An Initial Report of a Radiation Dose-Escalation Trial in Patients with One to Five Sites of Metastatic Disease

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Abstract

Purpose: Previous investigations have suggested that a subset of patients with metastatic cancer in a limited number of organs may benefit from local treatment. We investigated whether cancer patients with limited sites of metastatic disease (oligometastasis) who failed standard therapies could be identified and safely treated at one to five known sites of low-volume disease with radiotherapy.

Experimental Design: Patients with one to five sites of metastatic cancer with a life expectancy of >3 months and good performance status received escalating doses of radiation to all known sites of cancer with hypofractionated radiation therapy. Patients were followed radiographically with computed tomography scans of the chest, abdomen, and pelvis and metabolically with [^{18}F]fluorodeoxyglucose-positron emission tomography 1 month following treatment and then every 3 months. Acute toxicities were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and late toxicities were scored using the Radiation Therapy Oncology Group late toxicity scoring system.

Results: Twenty-nine patients with 56 metastatic lesions were enrolled from November 2004 to March 2007, with a median follow-up of 14.9 months. Two patients experienced acute (radiation pneumonitis and nausea) and one experienced chronic (gastrointestinal hemorrhage) grade ≥ 3 toxicity. Fifty-nine percent of patients responded to protocol therapy. Twenty-one percent of patients have not progressed following protocol treatment. Fifty-seven percent of treated lesions have not progressed at last follow-up. Progression was amenable to further local therapy in 48% of patients.

Conclusions: Patients with low-volume metastatic cancer can be identified, safely treated, and may benefit from radiotherapy.

Metastasis is the leading cause of cancer death. Standard treatment regimens for most metastatic cancer patients consist of systemic cytotoxic chemotherapy, hormonal manipulation, and agents interacting with a broader range of targets than traditional chemotherapy (e.g., antibodies against specific receptors, antiangiogenic agents, and kinase inhibitors). How-

ever, with few exceptions, such as testis cancer (1) and hematologic malignancies (2, 3), the treatment of metastatic cancer by systemic agents is rarely curative and in many instances ineffective with short survival following treatment failures (4–9).

We previously proposed that during the evolution of some tumors, a clinical state of oligometastasis may exist when metastases are limited in number and/or in destination organs (10). A recent analysis of non–small cell lung cancer patients supported this hypothesis, revealing that 50% of non–small cell lung cancer patients had metastasis limited to three additional sites other than the primary tumor (11). Therefore, metastatic cancer is not always widespread, and there may be a role for local therapy in these patients. The role of local therapy for long-term disease control of oligometastases is supported by reports indicating that surgery may be curative for a percentage of patients with limited lung (12), liver (13), synchronous lung and liver (14), or adrenal metastasis (15). However, most patients who have several metastases to multiple organs have not generally been considered for curative surgical treatment. In addition, half of metastatic non–small cell lung cancer patients treated with systemic therapy do not progress or only suffer progression initially in previously involved sites (11). Potentially, local therapy may benefit these patients as well. Recently, improvements in radiotherapy

planning and delivery, termed stereotactic body radiotherapy or image-guided hypofractionated radiotherapy, allow the delivery of few tightly focused high radiation doses while sparing dose to adjacent normal organs. Phase I/II studies have shown potentially improved local control over conventional techniques in both primary tumors (16, 17) and metastasis in one (18) or two organs (19). However, although previous investigations have determined the maximally tolerated doses of hypofractionated stereotactic body radiotherapy to a single organ (16, 20), the application of this technique to multiple organs has not been prospectively tested. Therefore, we conducted a dose-escalation trial to determine the maximally tolerated dose of hypofractionated image-guided radiotherapy simultaneously to multiple organs. Additionally, we attempted to test the hypothesis that a simple set of clinical criteria, based on the number of lesions, tumor location, and performance status, could identify patients as having oligometastatic disease and that these patients could be safely treated to multiple organs with hypofractionated image-guided radiotherapy.

