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Clinical Investigation: Metastases

Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study

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Summary

This study analyzed outcomes among patients treated with SBRT for metastases limited in number and extent. Breast cancer patients fared best with 6-year overall survival and freedom from distant metastases of 47%, and 36%. Lower rates were seen for non-breast cancer patients. Worse survival was seen in those with a larger tumor burden or radiographic progression after prior systemic therapy. Select patients with limited metastases can, therefore, achieve long-term survival after treatment with SBRT.

Purpose: To analyze the long-term survival and tumor control outcomes after stereotactic body radiotherapy (SBRT) for metastases limited in number and extent.

Methods and Materials: We prospectively analyzed the long-term overall survival (OS) and cancer control outcomes of 121 patients with five or fewer clinically detectable metastases, from any primary site, metastatic to one to three organ sites, and treated with SBRT. Freedom from widespread distant metastasis (FFDM) was defined as metastatic disease not amenable to local therapy (*i.e.*, resection or SBRT). Prognostic variables were assessed using log−rank and Cox regression analyses.

Results: For breast cancer patients, the median follow-up was 4.5 years (7.1 years for 16 of 39 patients alive at the last follow-up visit). The 2-year OS, FFDM, and local control (LC) rate was 74%, 52%, and 87%, respectively. The 6-year OS, FFDM, and LC rate was 47%, 36%, and 87%, respectively. From the multivariate analyses, the variables of bone metastases ($p = .057$) and one vs. more than one metastasis ($p = .055$) were associated with a fourfold and threefold reduced hazard of death, respectively. None of the 17 bone lesions from breast cancer recurred after SBRT vs. 10 of 68 lesions from other organs that recurred ($p = .095$). For patients with nonbreast cancers, the median follow-up was 1.7 years (7.3 years for 7 of 82 patients alive at the last follow-up visit). The 2-year OS, FFDM, and LC rate was 39%, 28%, and 74%, respectively. The 6-year OS, FFDM, and LC rate was 9%, 13%, and 65%, respectively. For nonbreast cancers, a greater SBRT target volume was significantly adverse for OS ($p = .012$) and lesion LC ($p < .0001$). Patients whose metastatic lesions, before SBRT, demonstrated radiographic progression after systemic therapy experienced significantly worse OS compared with patients with stable or regressing disease.

Conclusions: Select patients with limited metastases treated with SBRT are long-term survivors. Future research should address the therapeutic benefit of SBRT for these patients.

Keywords: Oligometastases, Stereotactic body radiotherapy, Breast cancer, Metastases, Survival

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Introduction

Systemic therapy remains the standard of care for patients with metastatic disease. Patients presenting with newly diagnosed or recurrent metastatic disease, in which the radiographically apparent metastases are limited in number and extent, are also amenable to localized therapy directed at their metastases (1), including surgical resection, radiofrequency or cryoablation, and radiotherapy (2). Surgery (3, 4) and radiotherapy (4) for limited metastases have been practiced for many decades. Several studies have investigated surgical resection of liver metastases (2, 5), particularly from colorectal cancer (6–9); likewise, surgical resection of lung metastases (2, 10, 11), particularly from sarcoma (12, 13), has been well-studied.

In 1995, Hellman and Weichselbaum (14) coined the term "oligometastases" to describe a less-advanced state of metastatic disease, amenable to potentially curable local therapy (1). In the 1990s, radiation planning and delivery technology were burgeoning, with the development of three-dimensional planning systems allowing more conformal radiation delivery. Hellman and Weichselbaum (14) noted that these technologies allow for an "increase in the tumor dose and a reduction in normal tissue toxicity by restricting as much as possible the radiation to the accurately imaged tumor while avoiding critical normal tissues." Since that 1995 editorial, more novel technologies have become readily available, including intensity-modulated radiotherapy, enabling more conformal dose delivery by beam modulation and inverse planning (15), four-dimensional planning and/or respiratory gating, accounting for respiratory motion during treatment; image-guided radiotherapy, allowing for greater targeting accuracy with daily image guidance (16); and stereotactic body radiotherapy (SBRT) (17–19). SBRT implies the use of a three-dimensional frame of reference, such as internal fiducials, external markers, three-dimensional imaging, or surface imaging, to more accurately localize the target and allow for hypofractionated (large dose per fraction) radiation delivery.

