78% (imaging and/or pain)	NS
	25	24 Gy/3	7	92% (imaging and/or pain)	NS
Nguyen et al. [75]	48	30 Gy/5	13.1	78% (imaging)	52%
		24 Gy/3			
Tsai et al. [76]	69	15.5 Gy/2	10	10-mo, 96.8% (imaging)	Improved pain control, 88%
Chang et al. [58]	63	30 Gy/5	21.3	77% (imaging)	Narcotic use declined 60% to 36%
		27 Gy/3			
Gibbs et al. [77]	74	14–25 Gy/1–5	9	NS	Clinical benefit, 84%
Gerstzen et al. [78]	393	20 Gy/1	21	88% (imaging)	Clinical benefit, 86%

Abbreviation: NS, not significant.

the lack of actuarial data overall makes it difficult to come to any firm conclusions other than that the rates of control are promising. There are no randomized trials comparing stereotactic radiotherapy with conventional radiotherapy with regard to pain control (another issue is that, for conventional treatments, local control is not typically assessed using imaging but based on clinical benefit). Stereotactic radiotherapy is also an option as retreatment for previously irradiated sites, with results on pain control that are comparable with those obtained in patients not previously treated [57]. Table 5 summarizes the results of several studies including stereotactic radiotherapy for spinal tumors. There are several dose prescription schedules and total doses or doses per fraction, making direct comparison difficult, with a follow-up time globally of a few months. The predominant pattern of failure after SBRT for spinal metastases is characteristic of the procedure because the principle of SBRT is to treat only the target region, and areas close to the spinal cord are frequently underdosed. Failure at the epidural space is commonly reported. Chang et al. [58] reported eight of 17 failures in this area occurring in 74 tumors. The posterior part of the vertebral body is at higher risk for recurrence. In some series, the whole vertebral body is contoured; in others, only the tumor is contoured using magnetic resonance imaging (the optimal target contouring is still debated). SBRT can also be safely applied in the postoperative setting, as reported by Sahgal et al. [56], with the intent of reducing the extent of surgery (which can be limited to epidural decompression and fixation). The available data suggest that SBRT is a promising technique for spinal metastases, but its application is still experimental and requires prospective controlled studies.

Several other new effective ablation treatment strategies have recently been reported for the treatment of metastatic disease involving bone. These include the use of RFA, cryoablation, laser ablation, and microwave ablation. As shown in a recent review by Rosenthal and Callstrom [59], of these minimally invasive methods, RFA and cryoablation have been the most studied. The patient selection criteria are similar to those using SBRT. RFA is effective in reducing pain resulting from skeletal metastatic disease, as demonstrated in two multicentric trials [60, 61], even though the results of the two studies are different because of factors that include patient selection, the level of anesthesia, and the degree of tumor destruction. At the 3-month time point, there was a reduction in pain of 14 points in the American College of Radiology Imaging Network study and of 28 points in the Goetz et al. [60] study, wherein up to 95% of patients experienced pain relief. Toxicity included neuropathic pain, pain exacerbation, and bone fracture. Globally, grade 3 toxicity was reported in 5% of cases. These results need further evaluation, but in selected cases RFA could be comparable with SBRT. Cryoablation could be an alternative to RFA, but the currently available clinical data are very limited.

COST-EFFECTIVENESS

Because SBRT is becoming used in more clinical situations, it is imperative to assess its cost-effectiveness as well as its efficacy. SBRT employing image guidance, high-precision dose delivery, more accurate target definition with better anatomical and biological imaging, and the possibility of dose verification during treatment via dose-adaptive radiation therapy permits a higher probability of tumor control. Such major technological progress certainly comes at a higher cost, and there are many concerns regarding the value of that progress. On the other hand, the higher equipment and resource costs associated with cutting-edge radiation oncology technologies can be partly mitigated by shorter treatment courses.

Additionally, better tumor control, less toxicity, and fewer treatment courses decrease the indirect costs of cancer care, including lost time and economic productivity secondary to treatment-related and cancer-related illness and death [62]. The U.S. National Institutes of Health estimate that 53% of the total costs of cancer care in 2010 was attributable to indirect mortality costs, and 8% was attributable to indirect morbidity costs [63]. Therefore, advances in radiation therapy can poten-

tially result in substantial direct and indirect cost savings [64]. Beyond the given assumption that SBRT would be less expensive in most health systems than alternative options requiring anesthesia and/or hospitalization, few data in the literature explicitly address this issue. One of the most interesting studies was recently published by Sher et al. [65], who performed a cost-effectiveness analysis of SBRT versus RFA for patients with medically inoperable, early-stage NSCLC. Those authors concluded that, based on the currently available data, SBRT is the most cost-effective nonsurgical treatment for peripheral, early-stage lung cancers, rendering an incremental cost-effectiveness ratio for SBRT over RFA of $14,100/quality-adjusted life-year.

CONCLUSIONS

From preliminary published results, thanks to the more extensive prescription of SBRT and SABR, the role of radiation therapy for metastatic disease has evolved from palliating symptoms to a potentially curative purpose, as shown in specific patient settings, including promising data from oligometastases [66, 67].

A crucial criticism in oligometastatic patients remains the appropriateness of aggressive treatment, such as metastasectomy or SBRT, when the real survival advantages are not yet established. Excluding selected cases, usually weak or no evidence of longer survival times was shown when aggressive local treatments were used. An artifact of patient selection has also been denounced in several surgical series: clinicians rely on presumed benefit based on comparisons with poorly characterized survival estimates from other patients with advanced disease [68, 69].

In the subgroup of patients with a solitary metastasis, investigating SBRT dose escalation in order to optimize local control may be worthwhile. For cases with more than one metastasis, especially if more than one organ is involved, the selection criteria for SBRT should be evaluated with extreme attention to life expectancy and toxicity.

Crucial open issues are: (a) what is the real cutoff between pure palliative and hypothetical curative intent therapy in oligometastatic patients, (b) what is the correct timing with chemotherapy, and (c) what is the optimal target and how can the radiation oncologist define it as best as possible considering the risk for other potential microscopic foci of disease?

Considering the high propensity for distant progression in these patients, the combination of novel drugs and SBRT needs to be deeply explored. With this background and rationale, prospective trials of high-dose SBRT should be proposed to definitively assess its role in selected oligometastatic cancer patients. An international randomized phase II controlled trial called Comprehensive Treatment of Oligometastatic Tumors (ClinicalTrials.gov identifier, NCT01446744) is currently accruing patients. The intent of the investigation is to compare SBRT at ablative doses with the current approaches of chemotherapy and conventional radiotherapy. Clinicians are looking forward to finding out, from the results of this and other prospective randomized trials, the real impact of SBRT on OS and quality of life outcomes of oligometastatic patients [70].

AUTHOR CONTRIBUTIONS

Conception/Design: Filippo Alongi, Stefano Arcangeli, Andrea Riccardo Filippi, Umberto Ricardi, Marta Scorsetti
Provision of study material or patients: Filippo Alongi, Stefano Arcangeli, Andrea Riccardo Filippi, Umberto Ricardi, Marta Scorsetti
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