

A Prospective Pilot Study of Curative-intent Stereotactic Body Radiation Therapy in Patients With 5 or Fewer Oligometastatic Lesions

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BACKGROUND. It is hypothesized that oligometastatic disease represents a state of potentially curable, limited metastases. Stereotactic body radiation therapy (SBRT) is an option for patients who are not amenable to or do not want resection.

METHODS. From 2001 to 2006, 121 patients with ≤ 5 detectable metastases were enrolled in 2 prospective studies that used curative-intent SBRT. Most patients were treated with 10 fractions of 5 Gray. Stereotactic radiosurgery was offered to patients with brain metastases.

RESULTS. The 2-year overall survival (OS), progression-free survival (PFS), local control (LC), and distant control (DC) rates were 50%, 26%, 67%, and 34%, respectively; and the respective 4-year rates values were 28%, 20%, 60%, and 25%. A greater net tumor volume predicted significantly worse OS, PFS, LC, and DC. Patients with breast cancer fared significantly better with respect to OS, PFS, LC, and DC; and patients with adrenal metastases had significantly worse OS, PFS, and DC despite the small number of such patients enrolled. Neither the number of metastatic lesions nor the number of organs involved was a significant predictor of outcome. Among 45 patients who remained alive at the last follow-up, 29 patients had no evidence of disease, including 23 patients with ≥ 2 years of follow-up.

CONCLUSIONS. Oligometastatic disease is a potentially curable state of distant cancer spread. In this hypothesis-generating analysis, patients with less volume burden of their metastatic disease and those with primary breast cancer fared better. SBRT delivered with curative intent in patients with limited metastases should be investigated further. The Southwest Oncology Group is developing a prospective protocol to treat women who have limited breast cancer metastases with SBRT. *Cancer* 2008;112:650-8. © 2007 American Cancer Society.

KEYWORDS: disease burden, local control, oligometastases, stereotactic body radiation.

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum.¹ They hypothesized that, in some patients with a limited number of clinically detectable metastatic tumors, the extent of disease exists in a transitional state between localized and widespread systemic disease. In this model, oligometastatic disease has the potential of progressing to widespread metastatic disease. Thus, local control (LC) of oligometastases may yield improved systemic control.^{1,2} An alternative hypothesis is that oligometastatic disease represents a clinical manifestation of few detectable lesions in the setting of widespread occult disease. Such a model argues that local therapy alone

probably would not be curative. Arguably, both models may be correct, and patients may exist in a spectrum between orderly metastatic progression and widespread occult disease, a model that also has been proposed for primary cancer spread.^{1,3}

It has been proposed that progressive growth of oligometastatic tumors beyond a threshold size results in an exponential rise in the risk of further metastatic progression.⁴ In the absence of micrometastatic disease or in the situation in which micrometastatic disease is controlled by systemic therapy, aggressive treatment of oligometastatic disease can be considered curative-intent therapy, as evidenced by the prolonged disease-free survival observed in patients with resected oligometastatic tumors.^{1,5-10} Radiotherapy is another means with which to control oligometastatic tumors, particularly in patients who cannot tolerate or do not want surgery or when tumors are situated in areas in which resection would result in unacceptable morbidity. Several institutions use hypofractionated stereotactic body radiotherapy (SBRT) to treat oligometastases.¹¹

SBRT implies the use of a 3-dimensional frame of reference to localize the tumor accurately. Because setup uncertainty and tumor movement are reduced significantly, the planning target volume (PTV) margins can be reduced compared with the PTV margins of standard conformal radiation.¹² Consequently, SBRT limits the radiation dose to normal tissues and allows delivery of higher doses per fraction. SBRT is well suited for oligometastatic disease, because aggressive fractionation can be used to attempt improved disease control with acceptable toxicity.^{11,13} The American Association of Physicists in Medicine (AAPM) Task Group 101 report will review the available SBRT commercial products and relevant literature on SBRT, outline guidelines for commissioning SBRT, and develop standard protocols for quality assurance and SBRT treatment planning and delivery.¹⁴ A systematic review and guidelines for intracranial stereotactic radiosurgery (SRS) are offered in the AAPM Task Group 42 report.¹⁵

Since 2001, the University of Rochester has used hypofractionated SBRT to treat patients with oligometastatic disease. The outcomes in patients who were treated for liver metastases¹⁶ and lung metastases¹⁷ have been published recently. In an earlier analysis of patients with metastatic prostate cancer, our group demonstrated that patients with ≤ 5 metastatic lesions fared significantly better than those with > 5 lesions.¹⁸ Thus, extrapolating from these data, our protocol was designed so that the treatment of patients with > 5 lesions was considered palliative. The focus of the current study was patients

who were treated with curative-intent SBRT for ≤ 5 metastatic lesions, and the objective of the study was to determine patient and tumor variables that predict a better outcome.

