Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases

An International Survey of >1000 Radiation Oncologists

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Purpose: Stereotactic body radiotherapy (SBRT) is often used to treat patients with oligometastases (OM). Yet, patterns of SBRT practice for OM are unknown. Therefore, we surveyed radiation oncologists internationally, to understand how and when SBRT is used for OM.

Methods: A 25-question survey was distributed to radiation oncologists. Respondents using SBRT for OM were asked how long they have been treating OM, number of patients treated, organs treated, primary reason for use, doses used, and future intentions. Respondents not using SBRT for OM were asked reasons why SBRT was not used and intentions for future adoption. Data were analyzed anonymously.

Results: We received 1007 surveys from 43 countries. Eighty-three percent percent began using SBRT after 2005 and greater than one third after 2010. Eighty-four percent cited perceived treatment response/durability as the primary reason for using SBRT in OM patients. Commonly treated organs were lung (90%), liver (75%), and spine (70%). SBRT dose/fractionation schemes varied widely. Most would offer a second course to new OM. Nearly all (99%) planned to continue and 66% planned to increase SBRT for OM. Of those not using SBRT, 59% plan to start soon. The most common reason for not using SBRT was lack of clinical efficacy (48%) or lack of necessary image guidance equipment (34%).

Conclusions: Radiation oncologists are increasingly using SBRT for OM. The main reason for not using SBRT for OM is a perceived lack of evidence demonstrating clinical advantages. These data strengthen the need for robust prospective clinical trials (ongoing and in development) to demonstrate clinical efficacy given the widespread adoption of SBRT for OM.

Key Words: oligometastasis, SBRT, survey, metastasis, radiation oncology

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A series of technological advancements in the hardware and software that calculates and delivers radiotherapy now enables radiation oncologists to deliver focused doses of ablative radiotherapy to tumor(s), while reducing exposure of normal tissues. These technologies, accounting for respiratory motion, providing daily high-resolution image-guided tumor targeting, precise patient immobilization, as well as advanced treatment planning techniques creating sharp radiation dose fall-off between tumors and normal tissues, are often referred to as stereotactic body radiotherapy (SBRT). SBRT has been adopted as a standard therapy for medically inoperable early-stage non-small cell lung cancer, and is being actively investigated to treat primary tumors of the prostate, pancreas, kidney, and liver.

The oligometastatic state is often defined as a clinically meaningful condition, potentially having a more favorable prognosis, when metastases are limited in number and distribution organ. It has been proposed that aggressive therapy to all oligometastases (OM) may improve progression-free and/or overall survival (OS) in these patients. Large series of patients undergoing surgical removal of OM in the lung, liver, brain, and adrenals (among other organs) suggest high rates of metastasis control and potentially improved OS. Clinical trials employing SBRT for limited metastases are comparable with surgery, reporting 70% to 90% treated metastasis control, with minimal toxicity, leading to ongoing randomized trials.

Despite increasing numbers of published series and ongoing trials using SBRT to treat OM, current patterns of practice are unknown. We postulated that differences in equipment availability, clinician acceptance of the OM state, and the wide variation in metastases presentation, substantially contribute to differences in patterns of practice. To better understand patterns of practice and assess the current use of SBRT to treat limited metastatic disease, we conducted an international survey of practicing radiation oncologists.

METHODS

A 25-question survey was developed using Redcap database survey software. Data gathered included demographic information, country of practice, zipcode (if in the...
United States), in addition to practice setting and size. In addition, radiation oncologists were asked if they were currently treating patients with limited extracranial metastases defined as ≤3 metastases with definitive hypofractionated radiation therapy using >4 Gy per fraction. Respondents using SBRT to treat metastases were asked how long SBRT had been used for OM disease, as well as the number of patients treated, organs treated, primary reason for use, dose fractionation schedules used, treatment device used, and intentions for future use. Respondents not using SBRT to treat metastases were asked reasons for not using this technique, intentions for future adoption, and their reasoning. The complete survey is available online in Appendix 1 (Supplemental Digital Content 5, Appendix, http://links.lww.com/AJCO/A85).

The survey was distributed to members of the American Society for Radiation Oncology (ASTRO), the Canadian Association of Radiation Oncology (CARO), the European Society for Radiotherapy and Oncology (ESTRO), the Japanese Society for Therapeutic Radiology and Oncology (JASTRO), and the Trans-Tasman Radiation Oncology Group (TROG). Surveys were primarily distributed through email link facilitated by collaborators from each organization. The survey was also available as a link on the TROG Web site.

