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ORIGINAL ARTICLE

A multi-national report on stereotactic body radiotherapy for oligometastases: Patient selection and follow-up*

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ABSTRACT

Aims Stereotactic body radiotherapy (SBRT) for oligometastases is increasingly used with few evidenced-based guidelines. We conducted a survey to determine patient selection and follow-up practice patterns.

Materials and methods Seven institutions from US, Canada, Europe, and Australia that recommend SBRT for oligometastases participated in a 72-item survey. Levels of agreement were categorized as strong (6–7 common responses), moderate (4–5), low (2–3), or no agreement.

Results There was strong agreement for recommending SBRT for eradication of all detectable oligometastases with most members limiting the number of metastases to five (range 2–5) and three within a single organ (range 2–5). There was moderate agreement for recommending SBRT as consolidative therapy after systemic therapy. There was strong agreement for requiring adequate performance status and no concurrent chemotherapy. Additional areas of strong agreement included staging evaluations, primary diagnosis, target sites, and follow-up recommendations. Several differences emerged, including the use of SBRT for sarcoma oligometastases, treatment response evaluation, and which imaging should be performed during follow-up.

Conclusion Significant commonalities and variations exist for patient selection and follow-up recommendations for SBRT for oligometastases. Information from this survey may serve to help clarify the current landscape.

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Oligometastases is a term used to define a state of limited metastatic disease in which, it is theorized, a cancer has not reached the capacity for widespread dissemination [1]. During the oligometastases phase it is theorized that ablation of metastatic deposits can render a patient cured or in a durable state of remission [2,3]. Stereotactic body radiotherapy (SBRT) is an advanced radiotherapy technique that is used to target relatively small deposits of solid tumors with highly conformal doses of radiation using high-precision image-guided therapy, thereby limiting the dose to surrounding normal tissues [4–7]. This technique evolved from stereotactic radiosurgery for targets in the brain and, while its efficacy is best documented in the treatment of early-stage non-small cell lung cancer, it is now used in the treatment of tumor sites throughout the body. During the past decade, there has been an upsurge in the use of SBRT for oligometastases with a relative lack of clinical evidence documenting efficacy, appropriate indications, and clinical guidelines for best practices [8–11]. We conducted a survey and analysis of academic medical centers that treat oligometastases with SBRT with the goal of identifying commonalities and controversies regarding the appropriate indications for patient selection for oligometastases and recommendations for follow-up and response assessment.

Methods

Investigators from seven cancer centers in the US ($n = 3$), Europe ($n = 2$), Canada ($n = 1$), and Australia ($n = 1$) constituting the Elekta International Oligometastasis Consortium participated in a comprehensive survey. The participating centers were chosen by lead investigators at Sunnybrook Health Sciences Center (Toronto, ON, Canada). The industry sponsor had no role in selecting the centers, or in the design or conduct of the survey, analysis of the data, or preparation of the manuscript. The centers were chosen because of their extensive experience in treating patients with SBRT for oligometastases and their willingness to collaborate in research focused on SBRT for oligometastases. Each center treats approximately 50–100 patients with SBRT for oligometastases annually. The survey consisted of 72 questions covering the

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major aspects of patient selection, tumor/treatment characteristics, indications for therapy, technical aspects of treatment planning and delivery, response evaluation, and follow-up. The technical aspects will be addressed in a separate report. The following analysis is limited to the 30 survey questions focusing on patient characteristics and pretreatment evaluations, indications for SBRT, tumor/disease characteristics, and recommendations for response evaluation and follow-up.

Participants were blinded to each other's responses when completing the survey, but the results were shared among all participants once the surveys were completed. The degree of agreement for each survey item was categorized as follows based on the number of responses with the same answers: strong agreement (6–7), moderate agreement (4–5), low agreement (2–3), or no agreement.

Results

All participants completed all survey items. Considerable variation was noted regarding the patient selection criteria for SBRT for oligometastases; however, there were also considerable commonalities. Tables I–IV summarize the results of the survey.