MATERIALS AND METHODS

Between February 2001 and December 2006, 160 patients were enrolled on 2 University of Rochester Cancer Center (URCC) pilot studies using SBRT to treat limited oligometastatic disease and to assess the feasibility and outcome of such an approach. URCC U8700 was designed specifically to treat patients with metastatic breast cancer without brain metastases, whereas URCC U9700 included patients with any primary cancer and any involved sites. Patients on URCC U9700 with limited brain metastases were offered SRS. Both studies were approved by the University of Rochester Research Subjects Review Board, and all patients signed informed consent.

Prior treatment of metastatic tumors (including radiation or surgery) did not exclude patients from the study unless the treating physician determined that radiation could not be delivered safely. Prior chemotherapy was allowed; in fact, most patients had received ≥ 1 courses of chemotherapy before they enrolled. Eligibility requirements included age ≥ 18 years and a Karnofsky performance status ≥ 70 .

All patients were assessed with a diagnostic body computed tomography (CT) scan to identify and discern metastatic lesions. For brain lesions, magnetic resonance imaging (MRI) was required for diagnostic and planning purposes. MRI was also used to assess liver metastases and bone metastases in some patients. Many patients underwent positron emission tomography (PET) scanning. Patients with bone metastases generally had a bone scan and/or PET scan in addition to CT scans.

No more than 5 lesions were treated in a single course of treatment. The treatment of ≤ 5 lesions in patients who presented with > 5 lesions was considered palliative. Patients who presented initially with > 5 clinically apparent, oligometastatic tumors may have received treatment to all of their lesions over ≥ 2 courses of treatment, but these patients were excluded from the current analysis, because they were treated with palliative intent.

The current study includes patients who were enrolled in either URCC U8700 or U9700 with ≤ 5 metastatic lesions at the time of enrollment who were treated with curative intent. In total, 121 of 160 enrolled patients are included in the current analysis. Patients who experienced local failure after SBRT in ≥ 1 sites or who developed further metastatic disease were allowed to receive additional courses of SBRT.

SBRT Technique

The technique of SBRT employed at the University of Rochester is discussed in detail in previous publications^{16,17,19} and is summarized briefly here. During the initial simulation and with all treatments, patients were immobilized with a vacuum bag, and treatment setup was reproduced by using a relaxed, end-expiratory breath-hold technique and the Novalis ExacTrac patient-positioning platform (BrainLAB, AG, Heimstetten, Germany). Treatment planning was performed by using the BrainSCAN system (BrainLAB). The gross target volume (GTV) was contoured on axial CT images; MRI and PET scans, when available, were fused with the planning CT scan for more accurate delineation of the GTV. No margin was added for the clinical target volume. The PTV was generated with a minimum GTV expansion of 10 mm in the craniocaudal direction and 7 mm in other directions. We previously demonstrated that these margins allow for coverage of 2 to 3 standard deviations of motion.¹⁹

Treatment was prescribed to the 100% isodose line, with the 80% isodose line covering the PTV. SBRT was delivered by using conformal arcs or multiple, fixed, coplanar beams. The dose per fraction and total dose were determined by using the dose volume histogram of organs at risk with a preferred schedule of 50 Gray (Gy) in 5-Gy fractions over 2 weeks. The normal tissue constraints for the liver and lung are detailed in our previous publications.^{16,17} Concurrent chemotherapy with a nonanthracycline-containing regimen was permitted.