The data were analyzed anonymously as an entire group, and also by country and region as deemed applicable, based on the number of respondents. Survey results were generally presented as percentages of evaluable responses. Comparisons were then made regarding patterns of practice within different countries and regions. No attempt was made to define null hypotheses or determine statistical significance.

RESULTS

Characteristics of Respondents

A total of 1007 completed surveys from radiation oncologists in 43 countries were analyzed from 8703 distributed for a response rate of 11.5%. Table 1 lists respondent characteristics. Responses came primarily from the United States (42%), Canada (11%), Japan (10%), Western Europe (7%), and Australia/New Zealand (6%). Forty-two percent of respondents were academic-affiliated physicians, 32% were associated with hospitals or stand-alone cancer centers, and 12% were from a community practice.

Use of SBRT to Treat ≤3 Metastases

Overall, 61% of respondents use SBRT to treat patients with ≤3 extracranial metastases. The majority of respondents (83%) using SBRT to treat metastases adopted this practice after 2005 (Fig. 1). Most physicians (69%) were willing to target 2 to 3 OM lesions with SBRT in an individual treatment course. Physicians in the United States (69%), Western Europe (76%), and Korea (78%) were most likely to use SBRT to target ≤3 extracranial metastases, whereas physicians in Australia/New Zealand (27%) were least likely. Academically affiliated physicians (67%) were most likely to treat patients with limited metastatic disease with SBRT, whereas 60% of private practice radiation oncologists, and 52% of those associated with hospitals/stand-alone cancer centers would treat patients with definitive SBRT. Furthermore, 88% of users were willing to offer a second course of SBRT to a new site after limited metastatic progression.

SBRT for >3 Extracranial Metastases

The use of SBRT in patients with >3 extracranial metastases was uncommon (23% of respondents). Even fewer (6%) use SBRT to target >3 extracranial metastases in a single treatment course. Physicians willing to treat >3 extracranial metastases with SBRT in an individual patient were more likely to be located in the United States (52%); although this represented only 25% of US-based physicians that responded to the survey. Among this 25%, were equal numbers of physicians’ private practice (23%), hospital/stand-alone cancer centers (21%), and academic centers (25%). Otherwise no worldwide or regional practice patterns were discernible. There was no association with length of experience with SBRT and willingness to treat >3 OM with this technology.

Correlation of SBRT With Metastasectomy

Sixty percent responded that surgeons routinely perform metastasectomies at their institutions. However, equal numbers of these physicians felt that increased (35%), decreased (30%), or did not affect (35%) their opportunity to treat limited metastatic disease with SBRT. Almost all of those who offer SBRT to patients with ≤3 OM (98%) responded that surgeons at their institutions routinely performed metastasectomies.

TABLE 1. Survey Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Respondents Using SBRT for OM (%)</th>
<th>Respondents NOT Using SBRT for OM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation oncologists</td>
<td>1007 (100)</td>
<td>61.0</td>
</tr>
<tr>
<td>Geographic location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>426 (42)</td>
<td>68.5</td>
</tr>
<tr>
<td>Canada</td>
<td>113 (11)</td>
<td>47.8</td>
</tr>
<tr>
<td>Japan</td>
<td>101 (10)</td>
<td>45.2</td>
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<tr>
<td>Western Europe</td>
<td>67 (7)</td>
<td>76.1</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>64 (6)</td>
<td>27.0</td>
</tr>
<tr>
<td>South Korea</td>
<td>26 (3)</td>
<td>78.3</td>
</tr>
<tr>
<td>Miscellaneous</td>
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<tr>
<td>Practice type</td>
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<tr>
<td>Academic</td>
<td>421 (42)</td>
<td>66.6</td>
</tr>
<tr>
<td>Private</td>
<td>117 (12)</td>
<td>60.1</td>
</tr>
<tr>
<td>Hospital or stand-alone cancer center</td>
<td>321 (32)</td>
<td>52.8</td>
</tr>
<tr>
<td>Other or unreported</td>
<td>148 (15)</td>
<td>6.8</td>
</tr>
</tbody>
</table>

OM indicates oligometastases; SBRT, stereotactic body radiotherapy.

FIGURE 1. Cumulative percentage of respondents using stereotactic body radiotherapy (SBRT) for oligometastases during the defined time intervals.
Protocol Versus Nonprotocol SBRT Treatment for OM

Interestingly, many of those treating metastases with SBRT had treated between 1 and 20 patients on a clinical protocol (82%), whereas 53% had treated up to 20 patients off of a clinical trial. More than half of those treating on a protocol also reported treating up to 20 patients off protocol. Few practitioners had treated 20 to 50 patients with SBRT for metastases whether on (10%) or off (28%) protocol, and fewer still had treated >50 patients, on (8%) or off protocol (19%).

