Stereotactic Body Radiotherapy for Oligometastases: An Opportunity for Cure?

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Abstract

Advances in radiation oncology have enabled the delivery of ablative doses of radiotherapy (RT) to a variety of anatomic sites with increased precision and minimal toxicity. Stereotactic body radiotherapy (SBRT) has emerged as an attractive alternative to surgical resection. In this review, we will discuss the following: the proposed state of limited metastatic disease (commonly referred to as oligometastases) and the growing role of SBRT in the management of these patients; potential challenges in selecting patients with limited metastases who are most likely to benefit from aggressive local interventions; some of the key nonrandomized studies that have demonstrated the feasibility and safety of SBRT to treat multiple metastatic sites; important questions including the safety of SBRT in combination with systemic therapies; and the existing randomized data to support treatment of limited metastases and the multiple ongoing randomized trials. Lastly, we will examine the interaction between SBRT and the immune system, and explore future applications that include combining SBRT with immunotherapy.

Introduction

Technical advances in radiotherapy (RT) oncology have enabled the delivery of highly conformal, ablative doses of RT to multiple extracranial sites, referred to as stereotactic body radiotherapy (SBRT). In contrast to conventionally fractionated RT, which often involves daily doses of 1.8 to 2.0 Gy delivered over 6 to 8 weeks, SBRT utilizes higher doses per treatment (6-30 Gy) delivered over a shorter time frame (typically 1-5 fractions over 1-2 weeks).[1] Advances in RT treatment planning and image guidance have enabled delivery of SBRT with increased accuracy and precision to limit radiation exposure to surrounding normal tissues.[2] As a result, delivering ablative RT to limited metastases has become an attractive and increasingly utilized treatment paradigm for patients with good performance status. Questions remain regarding the benefits in treating limited metastases with ablative RT, how to identify optimal candidates, and the safety of incorporating newer RT techniques with novel systemic therapies. Herein, we describe the state of limited metastatic presentation commonly referred to as oligometastases. We explore the growing role of SBRT in the management of patients with limited metastases.

Oligometastases: Definitions and Patient Selection

The concept of oligometastases was first proposed by Hellman and Weichselbaum in 1995, who described it as an intermediate state of cancer pathogenesis between purely localized disease and widespread metastases.[3] Although no consensus definition exists, the oligometastatic state is defined as 5 or fewer clinically detectable metastatic lesions. As a consequence, it has been hypothesized that patients with a low number of metastases may benefit from metastasis-directed local therapies in addition to standard systemic therapies. It has been shown that long-term survival can be achieved after metastasectomy for well-selected patients with limited hepatic or pulmonary metastases.[4,5] Such studies are often cited as evidence of the oligometastatic state; however, it is unclear whether these favorable results should be attributed to aggressive interventions or indolent tumor biology.

Since the initial description of oligometastases by Hellman and Weichselbaum, additional terms have been introduced to help explain the range of clinical behavior observed in distinct metastatic settings. Oligorecurrence describes limited metastases in the setting of a controlled primary tumor, and oligoprogression describes the growth of only a limited number of metastases while other sites are controlled by or responding to systemic therapy.[6] The incidence and natural history of oligometastatic disease for different tumor histologies is still being defined. For example, in one study of patients with metastatic non–small cell lung cancer (NSCLC), 50% had 3 or fewer metastatic sites.[7] Similar reports have identified subsets of patients with limited metastases in other common malignancies, such as prostate, breast, and colorectal cancer.[8-10]

Currently, classifying patients as oligometastatic relies on the ability of diagnostic imaging to accurately identify the number of metastatic sites. Advanced imaging modalities such as PET/CT and MRI have improved the ability to evaluate patients for metastatic disease. In addition, novel prognostic biomarkers, such as