SRS Technique

Immobilization was achieved with a BrainLAB head frame attached to the patient's skull under local anesthesia. SRS was delivered with the Novalis linear accelerator, which was equipped with micromultileaf collimators, using 6-megavolt photons. A CT scan was obtained in the axial plane with the Novalis localizer frame in position. The GTV was defined based on MRI and CT images. A margin from 0 mm to 1 mm was added to the GTV to create the PTV. The prescribed isocenter dose was from 10 Gy to 20 Gy with the 80% isodose line covering the PTV. BrainLAB planning software was used to generate the treatment plan, which employed multiple arcs with fixed-shaped fields. The dose to the critical structures was evaluated carefully before finalizing the plan. Quality assurance was carried out as discussed in a prior publication.²⁰

Follow-up

Follow-up visits were planned 1 month after completing SBRT and every 3 months subsequently for

2 years. Thereafter, intervals ranged from 3 months to 6 months, based on physician preference. Patients underwent diagnostic imaging studies before all follow-up visits after the initial 1-month visit. Toxicity in patients was evaluated by using the Common Terminology Criteria for Adverse Events criteria (version 3.0).

Endpoints

Several time points were recorded for each patient, including the dates of primary cancer diagnosis, metastatic disease diagnosis, and first appearance of lesions treated on protocol. Overall survival (OS) and progression-free survival (PFS) were calculated by using Kaplan-Meier actuarial survival analyses, with survival and failure times defined from the day of enrollment until either an event or last follow-up. Local failure either was scored as an event if any treated lesion grew by $\geq 20\%$, based on the Response Evaluation Criteria In Solid Tumors criteria²¹ or was confirmed pathologically. Distant failure was scored as an event if a patient progressed with distant metastases beyond what could be treated with curative-intent (ie, ≥ 5 metastases or incurable disease). Progression was defined as local or distant failure. Significant ($P < .05$) variables on univariate analyses (UVA) were tested with multivariate analyses (MVA). MVA were performed by using a Cox proportional hazards regression model. Stata software was used for all data analysis (version 9.2).

The net GTV is the sum of GTVs based on the contoured volumes on the planning CT scan. Because the net GTV was assessed at the time of enrollment, previously resected metastases were not included in the net tumor volume; likewise, changes in the tumor volume resulting from prior systemic therapy were not accounted for. Tumor grade was not included in these analyses because of the different spectrum of primary cancers involved.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. One patient had brain-only disease. Nine patients had bone-only oligometastatic disease, and 8 of those patients had primary breast cancer. The primary site was controlled at the time of enrollment in all patients, with the following exceptions: Four patients with primary nonsmall cell lung cancer presented initially with multiple lesions (including thoracic lymph nodes in 2 patients); 3 patients with primary T1 nonsmall cell lung cancer presented initially with synchronous, metastatic disease (adrenal,

TABLE 1
Patient Characteristics at Initial Presentation of Oligometastatic Disease

Characteristic	No. of patients (%)
No. of patients	121 (100)
Age, y	
Median [range]	60 [34–88]
Mean \pm SD	58 \pm 12
Enrolling institution	
University of Rochester, Rochester, NY	111 (92)
M. D. Anderson Cancer Center, Orlando, Fla	10 (8)
Primary cancer	
Breast	39 (32)
Colorectal	31 (26)
Lung, head and neck, or esophagus	23 (19)
Pancreas, biliary tract, or liver	7 (6)
Sarcoma	7 (6)
Other	14 (12)*
Primary histology	
Adenocarcinoma	89 (74)
Squamous cell carcinoma	7 (6)
Sarcoma	7 (6) [†]
Hepatocellular carcinoma	3 (2)
Renal cell carcinoma	3 (2)
Carcinoid	3 (2)
Other	9 (7) [‡]
Previously had >5 metastatic lesions	21 (17)
Prior curative-intent local therapy	36 (30)
Resection	30
Radiofrequency ablation	4
Radiation therapy	3
Cranial stereotactic radiosurgery	3
Sites involved with oligometastatic disease	
Lung	50 (41)
Thoracic lymph nodes	24 (20)
Liver	54 (45)
Pelvic or abdominal lymph nodes	4 (3)
Brain	5 (4)
Adrenal glands	2 (2)
Bone	15 (12)
No. of oligometastatic lesions	
1	37 (31)
2	32 (26)
3	28 (23)
4	12 (10)
5	12 (10)
No. of involved organs	
1	92 (76)
2	25 (21)
3	4 (3)
Sum of GTVs, mL	
Median [range]	28 [0.3–422]
Mean \pm SD	52 \pm 75

SD indicates standard deviation; GTV, gross tumor volume.

* Other primary cancers included carcinoid (n = 3), urinary bladder (n = 3), renal (n = 3), adrenocortical, ovarian, endometrial, endocervical, and melanoma.