These technologic advances have resulted in a greater comfort level in treating patients with oligometastatic disease, because they allow for target dose escalation (thus maximizing potential tumor control), while minimizing normal tissue exposure (minimizing the toxicity risks). Several institutions, including ours (20–24), have published prospective outcomes data from patients treated with curative-intent radiotherapy (25–28) for limited metastases to the lung (24, 29, 30), liver (20, 31–33), and other organ sites (25–28). Several studies have prospectively enrolled patients with metastases to more than one organ site (21–23, 34–38).

We previously published the survival (21) and tumor control (22) outcomes of 121 patients with five or fewer radiographically apparent metastases from any primary site, metastatic to any organ, treated with SBRT with curative intent. We reported a 2- and 4-year overall survival (OS) rate of 50% and 28% and a 2- and 4-year progression-free survival (PFS) rate of 26% and 20%, respectively. Statistically significant favorable prognostic factors included a smaller net gross tumor volume (GTV) and metastatic disease from breast cancer. In a separate analysis of patients with breast cancer (23), the 4-year OS and PFS rate was 59% and 38%, respectively, with one metastatic lesion (vs. two to five), a smaller GTV, bone-only disease, and stable or regressing lesions before SBRT associated with more favorable outcomes on univariate analysis (although not significant on multivariate analysis). The present study analyzed the survival and tumor control outcomes for these same patients, with $\leq$4 years' additional follow-up.

Methods and Materials

Between February 2001 and December 2006, 121 patients with one to five radiographically apparent metastatic lesions were enrolled in one of two prospective University of Rochester pilot studies using SBRT to treat limited oligometastatic disease (21, 23). The University of Rochester Research subjects review board approved both studies, and all patients provided written informed consent. The eligibility requirements included age $\geq$18 years, Karnofsky performance status $\geq$70, and one to five extracranial metastases. Five patients (each with fewer than five total metastases) also had brain metastases (seven lesions among 5 patients) treated with single-fraction radiosurgery. The patients who experienced local failure after SBRT in one or more sites, or who developed additional metastatic disease, were allowed to undergo additional courses of SBRT (39). The net GTV represented the sum of each lesion's GTVs according to the contoured volumes on the planning computed tomography scan. The net GTV was calculated at SBRT planning; thus, previously resected metastases were not included in the net GTV. Likewise, changes in the tumor volume resulting from previous systemic therapy were not accounted for.

SBRT technique

The SBRT technique has been discussed in greater detail in previous publications (20, 24, 40) and briefly summarized here. During initial simulation and with all treatments, the patients were immobilized with a vacuum cushion, and the treatment setup was reproduced using a relaxed end-expiratory breath hold technique and the Novalis ExacTrac patient positioning platform (BrainLAB AG, Heimstetten, Germany). Treatment planning was performed using the BrainSCAN system (BrainLAB AG). The PTV was generated with a minimal GTV expansion of 10 mm in the craniocaudal direction and 7 mm in other directions. The PTV was covered by the 80% isodose line. SBRT was delivered using conformal arcs or multiple fixed coplanar beams, shaped with multileaf collimators. The dose per fraction and total dose were determined using the dose–volume histogram of the organs at risk, with a preferred schedule of 50 Gy in 5-Gy fractions, as detailed in a previous study (22). Most (72%) of the 286 nonbrain lesions were treated with 10-fraction SBRT schedules; 5-Gy fractions were used in 74% of the 10-fraction schedules. The required normal tissue dose–volume constraints have been reported in previous publications (20, 24, 41).

Endpoints

Widespread distant metastases are defined as distant progression not amenable to resection or locally ablative therapy (*i.e.*, SBRT, stereotactic radiosurgery, radiofrequency ablation, embolization). The freedom from widespread distant metastasis (FFDM) and OS rates were calculated using Kaplan-Meier actuarial survival

analyses. OS was defined from the date of enrollment until death or the last follow-up visit, and FFDM was defined from the date of enrollment until death, an event (widespread distant progression), or the last radiographic study. Lesion local failure was scored as an event if any treated lesion increased by ≥20%, using the Response Evaluation Criteria In Solid Tumors criteria (42), or local failure was confirmed pathologically. Stata, version 9.2 (StataCorp, College Station, TX), was used for all data analysis.