TABLE 1. Select Studies of SBRT

Study	Year	Number of Patients	Median Follow-up (months)	RT Dose	Treated Metastasis Control	Overall Survival	Grade 3+ Toxicity
Pulmonary Multi-institutional (US)[13]	2009	38	15.4	48-60 Gy	2 years: 96%	2 years: 39%	8%
Hepatic Multi-institutional (US)[22]	2013	153	Mean, 25.2	27-46.5 Gy	1 year: 62%	1 year: 51%	3%
Spine MD Anderson Cancer Center[15]	2012	149	16	27-30 Gy	1 year: 80.5%	1 year: 72%	8%

RT, radiotherapy

circulating tumor cells and microRNA expression profiles, may improve the ability to select patients who have more indolent tumors, and who are perhaps most likely to benefit from aggressive local therapies.[11,12]

In a prospective study of metastasis-directed SBRT that included patients with 1 to 5 metastases, the estimated 5-year overall survival was 32%, demonstrating that long-term survival may be achieved in a subset of oligometastatic patients after metastasis-directed SBRT.[12] In general, several clinical factors appear to be associated with prolonged survival, such as primary tumor histology (ie, breast), fewer number of metastases, prolonged time from diagnosis to development of metastases, and stable or controlled disease prior to SBRT.[2] Despite efforts to stratify by clinical factors, patient seletion remains a major challenge, and many patients considered oligometastatic may harbor subclinical micrometastases that will progress despite metastasis-directed ablative therapies.

SBRT: Applications, Efficacy, and Safety

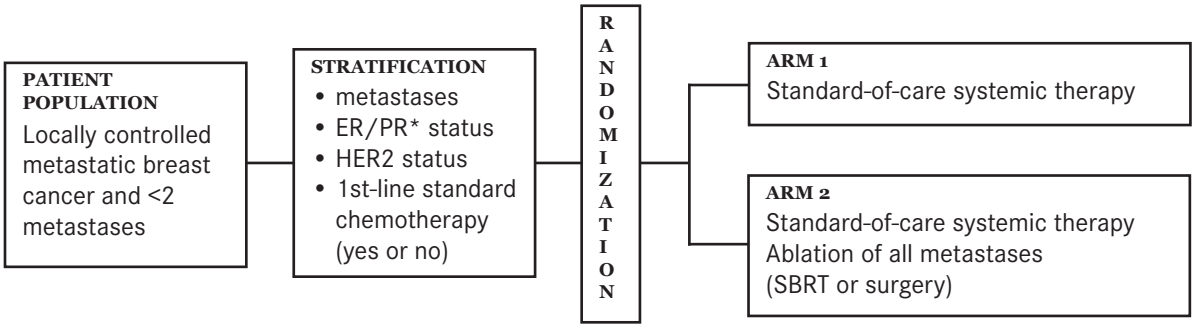
Early applications of stereotactic RT techniques focused on ablative treatments for intracranial metastases. The development of technologies to allow image guidance and real-time assessment of tumor motion have facilitated the application of SBRT to complex extracranial targets. A growing body of evidence suggests that SBRT is technically feasible for multiple extracranial sites with acceptable toxicity, including lung, liver, spine, and many others.[13-15] SBRT has potential advantages compared with surgical resection since SBRT is generally less invasive, can target anatomic locations not accessible by surgery, and can be administered with minimal interruptions in systemic therapy.

Thus far, the bulk of evidence supporting SBRT to treat oligometastases comes from single-institution retrospective experiences or single-arm dose-escalation trials. The **Table** summarizes results of select studies of SBRT for oligometastases with long-term follow-up. Treated metastasis control after SBRT appears to be comparable to metastasectomy, ranging from 70% to 90%.[16] Interestingly, ablative RT doses also appear to be equally effective in controlling metastases from historically radio-resistant histologies, such as sarcoma, melanoma, and renal cell carcinoma.[17-19] These findings are consistent with the notion that SBRT works through a different mechanism than conventional RT, such as endothelial cell damage.[20] Furthermore, RT dose is important for achieving local control. In an SBRT dose-escalation study from the University of Chicago, treated metastasis control was 100% in the highest-dose cohort (48 Gy in 3 fractions) compared with only 45.7% for the lowest-dose cohort (24 Gy in 3 fractions).