[†] Sarcoma subtypes included leiomyosarcoma (n = 3) and high-grade undifferentiated, synovial cell, spindle cell, and Ewing sarcoma.[‡] Other histologies included transitional cell carcinoma (n = 2), poorly differentiated nonsmall cell lung cancer (n = 2), large cell neuroendocrine carcinoma, small cell carcinoma, cystadenocarcinoma, and cortical carcinoma.

bone, and brain); and 2 patients presented with multiple liver lesions (carcinoid and hepatocellular carcinoma). The primary site(s) was treated in each of these patients with SBRT.

Thirty-five patients presented with metastatic disease during their initial diagnostic workup for cancer. Of these 35 patients, 27 presented with the lesions that were treated on the current protocol. For the remaining 8 patients, the interval between the initial diagnosis of metastatic disease to the appearance of the metastases treated on protocol was from 5 months to 91 months (median, 22 months). During the interval, all 8 patients received chemotherapy, and all 8 patients underwent at least 1 metastasectomy.

Eighty-six patients developed metastatic disease from 3 months to 136 months (median, 27 months) after their initial diagnosis of cancer. In 65 of these 86 patients, the lesions that were treated on the current protocol were evident at the time of proven metastases. For the remaining 21 patients, the interval between the initial diagnosis of metastatic disease and the development of the metastases treated on protocol was from 3 months to 56 months (median, 20 months). In this interval, all but 1 patient received curative-intent therapy for oligometastatic disease, including metastasectomy (n = 16 patients), radiofrequency ablation (n = 2 patients), fractionated radiation (n = 2 patients), and cranial stereotactic radiosurgery (n = 1 patient). One of these 21 patients was treated with whole-brain radiation for >5 brain metastases, which no longer were evident at the time of enrollment.

The time from the first appearance of the oligometastatic lesions treated on protocol to enrollment ranged from <1 month to 96 months (median, 7 months). Ninety-eight of the 121 patients received systemic therapy for metastatic disease before enrollment.

Thirty-six patients underwent curative-intent treatment for oligometastatic disease at some point before enrollment (see Table 1). Twenty-one patients were diagnosed with ≥ 5 metastases at some point before enrollment. These patients received systemic therapy and/or radiation, which ultimately resulted in ≤ 5 detectable metastases at the time of enrollment.

Toxicity of SBRT

No patient experienced grade 4 or 5 toxicity, and only 1 patient experienced grade 3 toxicity (described below). No patient experienced grade ≥ 2 fatigue or desquamation. The toxicity in patients who received SBRT for lung and mediastinal tumors was addressed

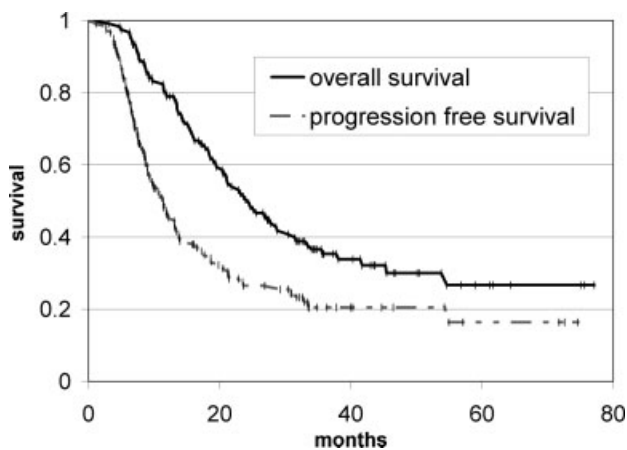


FIGURE 1. Kaplan-Meier actuarial overall survival and progression-free survival.

previously.¹⁷ The only grade 3 toxicity observed was a nonmalignant pleural and pericardial effusion. The toxicity in patients who received SBRT for liver metastases also was discussed previously.¹⁶ Among the 6 patients who were treated for adrenal metastases, pelvic lymph node metastases, or abdominal lymph node metastases, 2 patients experienced no discernable toxicity (excluding grade 1 fatigue and skin toxicity); toxicity included grade 1 vaginal bleeding that resolved ($n = 1$ patient), grade 2 diarrhea ($n = 1$ patient), grade 2 nausea ($n = 1$ patient), and grade 2 flank pain ($n = 1$ patient). Among the 15 patients who were treated for bone metastases, 11 patients experienced no discernable toxicity (excluding grade 1 fatigue and skin toxicity); toxicity included grade 1 nausea ($n = 1$ patient with sternal metastasis), grade 1 cough ($n = 1$ patient with sternal metastasis), grade 2 dysphagia ($n = 1$ patient with thoracic spine metastases), and grade 1 alopecia ($n = 1$ patient with a skull metastasis).