Results

Patient characteristics

The patient and tumor characteristics are summarized in Table 1, with the patients grouped by primary breast cancer vs. primary cancer other than breast cancer (nonbreast cancer). The breast cancer patients were significantly younger (mean age 53 vs. 61 years, $p = .001$), significantly more likely to be treated for bone metastases (28% vs. 5%, $p = .0003$), and less likely to be treated for lung metastases (28% vs. 48%, $p = .044$). The number of lesions treated was not significantly different between groups when analyzed as a continuous ($p = .16$) or discrete (one vs. more than one lesions, $p = .20$) variable. The net tumor GTV was nonsignificantly ($p = .58$) less in the breast cancer patient group (median 23 vs. 30 cm^3).

Our previous publications described in great detail the timing of a metastatic diagnosis relative to the primary cancer diagnosis and SBRT and previous therapies (local and/or systemic) for metastatic disease (21, 23). The patients were generally referred for SBRT (*1*) if they were not candidates for, or declined, systemic therapy; (*2*) for disease progression after receiving systemic therapy; (*3*) after experiencing a clinical response or stable disease after systemic therapy (and therefore referred for consolidation SBRT); (*4*) for local therapy of new limited metastases (in conjunction with systemic therapy starting just before or after SBRT); or (*5*) for growing metastases occurring >6 months after completing systemic therapy (Table 1). The breast cancer patients were significantly ($p = .007$) more likely to have received systemic therapy for metastatic disease.

Toxicity of SBRT

No patient experienced Grade 4−5 toxicity, and only 1 patient experienced Grade 3 toxicity of nonmalignant pleural and pericardial effusion, as described previously (21). No additional toxicity was reported in the subsequent follow-up period.

Follow-up duration

For breast cancer patients, follow-up ranged from 0.6 to 10.4 years (median 4.5). Among the patients alive at the last follow-up visit, the duration ranged from 4.6 to 10.4 years (median 7.1). For the patients who died, survival ranged from 0.6 to 7.3 years (median 2.3). For nonbreast cancer patients, follow-up ranged from 0.3 to 8.9 years (median 1.7). Among patients alive at the last follow-up visit, the duration ranged from 6.8 to 8.9 years (median 7.3). For patients who died, survival ranged from 0.3 to 5.8 years (median 1.5).

Survival outcomes

For all patients, the 2-, 4-, and 6-year OS rate was 50%, 28%, and 20% and the 2-, 4-, and 6-year FFDM rate was 35%, 26%, and 21%, respectively. Because of the significant discrepancy in OS ($p < .00001$) and FFDM ($p = .0012$) between the breast cancer patients and nonbreast cancer patients, the survival outcomes for the breast cancer patients were analyzed separately from those with nonbreast cancers. Fig. 1 summarizes the OS and FFDM of the patients. The breast cancer patients had a 2-, 4-, and 6-year OS rate of 74%, 54%, and 47% and a 2-, 4-, and 6-year FFDM rate of 52%, 43%, and 36%, respectively, with 31, 22, and 14 patients at risk at 2, 4, and 6 years, respectively. The nonbreast cancer patients had a 2-, 4-, and 6-year OS rate of 39%, 16%, and 9% and 2-, 4-, and 6-year FFDM rate of 28%, 17%, and 13%, respectively, with 36, 14, and 8 patients at risk at 2, 4, and 6 years, respectively.

