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REVIEW ARTICLE

Radical Irradiation of Extracranial Oligometastases

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A B S T R A C T

Advances in radiotherapy planning and delivery have been used to treat patients with limited metastatic disease. With these techniques, high rates of treated metastasis control and low toxicity have been reported. Some patients have long disease-free intervals after radiotherapy similar to those seen after surgical resection. Ongoing studies will determine the benefit of these irradiation techniques to treat limited metastases, identify appropriate candidates, and assist in integrating these treatments into management strategies for specific diseases.

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INTRODUCTION

To render patients with metastatic disease permanently free of cancer is an eminently worthwhile but often elusive goal. Advances in systemic therapies have improved long-term survival and cured some patients with pediatric, germ cell, and hematologic malignancies. With the development of therapies targeted to specific molecular mutations, some long-term remissions are now seen for a variety of nonhematologic malignancies. However, for adult solid tumors, rare is the patient cured with systemic therapy alone.

Systemic therapy remains standard as the initial treatment for most patients with metastatic cancer, allowing for improved survival and quality of life compared with best supportive care. The utility of systemic therapy is traditionally predicated on two fundamental principles.[1] First, the only way to deliver effective treatment to multiple metastases in many anatomic locations throughout the body is via the circulatory system, and second, microscopic metastases are present in nearly all patients with metastases, and systemic therapy is required to eradicate these deposits.

However, an alternative theory of the natural history of cancer, called the spectrum hypothesis,[2] may explain vastly different outcomes among metastastic patients. An intermediate clinical state between widespread metastases and locoregionally confined malignancy, referred to as oligometastases, was proposed by Hellman and Weichselbaum[3] based on the clinical behaviors of patients with metastatic cancer. In this intermediate state, it was hypothesized that treatment of all known macroscopic metastases may improve disease-free intervals and potentially survival, in addition to standard systemic therapy.

A growing body of evidence suggests that radical ablation with surgery or advanced radiotherapy is associated with improved outcomes for select patients with limited metastases. Although selectively using radiotherapy to eradicate metastases was described as early as the 1960s,[4] this approach was historically not successful, given less effective systemic therapy, supportive care, and technology. In recent years, advances in imaging, patient immobilization, and radiation treatment planning and delivery have allowed for improved targeting precision and accuracy, expanding the indications for radiotherapy. The high rates of tumor control in patients treated with ablative radiotherapy for limited metastases have prompted widespread implementation of stereotactic body radiation therapy (SBRT) for patients with limited metastatic disease of the lung, liver, adrenal gland, and spine.[5]

Much work remains to determine the benefit of radical irradiation (and surgery) in oligometastatic patients. How to appropriately select patients, although critical to successful long-term outcomes, is unclear at the moment. Furthermore, the integration of newer radiotherapy techniques with cytotoxins and targeted systemic therapies remains a work in progress, as does the best way to leverage the nonoverlapping toxicities of radiotherapy and surgery to best benefit patients. Finally, continuous refinement of radiotherapy techniques is an ongoing process, potentially allowing for treatment of more patients with limited metastatic disease.