Several studies have evaluated the safety of SBRT as applied to specific anatomic sites. In general, rates of grade 3+ pulmonary toxicity are relatively low (<10%) after lung SBRT.[13] However, serious and even fatal complications have been reported after SBRT for central lung tumors.[21] In a multi-institutional study of SBRT for liver metastases, rates of grade 2 and grade 3 toxicities were 1.9% and 3.2%, respectively.[22] In a large, multi-institutional study, there was a 6% rate of fracture after spine SBRT.[23] The ongoing NRG-BR001 trial will provide additional insight regarding the safety and treating multiple metastases with SBRT and the optimal dose-fractionation scheme (NCT02206334).

Aside from the ultimate goal of prolonging survival, SBRT for oligometastases might have other clinically meaningful benefits. One such benefit could be the use of SBRT as a means to delay the start of systemic therapy or allow for prolonged chemotherapy breaks. Furthermore, in the setting of oligoprogression, SBRT might enable the continuation of an otherwise effective targeted therapy. For example, in a study of patients with ALK-positive NSCLC and oligoprogressive disease, prolonged crizotinib use was seen in those who received ablative local therapy to all metastases compared with those who did not (median duration, 28 months vs 10.1 months).[24] In addition, it is possible that SBRT will result in more durable palliation and local disease control compared

FIGURE 1. Schema of NRG-BR002



ER/PR, estrogen receptor/progesterone receptor.

with conventionally fractionated RT. The RTOG 0631 study will evaluate whether spine SBRT improves pain control compared with conventional "palliative-dose" RT (NCT00922974).

Randomized Data and Ongoing Trials

Level I evidence showing a survival benefit to metastasis-directed ablative therapy is limited to surgical resection or radiosurgery for limited brain metastasis.[25,26] Although level I data are lacking, the use of SBRT for oligometastases has increased in the United States and internationally. According to an international survey of over 1000 radiation oncologists published in 2015, 61% of respondents reported using SBRT to treat extracranial oligometastases, with the majority of nonusers planning to start within the next 1 to 3 years.[27] More recently, results of a multi-institutional phase II randomized trial demonstrated improved progression-free survival (PFS) with the addition of consolidative local therapy with surgery or SBRT in patients with oligometastatic NSCLC and no disease progression following induction systemic therapy (median PFS, 14.4 months vs 3.9 months).[28]

Multiple clinical trials evaluating the role of ablative therapies for oligometastases are ongoing, although accrual has been challenging for some. In the United States, NRG-BR002 (**Figure**) is a randomized trial comparing ablation of all metastases versus standard-of-care systemic therapy for patients with oligometastatic breast cancer (NCT02364557). Internationally, a number of studies are accruing patients, including SABR-COMET (NCT01446744), CORE (NCT02759783), SARON (NCT02417662), and STOMP (NCT01558427) trials. Ideally, ongoing and future studies incorporating blood and tissue samples will add to our knowledge of prognostic and predictive biomarkers to aid in patient selection.

Future Directions: SBRT and the Immune Response

An intriguing application of SBRT is the potential to enhance tumor-specific immunity, and thus "prime" the immune system to immunotherapy. Beyond DNA damage and direct cell death, the therapeutic effects of SBRT appear to be mediated via CD8+ T cells.[29] Furthermore, in addition to tumor debulking, preclinical models suggest a synergistic antitumor effect when RT is combined with immunotherapy.[30,31] A number of mechanisms have been proposed to support this phenomenon, such as increased exposure to tumor antigens, enhanced T-cell function, and downregulation of immunosuppressive cell populations.[32]

With the recent emergence of cancer immunotherapy as a standard treatment for many solid tumors, there is growing interest in combining immunotherapy and SBRT as a means to improve response rates. However, the optimal RT dose, fractionation schedule, and timing of therapies is unknown. Numerous ongoing clinical trials combining RT with immunotherapy will hopefully shed light on these important questions.[33]

Conclusion

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