Patient characteristics and pretreatment evaluations used to determine selection for SBRT are shown in Table I. At the time of administering the survey, no center surveyed restricted a patient's access to SBRT based on age. A minimum performance status was used for patient selection at all centers, although there was variability regarding the minimum performance status: four centers required a minimum Karnofsky Performance Status (KPS) of 70; two centers required a minimum KPS of 50; and one center required a minimum KPS of 80. Although the level of agreement was categorized as moderate, most centers only considered patients for SBRT if they were free from serious comorbidities and not undergoing treatment with concurrent cytotoxic systemic therapy unless enrolled on a clinical trial. Nevertheless, there was no consensus regarding the appropriate interval from the last dose of chemotherapy to SBRT or how long chemotherapy should be withheld after SBRT. Responses ranged from a minimum of 3–5 days to a maximum of four weeks. All centers employed cross-sectional imaging of the chest, abdomen, and pelvis to adequately stage patients and evaluate the number of metastatic foci for consideration of SBRT. Imaging technologies used typically included computed tomography (CT), positron emission tomography (PET)-CT, and magnetic resonance imaging (MRI) of the spine in patients with spine metastases. Significantly elevated tumor markers, when available, were considered a contraindication for SBRT at only two centers.

There were significant commonalities regarding which indications were appropriate and inappropriate (Table II). All participants agreed that complete eradication of all detectable oligometastases was an appropriate indication for SBRT. Most centers used SBRT for consolidation after a favorable partial response to systemic therapy (moderate agreement). However, most centers did not consider cytoreduction or abscopal radiotherapy effects as an important indication of SBRT for oligometastases (moderate agreement).

The majority of the survey questions regarded tumor/disease characteristics (Table III). All participants agreed that patients with oligometastastic colorectal cancer, non-small cell lung cancer, and melanoma should be considered for SBRT, and there was moderate agreement for consideration of SBRT for oligometastastic breast and renal cell carcinoma. Only the centers treat patients with oligometastastic sarcoma with SBRT. All centers did not exclude patients with brain metastases who could be managed surgically or with SRS provided the total number of metastases, including brain metastases, met their definition for oligometastases. There was strong agreement for the use of SBRT for oligometastases involving the lung and spine, while most centers treated liver metastases and non-spine bone metastases, followed by adrenal and lymph nodes metastases. Control of the primary site was required at most centers. There was considerable variation regarding a threshold number and volume of metastases for selection for SBRT. Most survey participants only recommend SBRT for patients with five or fewer metastases, and three or fewer metastases within a single organ, while cumulative tumor volume was not considered a selection criterion at most centers. The maximum size of each individual metastasis was considered a contraindication for SBRT at all centers, although there was significant disagreement regarding a threshold. The most common response was 5 cm ($n = 3$), followed by 6–7 cm ($n = 2$), and two centers responded that the threshold varied depending on the treating physician.

Table IV summarizes the survey results for questions regarding recommendations for follow-up and disease response evaluations. All centers recommended follow-up by the treating radiation oncologist for disease response, adverse effects, and evaluation for systemic progression. The frequency of follow-up decreased as the time duration since treatment increased. Most centers either used Response Evaluation Criteria in Solid Tumors (RECIST) ($n = 5$, moderate agreement) or any documented increase in size on cross-sectional imaging ($n = 2$, low agreement) to determine local control and disease progression of treated metastases. Imaging recommendations varied depending on the treatment site, but nearly all centers recommended CT with additional studies, such as MRI for liver, spine, and non-spine bone metastases. Routine use of PET-CT for follow-up was not recommended by most centers regardless of the target site.

Discussion

As the term oligometastases was first proposed in 1996 by Hellman and Weichselbaum, there has been a significant shift in how local therapies are used to address metastatic disease. Whereas such treatments were once reserved for palliation, today surgery, SBRT, and interventional radiological procedures are applied with rapidly increasing frequency with the hopes that they will improve patient outcomes [12–14]. SBRT is an attractive option because it can be used on a wide variety of targets, it is typically a non-invasive, convenient outpatient procedure, and advanced radiation technology and expertise are now readily available throughout most modern health systems. The treatment is perceived to be relatively non-toxic when applied judiciously, and it is highly effective at

Table I. Patient factors and pretreatment evaluations.

Question	Responses(# of common responses)	Level of agreement
Are there age limitations on patient selection for SBRT?	No (7)	Strong
Is a minimum Karnofsky Performance Status required?	Yes (7)	Strong
Are serious comorbidities considered in patient selection?	Yes (4)	Moderate
Is a treatment break off of systemic therapy required?	Yes (6)	Strong
What staging evaluations are performed for patient selection		
CT with contrast	Yes (7)	Strong
PET-CT	Yes (6)	Strong
MRI (spine metatastases)	Yes (6)	Strong
Are tumor markers considered in patient selection?	No (5)	Moderate

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

Table II. Indications for SBRT.