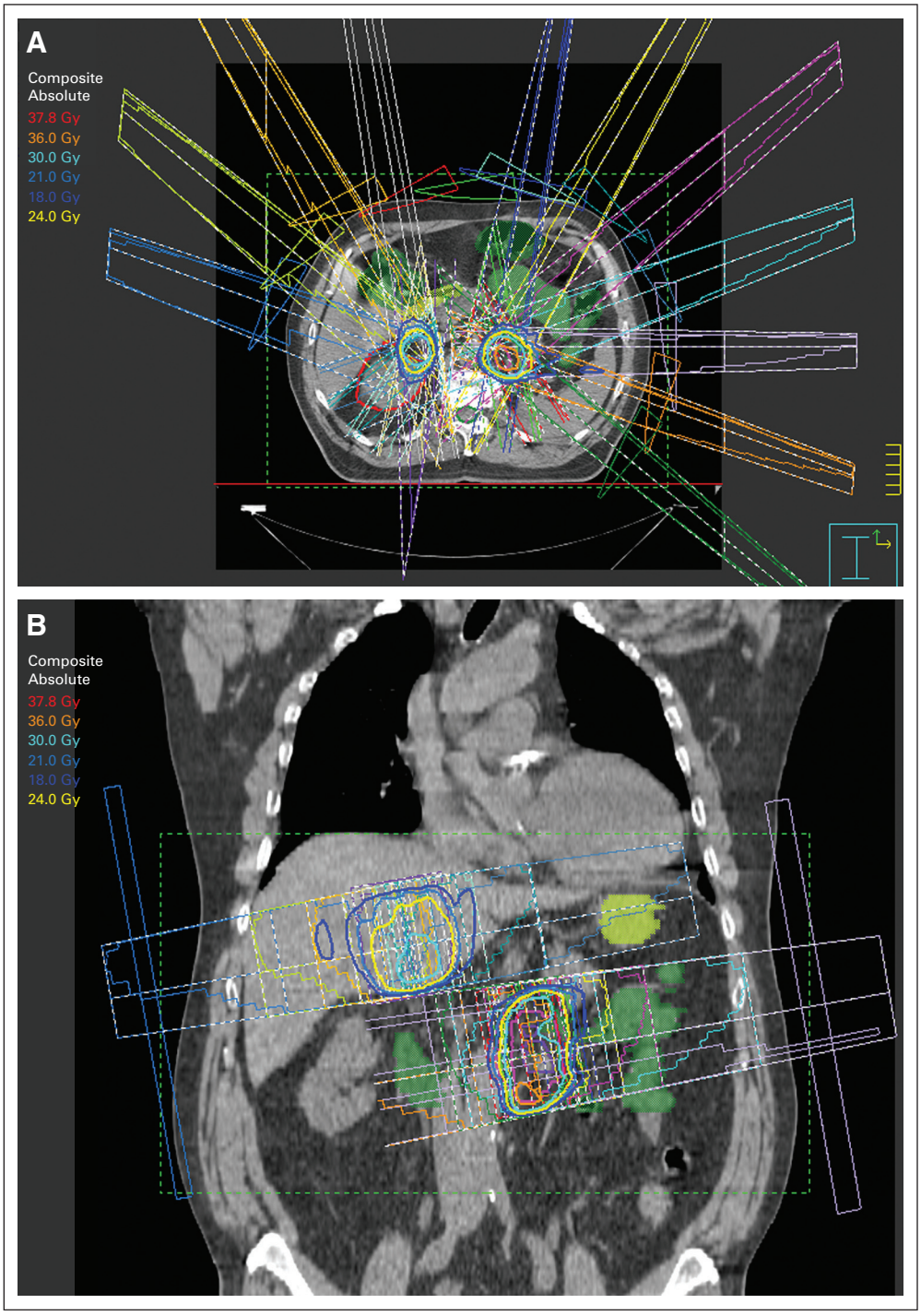

Fig 1. Example of patient with limited metastatic disease in abdomen treated with stereotactic body radiation therapy to both metastases simultaneously. (A) Coronal and (B) axial slices show how radiotherapy planning needs to account for contributions of entrance and exit doses from one metastasis to another.

DO PATIENTS WITH LIMITED METASTASES EXIST?

Although discussions of theories underlying the natural history of metastatic cancer are largely academic, a pertinent clinical question is, "Do patients with limited metastases exist?" with the corollary, "If so, how many of these patients have metastases limited in number and distribution with a slower natural history (ie, true oligometastatic disease)?" Among patients initially diagnosed with metastatic disease as well as those who experience progression from locoregionally confined disease with metastases after initial treatment, subsets with limited involvement have been observed. In a study of patients with newly diagnosed stage IV non–small-cell lung cancer (NSCLC) from the University of Chicago, 74% presented with metastases confined to one to two organs, and 50% had ≤ three metastatic sites in addition to the lung primary tumor.[6] Long-term follow-up of more than 1,700 surgically managed patients with early-stage NSCLC found that of those experiencing progression with metastases, 33% had solitary metastases, with an additional 19% limited to two to three metastases.[7]

Similarly, in men with biochemical recurrence after locoregional therapy for prostate cancer who experienced progression to metastatic disease, 40.5% presented with ≤ five metastases on annual imaging.[8] Limited metastatic presentation is also common in women in breast cancer therapeutic clinical trials. Recently reported phase II and III studies of modern systemic therapies including more than 2,500 patients with breast cancer showed that 43% to 77% had disease limited to ≤ two metastases.[9-14] Similarly, landmark series of patients with colorectal cancer (CRC) demonstrated that 38% had disease limited to one metastatic site,[15] and 55% to 85% had disease limited to two metastatic sites.[16,17] Therefore, a significant proportion of patients present with limited metastatic disease in the most commonly seen cancers.

DO PATIENTS WITH LIMITED METASTATIC DISEASE BEHAVE DIFFERENTLY THAN THOSE WITH MORE WIDESPREAD METASTASES?

For the oligometastatic state to be clinically relevant, an appreciable percentage of patients presenting with few sites of metastases should have a different clinical behavior than those with polymetastases. This has been shown for many different tumor types. Not only do patients with prostate cancer with ≤ five metastases have survival similar to those without metastases (73% and 36% at 5 and 10 years *v* 75% and 45% at 5 and 10 years, respectively), they have significantly better survival than those who develop more than five metastases (45% and 18% at 5 and 10 years, respectively; $P = .02$).[8] Furthermore, patients with early-stage breast cancer who experience progression to less than five metastases have improved 5-year (59.6% *v* 11.6%) and median survival (107.7 *v* 22 months; $P = .001$) after progression compared with those with more than five.[18] Finally, longer median survival is seen in patients with early-stage NSCLC with oligometastases compared with those with diffuse metastases (13 *v* 7 months; hazard ratio, 0.53; 95% CI, 0.41 to 0.69; $P < .001$).[7] Those with limited metastases are often likely to experience progression in known sites of cancer rather than in new sites, as shown in two studies of patients with metastatic NSCLC.[6,19] Furthermore, if progression does happen in new sites, those sites are often limited in number.[20-22]