Outcome

One patient with a 397-mL liver metastasis progressed during radiation therapy and died shortly thereafter, and 35 patients had a documented local failure from 1 month to 54 months (median, 9 months) after the completion of SBRT. For these 36 patients, the median and mean net GTV was 36 mL and 80 mL, respectively, versus 26 mL and 40 mL for patients without a documented local failure ($P = .007$; 2-tailed t test). Among these 36 patients, 29 also developed distant failure, and 1 was not assessable for distant failure. In 20 patients, the distant failure was synchronous with local failure, 6 patients developed distant failure from 1 month to

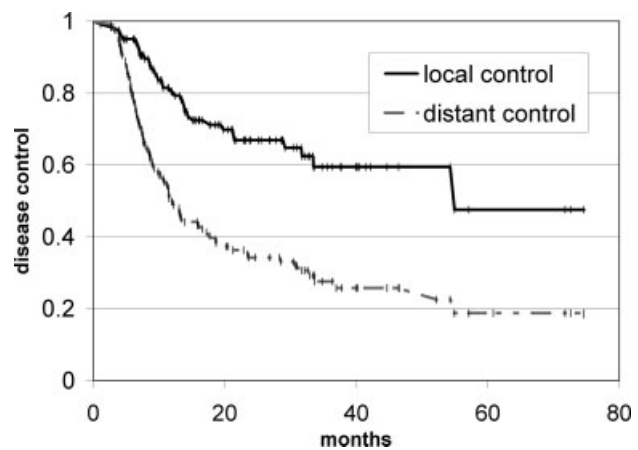


FIGURE 2. Kaplan-Meier actuarial local control and distant control.

19 months after local failure, and 3 patients had distant failure discovered from 1 month to 6 months before local failure. In addition to the patient who progressed during radiation, 2 patients died from local progression (1 with brain metastases and the other with liver metastases).

Among the patients who had local failure after SBRT, 11 patients underwent a second course of curative-intent treatment for their locally recurrent disease. Several patients were retreated with palliative-intent SBRT. Curative-intent salvage therapy included SBRT ($n = 5$ patients), resection ($n = 3$ patients), SRS ($n = 1$ patient), liver transplantation ($n = 1$ patient), and embolization ($n = 1$ patient). Three patients remained without evidence of active disease at 29 months, 47 months, and 62 months. In addition to the 6 patients who underwent attempted curative reirradiation, 25 patients received additional courses of SBRT for further oligometastatic disease.

The OS and PFS curves are depicted in Figure 1. The median survival (MS) was 24 months, and the median PFS was 11 months. The 2-year and 4-year OS rates were 50% and 28%, respectively, and the 2-year and 4-year PFS rates were 26% and 20%, respectively. The median PFS, which was calculated so that salvaged local failures were not considered events, was 12 months; and the 2-year and 4-year PFS rates were 31% and 21%, respectively. The LC and distant control (DC) curves are depicted in Figure 2. The 2-year and 4-year patient LC rates were 67% and 60%, respectively. The actuarial LC rates, which measured the control of individual lesions, were 77% and 73% at 2-years and 4-years, respectively. The 2-year and 4-year DC rates were 34% and 25%, respectively. Fifty-seven patients survived for ≥ 2 years, and 36 of those patients were alive at the last follow-up. Table 2 summarizes these patients' characteristics. Twenty-