For the 11 breast cancer patients who before SBRT experienced progression of lesions after systemic therapy vs. the 16 patients who experienced stable or regressing disease, the 2-year OS rate was 55% vs. 81% ($p = .033$) and the 2-year FFDM rate was 23% vs. 60% ($p = .079$). For the 20 nonbreast cancer patients who before SBRT experienced the progression of lesions after systemic therapy vs. the 20 patients who experienced stable or regressing disease, the 2-year OS rate was 15% vs. 55% ($p = .0001$) and the 2-year FFDM rate was 12% vs. 37% ($p = .041$), respectively. The hypothesis-generating univariate and multivariate analyses of other potential prognostic factors for OS and FFDM are listed in Table 2. For breast cancer patients, the variables of bone metastases and one (vs. more than one) metastasis were associated with a fourfold and threefold reduced hazard of death, respectively, albeit of only borderline significance ($p > .05$ but $p < .06$), and were associated with threefold and greater than twofold reduced risk of developing widespread distant metastases, although with $p \geq .1$. The GTV was not significant. For nonbreast cancers, only the net GTV was significant for OS. The Supplemental Table shows the characteristics of the long-term (>4-year) survivors. Although most (57%) long-term breast cancer survivors had 1 initial metastatic lesion, most (62%) long-term survivors with nonbreast cancers had two to three initial metastatic lesions. All 6 patients with nonbreast cancers who died >4 years after SBRT had developed local failure 1.5−4.5 years (median 2.1) after initial SBRT. In 4 patients, local failure preceded distant failure, and in 2, distant failure and local failure were diagnosed concurrently. In contrast, none of the breast cancer patients who died 4 years after SBRT had developed local failure (and all but 1 died of distant failure). Two long-term breast cancer survivors had local failure that was successfully salvaged with surgery or SBRT.

Lesion local control

As with the survival outcomes, lesion local control (LC) of breast cancer patients was analyzed separately from other patients because of the significant ($p = .0005$) difference in LC between these two groups. The breast cancer patients had a 2-, 4-, and 6-year lesion LC rate of 87%; the nonbreast cancer patients had a 2-, 4-, and 6-year lesion LC rate of 74%, 68%, and 65%, respectively. Fig. 2 summarize the lesion LC of the patients. The hypothesis-generating univariate and multivariate

Table 1 Patient characteristics at initial presentation of oligometastatic disease

Characteristic	All patients	Breast cancer patients	Nonbreast cancer patients	*p*
Patients (*n*)	121	39	82	
Age (y)				0.001*,†
Range	34–88	34–83	41–88	
Mean ± SD	58 ± 12	53 ± 14	61 ± 11	
Median	60	52	60	
Primary cancer				
Breast	39 (32)	39 (100)	0	NA
Colorectal	31 (26)	0	31 (38)	
Lung, head/neck, esophagus	23 (19)‡	0	23 (28)	
Other	28 (23)§	0	28 (34)	
Primary histologic type				NA
Adenocarcinoma	89 (74)	39 (100)	50 (61)	
Squamous cell carcinoma	7 (6)	0	7 (9)	
Sarcoma	7 (6)¶	0	7 (9)	
Other	18 (15)¶	0	18 (22)	
Initial sites involved with oligometastatic disease				
Lung	50 (41)	11 (28)	39 (48)	0.044
Thoracic lymph nodes‖	24 (20)	9 (23)	15 (18)	0.54
Liver	54 (45)	13 (33)	41 (50)	0.085
Pelvis/abdomen	6 (5)	2 (5)	4 (5)	0.95
Brain	5 (4)	1 (3)	4 (5)	0.55
Bone	15 (12)	11 (28)	4 (5)	0.0003*,†
Initial oligometastatic lesions (*n*)				0.16*,†
1	37 (31)	15 (38)	22 (27)	0.20
2	32 (26)	12 (31)	20 (24)	
3	28 (23)	6 (15)	22 (27)	
4–5	24 (20)	6 (15)	18 (22)	
Initial involved organs (*n*)				0.33*
1	92 (76)	32 (82)	60 (73)	
2–3	29 (24)	7 (18)	22 (27)	
Sum of GTVs (cm^3)				0.58*
Range	0.3–422	1–402	0.3–422	
Mean ± SD	52 ± 75	47 ± 73	55 ± 76	
Median	28	23	30	
Reason for referral for SBRT				
Not candidates for/declined systemic therapy	26 (21)	2 (5)	21 (26)**	0.007†
Disease progression after systemic therapy	31 (26)	11 (28)	20 (24)	0.65
Consolidation after response or stable disease from systemic therapy	36 (30)	16 (41)	20 (24)	0.062
New limited metastases (systemic therapy just before or after SBRT)	23 (19)	9 (23)	14 (17)	0.43
Growing metastases >6 mo after systemic therapy	8 (7)	1 (3)	7 (9)	0.22

Abbreviations: NA = not applicable; SD = standard deviation; GTV = gross tumor volume.
Data in parentheses are percentages.