It is possible that some measure of the improved survivorship of patients with oligometastatic disease is related to lead-time bias, whereby patients are being seen at an earlier point in the natural history of their cancer dissemination. Arguing against this explanation as the sole reason for higher rates of overall survival in patients with limited metastatic disease are preclinical and clinical observations of the multistep nature of the molecular process of cancer evolution within a host from initial to subsequently more and more aggressive genotypes.[23-26] Therefore, these data suggest that patients with fewer metastases tend to behave less aggressively than those with more metastases at diagnosis, resulting in improved survival. When progression occurs, it often does so in known metastases or in few new metastases.

HAS THE AGGRESSIVE TREATMENT OF METASTASES ALREADY IMPROVED OUTCOMES?

Intensifying the treatment of metastatic disease (although not strictly oligometastatic disease) has improved patient outcomes in some randomized phase III studies. For example, patients with metastatic spinal cord compression undergoing immediate direct circumferential decompression of the spinal cord in addition to irradiation had not only improved ambulation and continence but also had improved survival compared with those receiving radiotherapy alone (126 *v* 100 days; $P = .033$).[27] Furthermore, the use of surgery[28] and radiosurgery[29] in addition to whole-brain radiotherapy has been shown to improve survival for patients with limited brain metastases. Finally, irradiation of all known metastases in some pediatric malignancies has improved outcomes, such as whole-lung radiotherapy in Ewing's sarcoma, which improved 4-year event-free survival from 40% to 19% ($P < .05$).[30]

For adult patients with metastases confined in number and extent, it remains unknown to what extent resection and/or ablation of metastases have an impact on overall or progression-free survival. Aggressive resection of pulmonary,[31] hepatic,[32] adrenal,[33] and intracranial[34] metastases have been associated with long-term disease control for select patients. Additionally, analyses restricted to patients with breast cancer,[35,36] CRC,[37] and melanoma[38] have shown improved outcomes for those who underwent metastasectomy versus those who did not.

RADICAL IRRADIATION FOR OLIGOMETASTASES

A single or few focal, precise, high doses of radiation have been associated with high rates of irradiated tumor control. The use of stereotactic technologies, developed decades ago as ablative treatment for intracranial targets, has been extrapolated to body radiotherapy. These techniques, termed SBRT or stereotactic ablative radiation (SABR), but perhaps best described as hypofractionated image-guided radiotherapy (HIGRT), have become widely studied for the treatment of limited metastases. The unifying principles of these treatments are precise patient positioning and immobilization, accurate targeting, respiratory motion analysis and management, high dose per treatment, and steep dose gradients between tumors and surrounding normal tissues (Fig 1).[39] Various commercial systems are available that facilitate SBRT/SABR/HIGRT delivery. Although most outcomes reports involve the use of fractionation schedules of ≤ five treatments and apply the terms SBRT or SABR to describe the approach, many studies have reported highly favorable outcomes after slightly longer schedules of six to 10 fractions, still completing the entire course in a much shorter timeline than a conventional 6- to 8-week schedule of treatment.[40,41]

Appropriate treatment planning for radical irradiation of metastases usually includes minimal margin for microscopic spread beyond known radiographic or metabolic metastatic borders, although this may not apply to spinal metastases[42] or some cases of lymph node involvement.[43] The amount of respiratory-induced motion should be determined at time of radiation treatment planning. Additionally, techniques such as breath hold, respiratory gating, tumor tracking, or fiducial markers should be used to minimize margin for respiratory motion, and known organ tolerances should be respected.[44,45]

The optimal radiation fraction size and fraction number for oligometastatic tumor control and normal tissue tolerance are unknown for any given clinical situation and are likely affected by innumerable variables. When using a three-fraction regimen, doses > 54 Gy are associated with higher rates of tumor control for

lung and liver metastases.[46] However, when larger metastases are irradiated, a lower dose per fraction and higher number of fractions are likely warranted.[47]

Early SBRT reports focused on treating primary and metastatic tumors in specific organs as a means of implementing and refining treatment techniques. High treated metastasis control (TMC) rates (as opposed to local control, which inherently refers to primary tumors) were reported after SBRT for adrenal,[48-54] hepatic,[55-59] pulmonary,[60-63] spinal,[64-66] and abdominal metastases[43,67-73] (Table 1). Most toxicity was low grade, although rare significant toxicity was seen in patients with hepatic failure[79] or with tumors in close proximity to the spinal cord.[80] Although often reported in these studies, heterogeneous patient populations, presence of untreated metastases, and different radiation dose or fractionation schedules made interpretation of survival data difficult.