TABLE 2
Characteristics of Long-term (≥ 2 Years) Survivors

Characteristic	No. of patients (%)	Characteristic	No. of patients (%)
Total no. of patients	57*	Previously had > 5 metastatic lesions	8 (14)
No. alive at last follow-up	36	Prior curative-intent local therapy	20 (35)
No. with no evidence of disease	23	Resection	17 (30)
Follow-up of living patients, mo		Radiofrequency ablation	2 (4)
Range	27–77	Radiation therapy	1 (2)
Median	41	Cranial stereotactic radiosurgery	0
Deceased, with survival ≥ 2 y	21	Sites involved with oligometastatic disease	
Survival, mo		Lung	23 (40)
Median [range]	29 [24–55]	Thoracic lymph nodes	11 (19)
Age, y		Liver	25 (44)
Median [range]	57 [35–85]	Pelvic or abdominal lymph nodes	2 (4)
Mean \pm SD	57 \pm 21	Brain	2 (4)
Primary cancer		Adrenal glands	0
Breast	23 (40)	Bone	7 (12)
Colorectal	15 (26)	No. of oligometastatic lesions	
Lung, head and neck, or esophagus	7 (12)	1	18 (32)
Pancreas, biliary tract, or liver	1 (2)	2	18 (32)
Sarcoma	4 (7)	3	11 (19)
Other	7 (12) [†]	4	5 (9)
Primary histology		5	5 (9)
Adenocarcinoma	45 (79)	No. of involved organs	
Squamous cell carcinoma	1 (2)	1	45 (79)
Sarcoma	4 (7) [‡]	2	11 (19)
Hepatocellular carcinoma	1 (2)	3	1 (2)
Renal cell carcinoma	2 (4)	Sum of GTVs, mL	
Carcinoid	2 (4)	Median [range]	19 [0.3–403]
Other	2 (4) [‡]	Mean \pm SD	38 \pm 64

SD indicates standard deviation; GTV, gross tumor volume.

* Nine patients remain alive, 6 without evidence of recurrent disease, with a follow-up <2 years (range, 7–17 months); they are not included in this table.

[†] Other primary cancers included carcinoid (n = 2), renal (n = 2), endometrial, endocervical, and adrenal cortical carcinoma.[‡] Sarcoma subtypes included leiomyosarcoma (n = 3) and Ewing sarcoma. The other histologies were large cell neuroendocrine and cortical carcinoma.

nine patients remained alive and free of detectable disease for from 7 months to 77 months (median, 36 months).

UVA and MVA

Tables 3 and 4 summarize UVA and MVA for measured outcomes of OS, PFS, DC, and LC. Calculating PFS so that salvaged local failures were not considered events did not affect which variables were significant. Neither the numbers of organs involved nor the numbers of oligometastatic lesions were significant for the measured outcomes. Patients who had primary breast cancer (vs other primary sites) had significantly improved OS, PFS, LC, and DC. On UVA, the MS was 20 months (vs not reached), and the 2-year and 4-year survival rates were 38% and 18%, respectively (vs 72% and 64%, respectively) in patients with breast cancer. On UVA and MVA, patients with primary pancreatic, biliary or hepatic cancer (vs other sites) had significantly worse survival and DC. Patients with adrenal metastases

experienced worse OS, PFS, and DC. On UVA, the MS was 5 versus 24 months, favoring patients without adrenal metastases. On MVA, the net GTV was significant for all measured outcomes.

Additional Analyses

MVA were rerun with the following time intervals as continuous variables: from the diagnosis of primary cancer to the diagnosis of metastatic disease, from the diagnosis of metastatic disease to the development of oligometastases treated on protocol, and from the development of oligometastases treated on protocol to enrollment. These were not significant for OS or PFS. Age was not significant on MVA for any measured outcome. On UVA for DC, the occurrence of local failure was not associated with a significantly decreased rate of DC ($P = .28$). However, on UVA for LC, the presence of distant failure was associated with worse LC ($P = .005$) and remained significant on MVA ($P = .040$). In other words, patients who fail distantly are not more likely to

TABLE 3
Univariate and Multivariate Analyses for Overall Survival

Variable	P	
	UVA	MVA
History of >5 metastases prior to enrollment	.42	
History of prior curative treatment for oligometastatic disease	.64	
No. of organs involved	.50	
No. of treated lesions	.43	
Primary cancer site*		
Colorectal	0.32	
Lung, head and neck, esophagus (no*)	.007 [†]	.75
Pancreas, liver, biliary tract (no*)	.011 [†]	.035 [†]
Breast (yes*)	<.0001 [†]	.002 [†]
Sarcoma	.48	
Histology*		
Adenocarcinoma (yes*)	0.017 [†]	.68
Squamous cell carcinoma (no*)	.012 [†]	.15
Hepatocellular carcinoma	.53	
Renal cell carcinoma	.35	
Sarcoma	.48	
Carcinoid	.33	
Treated sites*		
Lung	.25	
Thoracic lymph nodes	.58	
Liver	.99	
Abdominal/pelvic lymph nodes	.80	
Adrenal (no*)	<.00001 [†]	<.0001 [†]
Brain	.089	
Bone (no*)	.022 [†]	.34
Net GTV (smaller*)	‡	.006 [†]

UVA indicates univariate analysis; MVA, multivariate analysis; GTV, gross tumor volume.