Question	Responses(# of common responses)	Level of agreement
What indications are considered for SBRT?		
Complete eradication of oligometastases	Yes (7)	Strong
Cytoreduction	No (4)	Moderate
Consolidation after systemic therapy	Yes (4)	Moderate
Abscopal effect	No (5)	Moderate
What are the indication for SBRT in lieu if metastatectomy or other local ablative therapies?		
Medically inoperable	Yes (7)	Strong
Patient preference	Yes (5)	Moderate
Physician preference based on safety	Yes (5)	Moderate
Physician preference based on efficacy	No (4)	Moderate
Abscopal effect	No (4)	Moderate

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

eradicating small deposits of cancers of diverse histologies. Treatment of metastatic disease with SBRT has become more frequent despite a relative lack of evidence, and the indications/contraindications, criteria for patient selection, goals of therapy, and guidelines for follow-up and response evaluation are ill-defined. We conducted a survey of seven academic centers that treat a substantial volume of metastatic patients with SBRT to identify commonalities and discrepancies within these domains.

The analysis yielded significant commonalities as well as areas of disagreement. There was strong agreement that SBRT should be reserved for patients with adequate performance status, without age restrictions, who are not actively on cytotoxic systemic therapy (outside the setting of a clinical trial), and who have been adequately staged to determine the full extent of metastatic disease. There was strong agreement that SBRT is indicated for eradication of all present oligometastases and should be used in lieu of metastatectomy in medically inoperable patients. There was strong agreement among the participating centers regarding the use of SBRT for colorectal, non-small cell lung cancer, and melanoma oligometastases involving the brain, lung, liver, and spine as well as non-spine bone metastases. However, there was no consensus regarding the number of metastases that should be used as a cut-off, although most centers only treat patients with five or fewer metastatic sites, and no more than three metastases in one organ. Additionally, most centers did not consider the cumulative tumor volume to be a contraindication for SBRT, despite evidence from Milano et al. [8] that cumulative tumor volume was associated with decreased target local control and overall survival for non-breast cancer histologies. The inclusion of brain metastases in the oligometastases management paradigm is another important finding from our study. While aggressive management of limited cranial metastases with SRS is well established, there are limited outcomes data published on patients with concurrent brain and extracranial oligometastases. Milano et al. included patients with cranial metastases, but they represented only 4% of the study population, and these patients were excluded from a similar study from the UK [15]. Most centers agreed that patients should be followed by the treating radiation oncologist in order to survey for tumor control, metastatic progression, and adverse effect with a relatively uniform schedule. However, the specific imaging used to assess disease control varied significantly among the participating centers with the exception of the use of MRI.

Currently, the US National Cancer Institute Cooperative Trial Group Program has sponsored only one trial of SBRT for oligometastases, although many other small single-institution and multi-institutional trials have either been reported or are currently accruing [16]. NRG BR-001 is a trial of SBRT for oligometastastic prostate, breast, and non-small cell lung cancer aimed at establishing its safety and documenting its efficacy in the treatment of multiple metastases in a single SBRT treatment course. Several commonalities are seen with the findings of our survey, the specifics of which are detailed in BR-001. The eligibility criteria of BR-001 allows for oligometastastic patients with up to four metastases involving the following sites: lung, mediastinal/cervical lymph node, liver, spinal/paraspinal, osseous, and abdominal/pelvic lymph nodes.

Table III. Disease and tumor characteristics.

Question	Responses (# of common responses)	Level of agreement
What primary cancers are considered for SBRT for oligometastases?		
Non-small cell lung cancer	Yes (7)	Strong
Breast cancer	Yes (5)	Moderate
Melanoma	Yes (6)	Strong
Renal cell carcinoma	Yes (4)	Moderate
Colorectal adenocarcinoma	Yes (6)	Strong
Sarcoma	Yes (2)	Low
Are the following metastatic sites considered for SBRT?		
Lung	Yes (7)	Strong
Liver	Yes (6)	Strong
Adrenal	Yes (5)	Moderate
Spine	Yes (7)	Strong
Non-spine bone	Yes (6)	Strong
Lymph nodes	Yes (5)	Moderate
Maximum number of metastases considered for SBRT	5 (5), 4 (1), 3 (1)	Moderate
Maximum number of metastases in a single organ	3 (3), 5 (1), 2 (1)	Moderate
Are patients with brain metastases considered oligometastastic	Yes (7)	Strong
Does the primary site need to be controlled to be considered for SBRT?	Yes (6)	Strong
After treatment of a primary localized tumor, is a minimum disease-free interval considered in patient selection?	No (4)	Moderate
Is tumor location considered a contraindication to SBRT?	No (5)	Moderate
Is tumor size considered for patient selection?	Yes (7)	Strong
Is cumulative tumor volume considered for patient selection?	No (5)	Moderate
Is prior radiotherapy to the target region considered a contraindication?	Yes (5)	Moderate

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

Table IV. Follow-up and disease response evaluation.