The next generation of studies restricted inclusion to limited metastases[1-6] and required irradiation of all metastases[20,41,81] (Table 2). Despite slightly different inclusion criteria and radiation doses,

Table 1. Selected Studies of SBRT Used to Treat Metastases in Many Different Organs

Study	Year	No. of Patients	Median Follow-Up (months)	Total Dose (Gy)	No. of Doses	TMC (%)	OS (%)
Pulmonary metastases							
Chinese Academy of Medical Sciences (Beijing, China)[63]	2011	71	24.7	30-60	2-12	3 years: 75.4	3 years: 40.8
University Hospital S. Giovanni Battista di Torino (Torino, Italy)[62]	2012	61	20.4	26-45	1-4	2 years: 89	2 years: 66.5
Kyoto University Graduate School of Medicine (Kyoto, Japan)[60]	2008	34	27	48-60	4-5	2 years: 90	2 years: 84.3
Multi-institutional (United States)[74]	2009	38	15.4	48-60	3	2 years: 96	2 years: 39
University of Rochester (Rochester, NY)[61]	2006	30	18.7	50-55	10	3 years: 91	2 years: 38
University of Heidelberg (Heidelberg, Germany)[74a]	2002	61	14	12-30	1	1 year: 59	1 year: 78
Hepatic metastases							
University of Rochester (Rochester, NY)[56]	2007	69		50	10	1 year: 76	14 months: 50
University of Toronto Princess Margaret Hospital (Toronto, Ontario, Canada)[57]	2009	68		27.7-60*	6	1 year: 71	18 months: 47
Multi-institutional phase I/II study (United States)[58]	2009	47		36-60	3	2 years: 92	2 years: 30
Multi-institutional pooled analysis (United States)[55]	2011	65	14.4	22-60; median, 42	1-6	1 year: 67	1 year: 72
Multi-institutional pooled analysis (United States)[59]	2013	153	Mean, 25.2	Variable	Variable	1 year: 62	1 year: 52
Adrenal metastases							
University of Rochester (Rochester, NY)[53]	2009	30 (14 with definitive RT)	9.8	40	10	1 year: 55	1 year: 44
Hokkaido University (Sapporo, Japan)[51]	2008	9	16	48	8	1 year: 100	1 year: 78
University of Florence (Florence, Italy)[50]	2011	48	16	36	3	1 year: 90	1 year: 40
University of Pittsburgh (Pittsburgh, PA)[49]	2011	7	14	16, one RT fraction; 27, three RT fractions	1 or 3	1 year: 63	NS
RWTH Aachen University (Aachen, Germany)[52]	2011	13	21	20-40	5	1 year: 77	Median, 23 months
Humanitas Cancer Center (Milan, Italy)/University of Turin (Turin, Italy)[54]	2012	34	41	32	4	1 year: 66	2 years: 53
University of Chicago (Chicago, IL)[48]	2013	10	15	24-50	3-10	1 year: 73	1 year: 90
Spinal metastases							
MD Anderson Cancer Center (Houston, TX)[65]	2012	149	16	27-30	3	1 year: 80.5	1 year: 72
Memorial Sloan-Kettering Cancer Center (New York, NY)[66]	2008	93		18-24	1	1 year: 90	
University of Pittsburgh (Pittsburgh, PA)[75]	2007	393	21	12.5-25	1	Crude, 88-90	NS
University of California San Francisco (San Francisco, CA)[76]	2007	38	8.5	7-30	1-5	1 year: 85	Median, 18 months
Henry Ford Hospital (Detroit, MI)[77]	2003	10	6	6-8*	1	NS	NS
Stanford University (Stanford, CA)[78]	2007	72	9	16-25	1-5	NS	1 year: 46

Abbreviations: NS, not stated; OS, overall survival; RT, radiotherapy; RWTH, Rheinisch-Westfaelische Technische Hochschule; SBRT, stereotactic body radiation therapy; TMC, treated metastasis control.
*All treatments delivered after prior radiation therapy of 25 Gy in 10 fractions.

Table 2. Selected Studies of Oligometastatic Patients Treated With Irradiation of All Known Metastases

Study	No. of Patients	No. of Metastases per Patient		Dose (Gy)		Follow-Up (months)		Metastasis Control (%)	OS (%)	Toxicity Grade ≥ 3 (%)
		Median	Range	Total	No. of Fractions	Median	Range			
Mt Sinai (New York, NY)[82]	21	1	1-5	40-60	10	10	2-18	1 year: 85	1 year: 75	NA
University of Rochester (Rochester, NY)[41]	121	2	1-5	50	10	85	55-125*	2 years: 67	4 years: 28	1†
University of Chicago (Chicago, IL)[20]	61	2	1-5	24-48	3	21	3-61	2 years: 53	2 years: 57	10†
Vrije University (Brussels, Belgium)[83]	309	2	1-5	40-50	10	12	1-84	2 years: 33	3 years: 32	NS