* For variables that were significant on UVA, this characteristic was a favorable predictor for survival.

[†] Significant ($P < .05$).[‡] Because this was a continuous variable, it was not assessed in the UVA.

develop or to have developed local failure, whereas patients who fail locally are at a greater risk of failing distantly as well.

DISCUSSION

We previously published results on 69 patients with 174 oligometastatic liver lesions who were treated with SBRT.¹⁶ In that series, the 20-month LC rate of all treated lesions was 57%, and the MS was 14.5 months. We also previously published our results in 49 patients with 125 oligometastatic lung lesions who were treated with SBRT.¹⁷ In those patients, the 3-year LC rate of the treated tumors was 91%, and the 3-year LC rate of treated patients was 82.5%. In patients who had ≤ 5 lesions confined to the thorax, the MS was 23.4 months versus 12.4 months in patients who had extrathoracic disease and/or > 5 sites treated ($P < .05$). We also separately examined 18 patients who were treated for adrenal metastases.

TABLE 4
Univariate and Multivariate Analyses of Progression-Free Survival, Local Control, and Distant Control*

Variable	P					
	UVA			MVA		
	PFS	LC	DC	PFS	LC	DC
Primary cancer site [†]						
Pancreas, liver, biliary tract (no [†])	.024 [‡]	.038 [‡]	.007 [‡]	.050 [‡]	.073	.034 [‡]
Breast (yes [†])	.0009 [‡]	.027 [‡]	.0007 [‡]	.014 [‡]	.016 [‡]	.006 [‡]
Histology [†]						
Adenocarcinoma (yes) [†]	NS	NS	.031 [‡]	—	—	.99
Treated sites [†]						
Adrenal (no [†])	.003 [‡]	NS	.004 [‡]	.020 [‡]	—	.026 [‡]
Bone (yes [†])	.031 [‡]	NS	NS	.43	—	—
Brain (no [†])	.031 [‡]	NS	NS	.023 [‡]	—	—
Net GTV (smaller [†])	— [§]	— [§]	— [§]	.005 [‡]	<.0001 [‡]	0.026 [‡]

UVA indicates univariate analysis; MVA, multivariate analysis; PFS, progression-free survival; LC, local control; DC, distant control; NS, nonsignificant ($P > .1$); GTV, gross tumor volume.

* All variables listed in Table 3 were tested on UVA; Only variables that were significant on UVA are shown.

[†] For variables that were significant on UVA, this characteristic was a favorable predictor for survival.

No variable was a significantly adverse predictor for 1 outcome (PFS, LC, or DC) and a significantly favorable predictor for another.

[‡] Significant ($P > .05$).[§] Because this was a continuous variable, it was not assessed in the UVA.

ses.²² The crude LC rate in those patients was 85%, whereas nearly all patients suffered distant failure. The MS of the 12 patients in that series who were treated with curative intent (some of whom were treated concurrently for liver or lung lesions) was 7 months. The results from our current series suggest that patients with adrenal metastases fare significantly worse with respect to OS and PFS. However, because only 2 of 121 patients were treated for adrenal metastases in the current study, this finding must be interpreted with caution. Nevertheless, the poor outcome is consistent with our retrospective data. Patients with brain metastases also fared poorly with respect to PFS, albeit with small numbers of patients.

There have been several single-institutional series in which patients were treated for oligometastatic lung lesions or oligometastatic liver lesions with SBRT. These are described in detail elsewhere.^{11,13} In our prior reports and in others' series, toxicity was minimal.

The current report examines all patients who were enrolled in 2 pilot studies who initially presented with ≤ 5 metastatic lesions, regardless of which organs were involved. Currently, there are very few studies that address a similar patient population.

Rush University retrospectively studied 23 patients with nonsmall cell lung cancer who were treated aggressively for oligometastatic disease, which

the authors defined as 1 or 2 metastatic sites.²³ Surgery and/or radiation was used. Metastases were confined to 1 organ, and most patients ($n = 14$) had brain metastases. All but 3 patients had 1 metastatic site. Their MS was 20 months, and 5 patients remained alive beyond 3 years.