Question	Responses (# of common responses)	Level of agreement
What follow-up interval is recommended?		
1st year after SBRT	Every 2–4 mo (7)	Strong
2nd year after SBRT	Every 3–6 mo (7)	
3rd–4th years after SBRT	Every 4–6 mo (7)	
Years 5 + after SBRT	Every 6–12 mo (7)	
What criteria are used to define local tumor progression?		
RECIST	Yes (5)	Moderate
Any enlargement in one dimension	Yes (2)	Low
What imaging modality is used to follow treated lung metastases?		
CT	Yes (7)	Strong
PET-CT	Yes (2)	Low
MRI	No (7)	Strong
What imaging modality is used to follow treated liver metastases?		
CT	Yes (3)	Low
PET-CT	Yes (2)	Low
MRI	Yes (6)	Strong
What imaging modality is used to follow treated adrenal metastases?		
CT	Yes (5)	Moderate
PET-CT	Yes (2)	Low
MRI	No (7)	Strong
What imaging modality is used to follow treated lymph node metastases?		
CT	Yes (5)	Moderate
PET-CT	Yes (2)	Low
MRI	No (7)	Strong
What imaging modality is used to follow treated spine metastases?		
CT	Yes (4)	Moderate
PET-CT	Yes (1)	Low
MRI	Yes (7)	Strong
What imaging modality is used to follow treated non-spine bone metastases?		
CT	Yes (4)	Moderate
PET-CT	Yes (3)	Low
MRI	Yes (5)	Moderate

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors; SBRT, stereotactic body radiotherapy.

In accordance with practices revealed as common among our survey participants, the NRG trial requires cross-sectional imaging of nearly the entire body to best assess the extent of metastatic disease with a PET-CT or CT of the chest, abdomen, and pelvis as well as a bone scan. A Zubrod performance score of 2 or less and the absence of severe co-morbid conditions is required for enrollment.

Internationally, two additional studies are underway addressing the role of SBRT for oligometastases. In Europe, there is a multicenter phase 2 trial of conventional care or radioablation

(SBRT) for extracranial oligometastatic disease in lung, breast, and prostate cancer (CORE) patients, and a Canadian-Dutch study entitled stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET) [17] should also help guide patient selection in the future. These studies demonstrate differences in patient selection. The CORE study will enrol patients with up to three extracranial sites of disease restricted to the primary disease treated in the NRG trial, and the SABR-COMET trial will include patients with up to five metastases including brain metastases. We look forward to being informed on optimal patient selection by all of these trials and perhaps even by pooled analyses.

To our knowledge, our study is the first to explore the controversies and consistencies regarding patient selection, response assessment, and follow-up recommendations for patients treated with SBRT for oligometastases. It is limited by a relatively small number of participating centers; however, all centers surveyed treat a high volume of patients with oligometastases with SBRT. Moreover, all participating clinicians have an academic interest in this specific oncology niche. A separate manuscript will similarly explore controversies and commonalities regarding technical factors of SBRT planning and delivery. Another limitation is that the standard used to define ''strong agreement'' (common responses among six or seven centers) is relatively arbitrary and using a standard of five or more to define ''strong agreement'' would have revealed substantially more commonalities among the participating centers. It is our hope that this data will help lay the groundwork for the development of clinical guidelines and practical clinical trials that will assist in determining the most appropriate application of SBRT for oligometastases.

Conclusions

Among seven academic centers that treat oligometastastic patients with SBRT, we identified strong agreement for the following standards: SBRT should be limited to adequately staged patients with oligometastastic colorectal cancer, non-small cell lung cancer, and melanoma with a specific performance status and metastases involving spine, non-spine bone, lung, liver, or brain. These patients are otherwise unsuitable for surgery. The goal of therapy should be eradication of all identifiable metastatic disease. Follow-up should be performed by the treating radiation oncologist and disease progression monitored with cross-sectional imaging at frequent intervals during the first two years, decreasing in frequency with time. Beyond these commonalities, there was only moderate or low agreement regarding a wide variety of issues.

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Declaration of interest

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