Abbreviations: NA, not applicable; NS, not stated; OS, overall survival.
*Surviving patients with breast cancer.
†Crude rate.

these studies had many important unifying findings. First, SBRT could be delivered simultaneously to multiple organs, with acceptable toxicity and promising TMC. Second, in each of these studies, there was a subset of patients rendered alive and free of disease (18% to 44%) with longer than 18-month follow-up. Those with fewer metastases and/or lower bulk of disease burden had better outcomes compared with those with more metastases. Finally, patterns of progression of these patients were most commonly in only a few locations. In fact, many patients (approximately 25% to 30%) were able to receive a second course of SBRT or other metastasis-directed therapy.[21]

Many issues regarding appropriate dose-fractionation schedules for irradiation of multiple oligometastases are still unresolved, particularly for tumors abutting critical normal tissues (ie, centrally located thoracic structures, GI visceral organs, and/or spinal cord). Although reports of SBRT for head and neck reirradiation are emerging,[84-87] there are few data about the use of SBRT for metastases to the head and neck region.[20,88] Care should be taken, given the potential to cause brachial plexopathy.[89] Although some radiotherapy schedules commonly used to treat oligometastases are safe to treat the mediastinum and central lung tumors,[40,90] others are not.[91] Volume design and dose selection for abdominal targets must take sensitivity of the stomach, small intestine, and liver into consideration.[20,79,92,93] Finally, when using single fractions to treat spinal metastases, doses should be kept ≤ 20 Gy to avoid treatment-related vertebral body compression fracture.[94]

These challenges are magnified when metastases in are in close proximity to one another such that the radiation-dose contribution from multiple different targets results in a relatively large volume of high dose to the surrounding normal tissues. Multi-institutional cooperative group studies are using different approaches to satisfy these goals. In the ongoing SABR Comet study, a risk-adapted schema is being used.[95] NRG BR001, however, will treat patients with two to four breast, NSCLC, or prostate metastases, with accepted doses determined by metastatic location. If toxicity occurs, doses will be de-escalated.

HOW HAS RADICAL IRRADIATION BEEN INTEGRATED INTO THE TREATMENT OF SPECIFIC DISEASES?

The next evolution of oligometastasis irradiation studies are those reporting the outcomes of patients with specific malignancies radically irradiated at all known metastases. Prospective phase II studies of patients with NSCLC[96] and CRC[93] have been completed, with other disease-specific investigations ongoing or planned. The remaining data from retrospective single-institution studies show similar trends, with high rates of TMC and patients rendered free of disease long after the completion of radiotherapy (Table 3). They also show differences in survival and disease-free survival based on varying inclusion criteria. Some have questioned if the promising outcomes are the result of underlying tumor biology that would have been present regardless of intervention in oligometastatic patients.[111] The studies described here, as well as ongoing studies, will help to elucidate the utility of radical metastasis-directed intervention for these patients.

NSCLC

Reported series of patients with oligometastatic NSCLC continue to describe a proportion of patients who are disease free long after the completion of SBRT to all known metastases. Median survival in these series is either on par or only slightly worse than that of stage III NSCLC at 14 to 28 months, and 2-year survival in these series ranges from 14% to 38%.[96,99,100,112] A recent systematic review of oligometastatic NSCLC including approximately 1,300 patients with a controlled primary tumor found that median progression-free survival was 12 months, and overall survival was approximately 19 months.[113] Two randomized studies have been attempted, one trying to determine the role of SBRT integrated into a standard chemotherapy regimen (NCT00887315) and another testing the role of consolidative SBRT to remaining sites after chemotherapy (NCT00776100). Both of these studies had difficulties accruing and were closed. Given increasing interest, additional studies are ongoing (NCT01185639, NCT01725165) or being planned.

A developing role for radical irradiation is integrated into the course of therapy for patients with epidermal growth factor receptor (*EGFR*) +, anaplastic lymphoma kinase (*ALK*) +, and other oncogene-driven diseases. Recent studies have shown that 49% of patients treated with EGFR or ALK inhibitors experience progression in ≤ four metastases, characteristic of oligoprogressive disease, wherein patients receiving systemic therapy are maintaining clinical benefit in all but a few sites that manifest resistant clones. In this setting, ablation of all metastases via SBRT or other aggressive local therapy can eradicate metastases resistant to systemic therapy, allowing for continued delivery of a systemic agent providing clinical benefit elsewhere. In patients with primarily ALK-positive oligoprogressive NSCLC, the addition of ablative therapy to all metastases resulted in continued crizotinib administration for a median duration of 28 months compared with 10.8 months in those not receiving

Table 3. Selected Studies of Oligometastatic Patients With Specific Diseases Treated at All Known Metastases