* Two-tailed *t* test; all others, chi-square test.

† Statistically significant.

‡ Non–small-cell lung cancer ($n = 17$), esophageal cancer ($n = 2$), head-and-neck cancer ($n = 2$), and small-cell lung cancer ($n = 1$).

§ Other primary cancers/histologic types included sarcoma ($n = 7$), pancreas ($n = 4$), hepatocellular ($n = 3$), carcinoid ($n = 3$), urinary bladder ($n = 3$), renal ($n = 3$), adrenocortical ($n = 1$), ovarian ($n = 1$), endometrial ($n = 1$), endocervical ($n = 1$), and melanoma ($n = 1$).

¶ Sarcoma subtypes included leiomyosarcoma ($n = 3$) and high-grade undifferentiated, synovial cell, spindle cell, and Ewing's sarcoma ($n = 1$ each).

‖ Of 24 patients, 17 had lung and thoracic lymph node metastases; thus, 47% had thoracic metastases.

** Primary sites/histologic features for which metastases were not treated with systemic therapy included lung ($n = 4$), hepatocellular ($n = 3$), colorectal ($n = 3$), head and neck ($n = 2$), esophagus ($n = 2$), sarcoma ($n = 2$), neuroendocrine ($n = 1$), melanoma ($n = 1$), pancreatic ($n = 1$), renal ($n = 1$), and adrenocortical ($n = 1$).

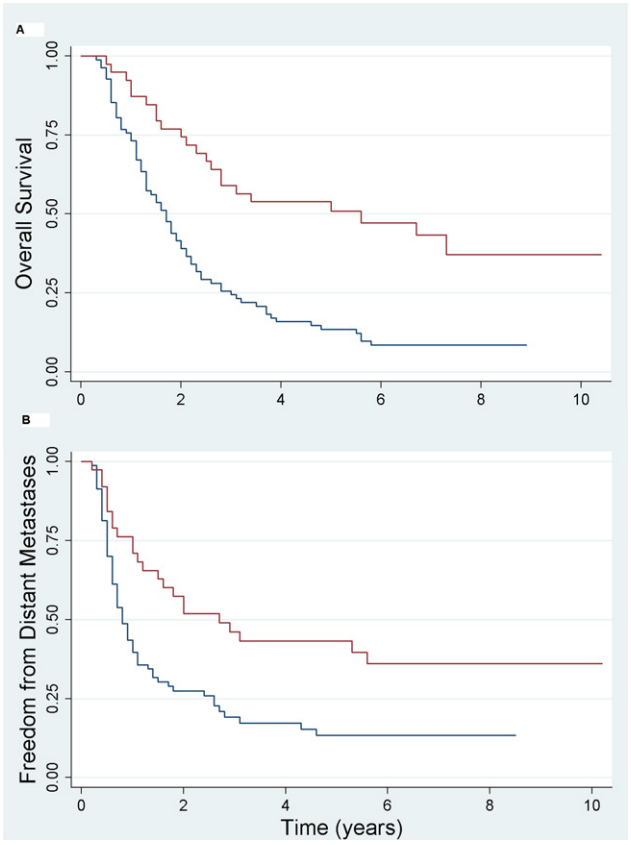

Fig. 1. Kaplan-Meier actuarial (A) overall survival and (B) freedom from distant progression for breast cancer (red line) and nonbreast cancer (blue line) patients. A color version of this figure is available at www.redjournals.com.

analyses of potential prognostic factors for lesion LC are listed in Table 3. For breast cancer patients, none of 17 bone lesions recurred after SBRT vs. 10 of 68 lesions from other organ sites that recurred ($p = .095$). The GTV was not a significant factor ($p = .13$) and remained nonsignificant ($p = .17$) even if the bone metastases, which tend to be larger than the liver or thoracic metastases (22), were omitted from the analysis. For the nonbreast cancer patients, the GTV proved to be highly significant ($p < .0001$) for lesion LC. On univariate analysis, the variables of a primary site of colon/rectum, lung, head and neck, or esophagus and sarcoma and metastatic lung and liver sites were of borderline significant for tumor control but were not significant on multivariate analysis.