Reasons for Adopting (or Not Adopting) SBRT for OM

The most common reasons cited for adoption of SBRT were demonstration of durable treated metastasis control and treatment of patients who were not surgical candidates (Fig. 2). Other reasons cited were quick completion of treatment and retreatment of previously irradiated patients. Respondents felt that there is similar evidence for use of SBRT to treat limited metastatic disease as compared with intensity-modulated radiation therapy (IMRT) when it became widely available (Supplemental Digital Content 1, Figure, http://links.lww.com/AJCO/A78). The most common reasons for not using SBRT in the limited metastatic setting was lack of convincing data to support its use (48%), lack of necessary equipment (34%), and lack of appropriate staff (21%).

Metastatic Locations Commonly Treated With SBRT

Metastases in many different organs were routinely treated with SBRT (Supplemental Digital Content 2, Figure, http://links.lww.com/AJCO/A79). The most common organs treated were the lung (90%), spine (68%), liver (63%), bones (58%), and adrenals (39%). Lymph nodes were also noted as a site treated by many. The most common adjacent critical organs that would prevent physicians from treating with definitive hypofractionated radiation included the lungs, small bowel, and heart. Furthermore, many respondents specifically mentioned central airways, brainstem, cranial nerves, large blood vessels, and esophagus, as well (Supplemental Digital Content 3, Figure, http://links.lww.com/AJCO/A80).

SBRT Doses Used to Treat OM

SBRT dose/fractionation schemes varied widely, and most users specified that fractionation was treatment site dependent. In addition, favored dose/fractionation schemes varied by geographic region as shown in Figure 3. The most common regimens were 50 Gy in 5 fractions, 48 Gy in 4 fractions, and 30 Gy in 5 fractions at 20.6%, 19.4%, and 9.4%, respectively. Eighty-six percent felt that there was a benefit to using regimens of ≤5 fractions, compared with ≥10 fractions when definitively treating limited metastases.

The treatment of multiple metastases in 1 treatment course, either within the same or different organs, with SBRT leads to increased technical demands and challenges. We inquired specifically how comfortable physicians were treating 2 targets with a high likelihood for overlapping radiation fields and dose. Less than half of those using SBRT to treat metastases (41%) were willing to treat with SBRT in this scenario, whereas 21% would not and 38% were unsure. Many users who answered yes to this question qualified their response, citing case-specific considerations would be paramount. Furthermore, most (57%) that would treat in this scenario said that they would use the same dose as when treating a single metastasis, whereas 40% would decrease the treatment dose.

Future Use of SBRT to Treat OM

Our respondents indicated that the use of SBRT to treat OM is likely to increase. Sixty-three percent of those currently treating OM with SBRT planned to increase treatments. Only 36% intend to maintain their level of utilization. More than half (59%) of respondents not currently using SBRT to treat limited metastatic disease intend to start, 88% within 1 to 3 years. The most common reason given for implementing SBRT for OM was to improve clinical outcome (81%). Other reasons cited included clinical research purposes (30%) and the need to remain competitive (23%), as shown in Figure 4.

DISCUSSION

The purpose of this survey was to assess current worldwide practice patterns regarding the use of SBRT to treat patients with OM. Our results suggest that SBRT is commonly used to treat OM as nearly two thirds of respondents are actively using SBRT for definitive treatment of OM. SBRT treatments for OM are going to increase, as approximately two thirds of those currently using this technology intend to treat more patients, and the majority of those not currently offering SBRT for metastases intend to start within the next 2 to 3 years.

The 1000 radiation oncologists who responded represent ~12% of the surveys distributed. This response rate was similar to another international survey with similar methods,12 and the absolute number of American respondents was similar to prior surveys.13,14 The response rate was likely affected by difficulty discerning radiation oncologists from affiliated professions (medical physicists, radiation therapists, medical dosimetrists, and radiobiologists) from society rosters, as well as survey fatigue, indifference, or prejudice against SBRT.

[Figures and tables are not included in this text.]
Technological advances are often integrated into clinical practice before evidence supporting specific uses. The recent expanded use of SBRT in the past decade is similar to the expanded use of IMRT in the decade preceding. In 2002, a survey on the use of IMRT, found that approximately one third of respondents in the United States were using IMRT at that time. It is noteworthy that most respondents to our survey felt that there was a similar amount of evidence for SBRT in the limited metastatic setting, as compared with the level of evidence for use of IMRT in general clinical practice in the early 2000s. This willingness to use SBRT may reflect increased access to and comfort with high-quality simulation, treatment imaging, and dose computation technologies. Correspondingly, many nonusers indicated that lack of adequate technology was the primary reason they were not currently treating limited metastatic disease with SBRT. In addition, it may also reflect a belief that the promising outcomes for patients treated with SBRT for early-stage medically inoperable non–small cell lung cancer, also translate to the treatment of limited metastases. In contrast to the 2002 IMRT survey by Mell et al, the use of SBRT for limited metastatic disease is similar between academic (67%) and private practice (60%) physicians perhaps reflecting the more widespread availability and comfort level with appropriate technology.