Study	No. of Patients	No. of Metastases per Patient		Dose (Gy)		Follow-Up (months)		Metastasis Control (%)	OS (%)	Toxicity Grade ≥ 3 (%)
		Median	Range	Total	No. of Fractions	Median	Range			
Colorectal cancer										
Aarhus University (Aarhus, Denmark)[93]	64	2	1-6	45	3	52	2-76	2 years: 86	4 years: 13	Crude, 55
Erasmus University (Rotterdam, the Netherlands)[97]	20	1	1-3	37.5-45	3	26	6-57	2 years: 74	2 years: 83	Crude, 10
Multi-institution pooled analysis (United States/Canada)[55]	65	1	1-4	22-60	1-6	14	4-62	1 year: 67	1 year: 72	Crude, 6
Korea Cancer Center Hospital (Seoul, Korea)[98]	13	1	1-3	39-51	3	28	15-57	3 years: 53	3 years: 65	0
NSCLC										
University of Rochester (Rochester, NY)[99]	38		1-8	50-60	5-10	13.5	1-87	NR	5 years: 14	NR
University Medical Centre Maastricht (Maastricht, the Netherlands)[96]			1-5						3 years: 17.5	
University of Chicago (Chicago, IL)[100]	25	2	1-5	24-50	3-10	14		1.5 years: 71	1.5 years: 53	NR
Rush University (Chicago, IL)[101]			1-2		Variable	17		NR	2 years: 40	Crude, 17
Breast cancer										
University of Rochester (Rochester, NY)[102]	40	2	1-4	40-60	10	NR		4 years: 89	4 years: 59	NR
Prostate cancer										
Ludwig-Maximilian University (Munich, Germany)[103]	44	1	1-2	20	1	14	3-48	1 year: 96	1.5 years: 75	0
University of Milan (Milan, Italy)[104]	19	1	1	33-36	3	17	3-35	100	NR	8
University of Firenze (Firenze, Italy)[105]	25	NS		30	3	29	14-48	3 years: 90	3 years: 92	0
RCC										
University of Chicago (Chicago, IL)[106]	18	2	1-7	24-48 and 50	3 and 10	21		2 years: 91	2 years: 85	0
University of Colorado (Aurora, CO)[107]	13	2	1-3	40-50 and 42-60	5 and 3	28	4-68	1.5 years: 88*	1.5 year: 60†	Crude, 7
Methodist Hospital (Houston, TX)[108]	14	NS		24-40	3-6	9		Crude, 87	NR	0
Karolinska Institutet (Karolinska, Sweden)[109]	50		1-4	32-45	4-5	37	7-80	Crude, 90	2 years: 60†	Crude, 33†
Melanoma										
University of Colorado (Aurora, CO)[107]	17	2	1-3	40-50 and 42-60	5 and 3	28	4-68	1.5 years: 88*	1.5 years: 60†	Crude, 7
Sarcoma										
University of Rochester (Rochester, NY)[110]	14	4	1-16	50	10	11	4-88	3 years: 82	2 years: 45†	0

Abbreviations: NR, not reported; NSCLC, non–small-cell lung cancer; OS, overall survival; RCC, renal cell carcinoma.
*Melanoma and RCC.
†Approximate.

ablative metastasis-directed therapy.[114,115] The single-arm phase II ATOM study (NCT01941654) is investigating if locally ablative therapy will improve 1-year progression-free survival in patients with a partial response to EGFR therapy and ≤ four positron emission tomography (PET) –avid sites of residual disease.

Extensive-Stage Small-Cell Lung Cancer

The irradiation of subclinical brain metastases, prophylactic cranial irradiation, improves survival for patients with extensive-stage small-cell lung cancer (ESCLC) responding to systemic therapy.[116] Additionally, irradiation to the chest in patients with ESCLC with a complete response to initial chemotherapy improved 5-year survival (9%) versus those who received only further chemotherapy (3.7%; $P = .041$).[117] For patients with ESCLC with more extensive metastases, a phase I/II study exploring the integration of hemi-body irradiation with standard systemic therapy had long-term survivors and promising 5-year overall survival of 16%,[118] although this came at the price of significant toxicity. On the basis of these results, the Radiation Therapy Oncology Group (RTOG) is conducting a randomized trial (RTOG 0937) investigating if prophylactic cranial irradiation (25 Gy in 2.5-Gy fractions), thoracic radiotherapy, and metastasis-directed radiotherapy (45 Gy in 3-Gy fractions) can improve 1-year survival compared with standard of care.[119]

Metastatic CRC

Promising outcomes with high rates of treated tumor control and survival are seen after irradiation of CRC metastastases,[93,98,120] which are similar to those seen fter surgical resection of hepatic,[121-126] pulmonary,[127] and other metastases.[128] The largest prospective study to date was a phase II study of 64 patients with one to six CRC metastases

treated with 45 Gy in three fractions.[93] The vast majority of patients (94%) had metastases to one organ, most (69%) with liver metastases. Median survival was 19 months, and 2-year overall survival was 38%. Other large analyses have reported similar 5-year survival of 28% to 29%,[129,130] despite including predominately nonhepatic, mostly lymph node metastases.