Discussion

In our prospective study of 121 patients with five or fewer metastases treated with SBRT, we demonstrated that roughly one-third of patients experience long-term (>4-year) survival, specifically ~1 of 2 patients with breast cancer (vs. ~1 of 6 of patients with cancer from other primary sites). Furthermore, one-third of the breast cancer patients were alive at the last follow-up visit (>4–10 years) without widespread metastatic disease. Also, 38% of breast cancer patients and 62% of nonbreast cancer patients, living >4 years, underwent additional local therapy (SBRT or surgery) for local failure and/or salvage for new oligometastatic lesions, suggestive of the chronic nature of oligometastatic disease (39). Nonbreast cancer patients with a lower volume disease burden fared significantly better in terms of OS and lesion LC; however, the tumor burden was not significant for breast cancer patients. The lack of discernable effect of the GTV on breast cancer patient outcomes might be related to a different tumor biology. Patients whose metastatic lesions, before SBRT, had demonstrated radiographic progression after systemic therapy fared significantly worse than patients with stable or regressing disease. This was previously reported for our patients with breast cancer (23) but not for cancers from other primary sites.

Overall survival

Our reported 2-year survival of 50% is similar to the 56% reported by Salama *et al.* (34) from the University of Chicago, whose patient population was similar in terms of the number of lesions and number of organs involved, although our study included more patients with thoracic (47% vs. 32%) and/or liver (45% vs. 16%) metastases. In the present study, we also reported a 4- and 6-year OS rate of 28% and 20%, respectively.

Although local therapy such as SBRT undoubtedly prevents or delays tumor progression of treated metastatic lesions in most patients, the survival benefit of such an approach has not been clearly ascertained from well-designed prospective randomized studies of SBRT, surgery, or other modalities. It is evident that local therapy improves control of the treated tumors. For non–small-cell lung cancer, two studies have demonstrated that among patients treated with chemotherapy alone, roughly two-thirds did not develop new metastases (43, 44). Arguably, these patients would benefit from local therapy in terms of delaying progression, estimated to be about 3 months (44). Prolonged OS after local therapy for non–small-cell lung cancer oligometastases might also be achievable, although only 2 (12%) of 17 non–small-cell lung cancer patients in our study survived >5 years. In a retrospective study from our group, the 5-year survival rate of 38 patients with limited metastases from non–small-cell lung cancer was 14% (45). The University of Chicago (available from: www.clinicaltrials.gov/ct2/show/NCT00887315) and North Central Cancer Trialists Group (available from: www.clinicaltrials.gov/ct2/show/NCT00776100) randomized patients with one to five metastases from non–small-cell lung cancer, receiving platinum-based chemotherapy, to receive or not receive radiotherapy (50 Gy in 5-Gy fractions for the University of Chicago study and 60 Gy in 2-Gy fractions for North Central Cancer Trialists Group study). Although the estimated benefit from non–small-cell lung cancer might prove to be modest, for relatively more indolent cancers, such as breast cancer, the anticipated benefit might be years. Both the Radiation Therapy Oncology Group and the Southwest Oncology Group are developing prospective protocols for breast cancer patients with oligometastases.

With the lack of randomized data or large cooperative group studies, one could assert that the benefit of local therapy is dubious and that the patients fared well because they were a select group with more indolent disease. Certainly, these patients were selected because of a small number of radiographically detected metastases and tumor bulk amenable to SBRT. The observation by us, and others (46–48), of better outcomes in patients with a lower disease burden (GTV) was not

Table 2 Univariate and multivariate analyses of prognostic factors for overall survival and freedom from distant progression