We identified regional variations in the use of SBRT for the treatment of limited metastases as approximately 75% of respondents in the United States, Western Europe, and Korea use SBRT to treat OM, whereas in Australia/New Zealand only 25% were treating patients this way. These regional variations likely contributed to the variable dose/fractionation schedules used. For example, the favored fractionation in Western Europe of (60 Gy in 8 fractions) was developed for central lung malignancies in The Netherlands demonstrating excellent local control, and the data regarding 50 Gy in 5 fractions (the most common fractionation cited by current users in the United States) had been developed in the United States.

Physicians currently offering SBRT for limited metastases most commonly treated organs that corresponded to sites of more frequent metastases including the lung, liver, and spine. This is in keeping with the majority of published literature on SBRT for metastatic disease. There appears to be significant clinical experience developing, as nearly one fifth of respondents have treated >50 patients off protocol, along with almost 90% willing to retreat patients to another site with limited progression of disease among current users. In addition, physicians offering SBRT for metastasis were likely to practice in centers where surgeons were also offering resection for metastatic disease, perhaps indicating a common institutional philosophy.

In hindsight, perhaps we failed to ask the important question, “do you believe in the clinical state of oligometastasis?”. It is likely that respondents treating limited metastatic patients with SBRT, would say yes. This may indicate a paradigm shift away from previously widespread belief in the systemic hypothesis of metastasis, first suggested by Keynes and advanced by Fisher, describing 2 principal types of cancer: those that have metastasized widely before clinical detection and those that cannot metastasize. The data presented here may suggest a progressive belief in the spectrum hypothesis of metastasis, reflecting the wide array of survival seen in clinical practice and encompasses patients with limited metastatic or oligometastatic disease.

In addition, we did not ask in our survey how radiation oncologists viewed potential advantages of SBRT versus standard systemic therapies. These include the cost, in particular compared with targeted or immunomodulatory therapies increasingly prescribed for metastatic disease. Furthermore, we did not ask about the role of SBRT to delay initiation of systemic therapy, and its associated side effects, or as a mechanism for a chemotherapy break in those with few nonprogression metastases. Further prospective investigations may elucidate the role of SBRT in these settings.

The increased use of SBRT treatments for metastases has significant cost implications, particularly important in the current era of medical cost containment. In a typical American market, there is a marked difference between palliative radiotherapy and SBRT for metastases. For example, $18,000 is typically billed for a conventional single fraction course of palliative radiotherapy compared with $72,476 for a single fraction course of SBRT. However, the difference shrinks dramatically when comparing the most commonly prescribed palliative radiotherapy regimen of 10 fractions ($56,900) to that of a single fraction SBRT course (Supplemental Digital Content 4, Table, http://links.lww.com/AJC/81). Differences are more dramatic in other international markets (UK, Japan) where a single fraction of SBRT is 8 to 14 times the cost of a single conventional radiotherapy dose, but less so in others (Canada, Australia). Prospective trials are needed to determine if the cost differential is justified in terms of improved disease control, pain relief, quality of life, or improved survival, with the more costly SBRT treatments.

Despite the current level of use, skepticism about the use of SBRT to treat limited metastases remains. The most commonly cited reason for not using this technology was the lack of clinical data to support it. Ongoing randomized studies should help to supply this much-needed data. The randomized phase II SABR-COMET trial will assess the impact of a comprehensive oligometastatic SBRT treatment program on OS and quality of life in patients with up to 5 metastatic cancer metastases, compared with patients who receive standard of care treatment alone. In addition, 2 NRG Oncology studies are in development to further elucidate the role of SBRT to treat OM. NRG Oncology BR002, a randomized phase II with direct rollover into a phase III (should there be sufficient progression-free survival signal) will attempt to determine if there is a progression-free survival or OS benefit in women with 1 to 2 asymptomatic breast cancer metastases who receive SBRT or surgery to all known metastases versus those who receive standard of care. NRG Oncology BR001 will determine appropriate SBRT doses for patients with 3 to 4 metastases or 2 metastases in close proximity from breast, non–small cell lung cancer, or prostate cancer.
REFERENCES