Studies assessing the role of SBRT in the overall management of oligometastatic CRC are ongoing. Most are investigating the integration of SBRT into the treatment of CRC hepatic metastases. These include the phase III RAS01 (Radiofrequency Ablation Versus Sterotactic Radiotherapy in Colorectal Liver Metastases) trial (NCT01233544), randomly assigning patients with one to four CRC liver metastases to either radiofrequency ablation or SBRT in the hope of determining which modality has the best local progression-free survival. Furthermore, in patients with limited hepatic CRC metastases, the integration of SBRT with systemic therapies including bevacizumab (NCT01569984) and low-dose irinotecan (NCT01847495) is ongoing.

The ORCHESTRA (A Randomized Multicenter Clinical Trial for Patients With Multi-Organ, Colorectal Cancer Metastases Comparing the Combination of Chemotherapy and Maximal Tumor Debulking Versus Chemotherapy Alone) study (NCT01792934) is looking to answer a more global question: Can ablative therapy to the majority of metastases improve overall survival in patients with CRC with multiorgan metastases. Patients with $\geq$ two CRC metastases and either more than three extrahepatic metastases, or $\geq$ one hepatic metastasis and positive para-aortal or celiac lymph nodes, or more than five hepatic metastases not limited to one lobe are being randomly assigned to maximal tumor debulking to at least 80% of known metastases with either SBRT, transarterial chemoembolization, surgery, radiofrequency ablation, or standard-of-care systemic therapy or systemic therapy alone.

Breast Cancer

The long natural history of some metastatic breast cancers, particularly those with bone-only metastases and those with hormonal responsive disease, as well as the radiosensitivity of breast cancer, may provide the ideal setting to demonstrate the utility of SBRT to prolong progression-free and overall survival when used to treat all known metastases. Many patients with oligometastatic breast cancer have been included in studies of irradiation of all known disease. When prospectively observed patients were analyzed, 4-year overall survival, progression-free survival, and TMC were 59%, 38%, and 89%, respectively. Single metastases (v two to five), smaller tumor volume, bone-only disease, and stable or regressing lesions before SBRT were associated with more favorable outcome.[102]

On the basis of these data, as well as promising data after surgical resection of all known breast cancer metastases,[35] the NRG (National Surgical Adjuvant Breast and Bowel Project, RTOG, and Gynecologic Oncology Group) is developing a phase II/III study (NRG BR-002) randomly assigning patients with one to two breast cancer metastases to ablative therapy (either surgery or irradiation) plus standard-of-care systemic therapy or standard-of-care systemic therapy alone (with radiotherapy reserved for palliation). The primary end point for the phase II study is improved progression-free survival, which, if seen, will roll over into the phase III trial with survival as its primary end point.

Renal Cell Cancer, Melanoma, and Sarcoma

Although renal cell cancer (RCC), sarcoma, and melanoma are often considered radioresistant, outcomes after SBRT in these patients are similar to those in patients with traditionally radiosensitive histologies.[107,110,131] This is likely because of the fact that these ablative doses of radiation act via different mechanisms than conventional radiotherapy, including endothelial cell damage[132,133] and immune mediation.[134] In patients with metastatic melanoma, recent studies have demonstrated that the cytotoxic T-lymphocyte antigen 4 (CTLA4) inhibitor ipilumumab and protein PD-1 inhibitors improve survival compared with standard chemotherapy.[135,136] Studies combining radical irradiation of metastases with ipilumimab (NCT01565837,[137] NCT01557114,[138] NCT01497808,[139] NCT01970527, and NCT01973608) and interleukin-2 (IL-2) are ongoing and will determine if any immune-mediated synergy exists regarding treated metastases.

CAN IRRADIATION OF METASTASES ENHANCE IMMUNOTHERAPY?

There is marked interest in combining SBRT and systemic immune modulators. The effects of ablative-dose radiotherapy have been shown to be mediated via $CD8^+$ T cells[57] as well as type I interferon-dependent innate and adaptive immunities.[140] The potential for enhanced responses with exposure to immunomodulatory therapies has been seen with SBRT followed by high-dose IL-2 in patients with metastatic RCC and melanoma, which resulted in higher-than-expected response rates (71% v 16% with IL-2 monotherapy; $P = .05$).[141] Studies are ongoing in melanoma (NCT01416831) and RCC (NCT01896271) assessing the utility of SBRT combined with IL-2 and ipilumumab (NCT01497808).