	Breast cancer		Nonbreast cancer	
Variable	OS	FFDM	OS	FFDM
Age (y) (UVA Cox)	0.80	0.95	0.17	0.83
Primary cancer (UVA log rank)				
Colorectal, *p*	NA	NA	0.74	0.44
Lung, head/neck, esophagus, *p*	NA	NA	0.23	0.56
Primary histologic type (UVA log rank)				
Adenocarcinoma, *p*	NA	NA	0.89	0.42
Squamous cell carcinoma, *p*	NA	NA	0.22	0.37
Sarcoma, *p*	NA	NA	0.91	0.19
Sites involved with oligometastatic disease (UVA log rank)				
Lung, *p*	0.21	0.45	0.99	0.57
Thoracic lymph nodes, *p*	0.53	0.45	0.73	0.80
Liver, *p*	0.17	0.024*	0.79	0.31
MVA *p*		0.84		
Bone, *p*	0.019†	0.029†	0.96	0.49
MVA				
p	0.057	0.10		
HR	0.24	0.34		
95% CI	0.05−1.04	0.09−1.23		
Oligometastatic lesions 1 vs. >1				
UVA (Cox), *p*	0.004†	0.010†	0.38	0.91
MVA				
p	0.055	0.12		
HR	0.32	0.44		
95% CI	0.10−1.02	0.15−1.26		
Involved organs (1 vs. 2−3)				
UVA (log rank), *p*	0.032†	0.016†	0.60	0.51
MVA		0.32		
p	0.19			
HR	0.51			
95% CI	0.18−1.41			
Sum of GTV (cm^3)				
UVA (Cox), *p*	0.23	0.081	0.012	0.23
UVA HR (95% CI)		0.72	1.04 (1.009−1.07)/10 cm^3	

Abbreviations: OS = overall survival; FFDM = freedom from distant metastasis; UVA = univariate analysis; NA = not applicable; MVA = multivariate analysis; HR = hazard ratio; CI = confidence interval.

Variables with $p < .1$ from UVAs were analyzed in MVA model using Cox proportional hazards modeling; HRs and 95% CIs shown for variables with $p < .2$ on MVA.

* Characteristic associated with greater risk on UVA.

† Characteristic associated with lower risk on UVA.

unexpected, because that has been demonstrated for patients with metastatic disease not treated with local therapy (49) and for nonmetastatic patients (50−54). Justifiably, the notion of metastatic disease existing along a disease spectrum, as described by Hellman and Weichselbaum (14), is not a hypothesis, but merely an observation, not only from studies such as ours and others, but also from the clinical experience of patients with metastatic disease far outliving expectations. For example, we previously showed that the OS of patients with oligometastatic non−small-cell lung cancer, including patients with limited metastases to any organs, exceeds that of unselected Stage III non−small-cell lung cancer patients treated with curative-intent radiotherapy or chemoradiotherapy (45). Thus, oligometastatic patients do represent a unique cohort compared with most patients with metastatic disease (1); thus, perhaps the TNM stage grouping should incorporate oligometastatic disease as a subclassification of Stage III disease. Host-related factors (*e.g.*, immune-mediated anticancer activity) and tumor-related factors (*i.e.*, genomics and proteomics) likely affect the spectrum of disease aggressiveness. The relevant potentially practice-changing hypothesis-driven question is whether patients with limited metastases benefit from local therapy and whether this benefit is also related to specific host and tumor factors.

Even if one were to hypothesize that local therapy does not prolong these patients' OS, a lack of PFS benefit resulting from local therapy would be unexpected; surgery and radiotherapy provide local tumor control, and not all patients rapidly progress with new metastatic disease. However, a PFS benefit arguably should translate into an OS benefit, in which case, perhaps the relevant question is not whether a benefit exists from local therapy for oligometastases, but rather which patients are likely to derive such a benefit. Understanding the aforementioned tumor- and

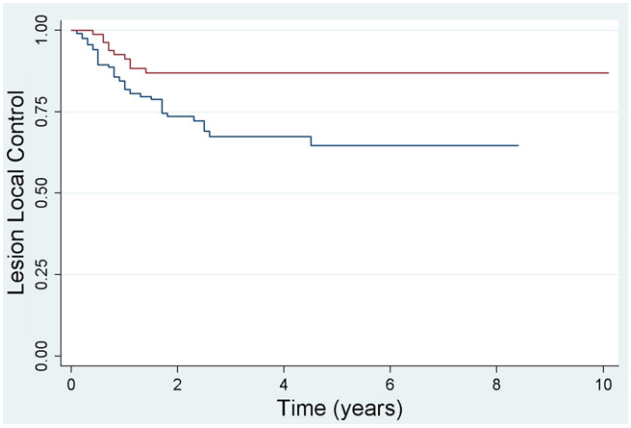

Fig. 2. Kaplan-Meier actuarial lesion local control for breast cancer (red line) and nonbreast cancer (blue line) patients. A color version of this figure is available at www.redjournals.com.

host-related factors might provide insight into this question. A recently published analysis of breast cancer patients from our study, demonstrating an OS and PFS benefit associated with radiation-induced antibreast cancer antibody formation and granuloctye-macrophage colony-stimulating factor and γ-interferon production, is suggestive of an immune-related host response (55). Formenti *et al*. (56, 57) have demonstrated tumor reduction in unirradiated tumors in patients for whom one tumor (of three or more) was irradiated. Certainly, our understanding of a possible host response remains superficial.