The University of Chicago is enrolling patients with from 1 to 5 oligometastases on a Phase I study with escalating doses from 30 Gy to 42 Gy over 3 fractions. In a preliminary analysis, treated lesions were controlled well.²⁴ Survival results from that study are pending.

In our current series, women with oligometastatic disease from primary breast cancer had a significantly better outcome versus other patients. We previously demonstrated that women with lung metastases from breast cancer fared better with respect to survival,¹⁷ and the current results confirmed this finding in a population of patients with oligometastatic disease to different sites. It is not known whether the improved outcome in women with oligometastatic breast cancer reflects a better response to radiation treatment or whether these findings are attributable to a better overall prognosis of metastatic breast cancer and more durable disease control with systemic therapy. We hypothesize that the availability of effective systemic therapy to control subclinical disease, combined with SBRT for clinically detectable disease, is the basis for this success. A recently open Southwest Oncology Group (SWOG) trial will study SBRT in women with oligometastatic breast cancer: Perhaps a larger cohort will help answer this question.

It is noteworthy that neither the number of organs involved nor the number of detectable oligometastatic lesions at enrollment significantly correlated with OS or PFS. Despite the possibility of being underpowered to detect such differences, the latter finding is consistent with our previous discovery that men with prostate cancer who have from 1 to 5 bony metastases fare equally well regardless of the number of metastases with which they present.¹⁸ In a study from the University of Pittsburgh in which 205 patients with ≥ 4 brain metastases underwent SRS, net treatment volume was significant for OS and LC, whereas the number of lesions (range, 4–18 lesions) was not significant.²⁵ Our current series also suggests that patients with a history of >5 metastases who present with ≤ 5 apparent metastases at the time of enrollment do not fare significantly worse in any measured outcome compared with patients who present initially with ≤ 5 metastases. We previously postulated that a complete or near-complete response to systemic therapy potentially may ‘downstage’

patients to an oligometastatic state by eradicating micrometastatic disease.¹⁷ Our current analysis suggests that systemic therapy also has the potential to ‘downstage’ patients with numerous clinically apparent metastases to an oligometastatic state.

It is particularly worth noting that, in our study, the net GTV was significant for OS, PFS, DC, and LC, consistent with the hypothesis that a larger tumor burden has a greater risk of local failure as well as increased metastatic potential. The net GTV in patients who experienced local failure was significantly greater than the net GTV in patients who did not experience local failure. Our data suggest that the risk of developing distant failure is not increased significantly by the occurrence of local failure, possibly reflecting the magnitude of patients who fail distantly despite LC. Distant failure is a competing risk with local failure, and, in some patients, the cancer will fail distantly before it has the opportunity to fail locally. Our data also suggest that patients who fail locally are more likely to fail distantly, suggesting the possibility of a greater risk of distant spread from local failure. An alternative explanation is that treatment-resistant tumors can synchronously fail locally and distantly. In the current study, only 3 patients died from local progression without distant progression, and 3 patients had successfully salvaged local failure without further disease progression. An interesting question, which we were unable to address in the current analysis, is whether or not a response to systemic therapy can improve outcome, not only by virtue of inherent sensitivity to treatment but also by virtue of reducing tumor bulk.

In summary, the results from our hypothesis-generating pilot study support the premise that aggressive local therapy of limited metastases can result in prolonged life. Conceivably, systemic therapy has the potential to downstage some patients to an oligometastatic stage, allowing for a chance for prolonged life or cure with aggressive local therapy. Arguably, our data suggest that patients with breast cancer have the greatest potential to derive benefit, providing a basis for the SWOG study mentioned above. Larger tumors may require a greater radiation dose to achieve more satisfactory LC rates. Different fractionation schemes, perhaps with a greater dose per fraction, also may help achieve improved LC, although risks of late toxicity must be considered carefully with more hypofractionated regimens, particularly with bulkier tumors. Certainly, further studies are needed to assess the impact of radiation therapy on patient survival, tumor control, and the

natural history of oligometastatic disease. We propose that the TNM metastasis staging system be expanded to incorporate an oligometastatic category, which would then allow and encourage more systematic testing of the oligometastatic hypothesis.

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