Reports of radiation-induced abscopal effects (ie, immune-mediated effects on nonirradiated metastases) after administration of chemotherapy or ipilumumab have generated much interest.[142-145] Although preclinical work suggested that fractionated radiotherapy[146] would better induce abscopal effects, they have also been seen clinically after single-dose radiotherapy.[147] Response of untreated metastases after irradiation of melanoma metastases and administration of ipilumumab has been associated with antibodies to melanoma-associated antigen A3, PAS domain–containing protein 1, and the central portion and c-terminus of cancer/testis antigen 1 (also known as autoimmunogenic cancer/testis antigen NY-ESO-1).[147] These immunologic responses might be attributable to enhanced antigen presentation within the tumor or stroma from radiotherapy.[148]

HOW DO WE COMBINE RADICAL IRRADIATION OF EXTRACRANIAL OLIGOMETASTASES WITH SYSTEMIC THERAPY?

As metastasis-directed therapies are offered more often, practitioners wonder how to integrate them with standard systemic therapy regimens. It is unknown if these treatments should be delivered before systemic therapy, concurrently with systemic therapy, immediately after systemic therapy, or at time of progression if metastases are limited in number. It is likely that these decisions will have to be guided based on studies specific to the underlying disease. However, for nonselected oligometastatic patients, sunitinib 37.5 mg daily can be

safely combined with 50 Gy in 10 fractions in patients with one to five metastases.[81]

HOW COMMONLY IS SBRT BEING USED FOR THE TREATMENT OF EXTRACRANIAL OLIGOMETASTSES?

A recent international survey suggests that more than 60% of the more than 1,000 radiation oncologists who responded offer radical irradiation to their patients with limited metastatic disease.[149] The most common reason for offering these treatments was durable TMC in nonsurgical patients, considered to be on par with intensity-modulated radiation therapy, another recent technologic improvement in radiotherapy planning and delivery. These treatments were commonly offered in both academic and community settings, 98% of the time at centers also offering surgical resection of metastases. Furthermore, the use of SBRT for oligometastases is going to increase; most of those already offering this treatment indicated plans to increase their treatment volume in the near future, and among those not offering the treatment, 59% planned to start in the next 3 years.

HOW DO WE OBSERVE PATIENTS TREATED WITH RADICAL IRRADIATION OF OLIGOMETASTASES?

For oligometastatic patients treated with SBRT to all known metastases, there is no accepted follow-up schedule. Although short follow-up for acute toxicity determination is routine, it is unclear when and how to image patients. Studies completed to date have varied, with some performing routine whole-body metabolic imaging and others performing only axial imaging of treated locations. Given the propensity of metastases to progress in limited number and the possibility to treat newly detected metastases with another course of SBRT, combined anatomic and metabolic imaging (PET–computed tomography [CT]) may be the best option. In addition, PET-CT has the ability to determine response in osseous metastases not typically considered measureable on CT imaging.[150] Care should be taken when interpreting PET-CT; in one study, 38% of responses that initially appeared to be partial responses to initial therapy later proved to be complete responses.[150] Liver lesions take approximately 5 months to reach lowest maximum standardized uptake value and may fluctuate upward before lowering again.[151] Some have proposed a maximum standardized uptake value of 6 to determine hepatic treated metastasis progression.

HOW SHOULD PATIENTS BE SELECTED FOR RADICAL IRRADIATION OF OLIGOMETASTASES?

Patients with few metastases should be considered for aggressive radiotherapy if they have good performance status and all metastases can be safely targeted with radiotherapy. Those with one to two metastases have had more favorable outcomes with HIGRT,[20] although those with more metastases can be considered for ablative radiotherapy. All patient cases should be discussed with a multidisciplinary team. In addition to number of metastases, primary tumor histology should be taken into consideration, because small-cell lung cancer and Ewing's tumors,[20] nonadenocarcinomas,[83] and lung, ovarian, and noncolorectal GI cancers[58] have all been associated with worse outcomes after SBRT. Additionally, the timing of systemic therapy should be considered, because prior treatment with systemic therapy before SBRT has been associated with worse overall survival.[74] However, upfront treatment with SBRT may make reliable measure of radiographic response to systemic therapy difficult.

Some have attempted to build prognostic models to aid in patient selection. In one of the largest analyses published to date, male sex, nonadenocarcinoma histology, presence of intracranial metastases, and synchronous presentation of metastases were all associated with poorer outcomes. Patients with zero to two risk factors had median survival $>$ 23 months compared with those with three (9 months) or four risk factors (4 months).[83] These factors likely contribute to underlying biologic processes that some have suggested are associated with specific microRNAs.[152,153] All patients should be enrolled onto a clinical trial if they qualify.

FUTURE CONSIDERATIONS

The promising early data on radiotherapeutic treatment of oligometastatic patients need to be validated in ongoing and planned randomized studies to determine the true benefit (if any) that radiotherapy offers and which subsets of patients are most likely to derive this benefit. So long as equipoise exists, there is an opportunity to develop and conduct meaningful studies. These studies will be challenging to develop, because the technology and prescription of radiotherapy (ie, dose fractionation and definition of target volumes) differ across institutions, and they will be challenging to conduct, because vigilant quality assurance is required with such complex radiotherapy techniques. Translational end points will be critical to identify prognostic and predictive markers of clinical outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
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