The strengths of our study included the large numbers of patients with lengthy follow-up, allowing investigation of clinically relevant patient- and tumor-related variables. The weaknesses include the diverse population, in terms of primary site, histologic features, and metastatic sites, and patients with metastases to more than one organ. Although we chose not to restrict the patient population to a specific patient subset to allow for greater patient accrual, specific patient cohorts (*i.e.*, breast cancer patients, colorectal cancer patients, patients with lung-only metastases, patients with liver-only metastases) represent smaller subgroups. Another weakness is the relatively lower biologically effective dose used for most of our patients compared with other studies. When the University of Rochester opened their studies in 2001, 5-Gy fractions delivered to body organs was novel, and doses >5 Gy were just beginning to be investigated. Although fractional doses >10−20 Gy have proved to be relatively safe using technologies such as SBRT and image-guided radiotherapy (41), we opted against using such doses (with unknown toxicity at the time) in patients with metastatic disease, whose benefit from SBRT was unknown. We expect improved tumor control from regimens with greater fractional doses (46), perhaps attributable to the novel radiation-biologic mechanisms occurring at supra-threshold doses (41, 58), or perhaps simply because of the greater dose delivery; this could potentially result in even improved OS.

Table 3 Univariate and multivariate analyses of prognostic factors for lesion local control

Variable	Breast cancer (n = 85 lesions)	Nonbreast cancer
Primary cancer		
Colorectal		
UVA (log rank)	NA	.085*,†
MVA p		.37
Lung, head/neck, esophagus		
UVA (log rank)	NA	.091*,‡
MVA		
p		.083
HR		0.38
95% CI		0.12−1.13
Sarcoma		
UVA (log rank)	NA	.071*,‡
MVA p		.21
Primary histologic type (UVA log rank)		
Adenocarcinoma	NA	.45
Squamous cell carcinoma	NA	.19
Sites involved with oligometastatic disease		
Lung		
UVA (log rank)	.84	.077*,‡
MVA p		.93
Thoracic lymph nodes		
UVA (log rank)	.13	.86
Liver		
UVA (log rank)	.61	.018*,†
MVA p		.89
Bone		
UVA (log rank)	.095†,§	.51
MVA p		
MVA HR (95% CI)		
GTV	.13	<.0001†
p		<.0001†
HR		1.11
95% CI		1.06−1.15/10 cm^3

Abbreviations: GTV = gross tumor volume; other abbreviations as in Table 2.

Variables with $p < .1$ from UVAs were analyzed in MVA model using Cox proportional hazards modeling; with MVA restricted to only $p < .05$, GTV remained significant ($p < .0001$), and liver metastases was associated with nonsignificant ($p = 0.12$) HR of 1.63 (95% CI 0.89−3.00).

HRs and 95% CIs shown for variables with $p < .2$ on MVA.

* Tumor characteristic associated with higher risk of local recurrence on UVA.

† Statistically significant.

‡ Tumor characteristic associated with lower risk of local recurrence on UVA.

§ None of 17 bone lesions recurred vs. 10 of 68 lesions from other sites; too few events prohibited Cox regression analysis.

Conclusions

We have shown promising long-term survival outcomes after SBRT for limited metastases, particularly in women with oligometastatic breast cancer. Future studies should address (*1*) what, if any, benefit SBRT (and other local therapies) offer for patients with limited metastases; (*2*) which patients are most likely to derive a benefit from SBRT (or other local therapies); (*3*) what are the optimal radiation dose-fractionation schemes in terms of efficacy and toxicity; and (*4*) what radiobiologic mechanisms are relevant in the treatment of the targeted tumor, as well as remote disease sites.

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