Materials and Methods

Patients were eligible for this trial if they had pathologically confirmed stage IV cancer of any histology with distant metastases. Additionally, patients were required to be 18 y or older, have a life expectancy of >3 mo, Eastern Cooperative Oncology Group performance status of ≤2, normal marrow and organ function, and no prior radiotherapy to involved tumor sites. Based on our prior report in metastatic lung cancer patients, we limited the number of metastasis to a maximum of five sites (11). Each individual lesion was restricted to a maximum tumor dimension of ≤10 cm or <500 cm^3 volume and had to be amenable to radiation therapy as seen on standard imaging (computed tomography, magnetic resonance imaging, positron emission tomography, or bone scan). Baseline computed tomography scans of the chest, abdomen, and pelvis as well as bone scan or preferably positron emission tomography scan were obtained no more than 1 mo before treatment. Other coexisting malignancies, uncontrolled intercurrent illness, active infectious processes, and exudative, bloody, or cytologically malignant effusions excluded patients from the trial. Additionally, patients were excluded from the trial if they were receiving any systemic chemotherapy during radiotherapy, although hormonal therapy was allowed. The trial was approved by the University of Chicago Institutional Review Board (Approval #13619B), and all patients signed Institutional Review Board–approved written informed consent before protocol therapy.

Radiotherapy planning was done using standard techniques including computed tomography simulation coordinated with the patient's respiratory cycle and aided by i.v. and oral contrast as needed. Tumors were contoured individually with no margin for microscopic extension using all available clinical, radiographic, and metabolic data. To account for set-up error between radiotherapy treatments, tumors were expanded 5 to 7 mm before radiotherapy planning. A variety of nonoverlapping axial fields and noncoplanar fields were combined to achieve the optimal radiation distribution around the tumors while minimizing radiation to surrounding noninvolved organs. Normal tissue tolerances were compounded from the available literature (18, 21, 22).

We assigned each metastatic lesion to one of five anatomic regions (lung, liver, abdominal, head and neck, and extremity) based on potential normal tissue complications. Within each anatomic region, three patients were assigned to each dose cohort. A standard 3 + 3 dose-escalation schema was used with cohorts escalated in 2 Gy increments. Each metastatic lesion received the same dose for each of the three treatments, but different lesions within the same patient could receive

different doses if they were in different anatomic regions. The starting dose for all sites was 24 Gy delivered in three 8 Gy fractions, and the protocol-specified maximum dose was 60 Gy in three 20 Gy fractions. Dose-limiting toxicity was defined as grade >3 nonhematologic toxicity (excluding nausea, vomiting, and alopecia) and grade 4 to 5 hematologic toxicity. Esophagitis and mucositis lasting >7 d were considered dose-limiting toxicities. The recommended phase II dose was defined as the dose at which fewer than two of six experienced dose-limiting toxicity.

Patients received three fractions of radiotherapy separated by a minimum of 48 h and a maximum of 192 h. At the discretion of the treating physician, patients treated to the abdomen or pelvis were prescribed antiemetic therapy before radiation delivery. Antianxiety and pain medications were frequently used to ensure patient comfort for the entirety of treatment. Following the completion of each radiation fraction, vital signs were monitored, and a complete physical examination was done.

Patients returned for follow-up every 2 wk for the first month, monthly for 3 mo, and then every 3 mo thereafter. At each follow-up, a complete history and physical examination was done. Acute toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0. Late toxicities were scored according to the Radiation Therapy Oncology Group late toxicity scoring system. Appropriate imaging studies (computed tomography scans of the chest, abdomen, and pelvis as well as [18F]fluorodeoxyglucose-positron emission tomography) were done 1 mo following the completion of treatment and then every 3 mo thereafter.

Table 1. Patient characteristics

	n	% (range)
No. patients evaluable	29	100
Primary sites (histology)*		
Lung		
Non–small cell lung cancer	6	20.7
Small cell lung cancer	2	6.9
Head and neck		
Squamous cell carcinoma	5	17.2
Breast		
Infiltrating ductal	3	10.3
Infiltrating lobular	1	3.4
Colon/rectum		
Adenocarcinoma	4	13.8
Renal		
Chromophobe	1	3.4
Clear cell	1	3.4
Papillary adenocarcinoma	1	3.4
Sarcoma extremity		
Malignant fibrous histiocytoma	3	10.3
Uterine		
Leiomyosarcoma	1	3.4
Ovary		
Papillary serous	1	3.4
No. metastatic lesions treated	56	100%
No. lung lesions	18	32%
No. liver lesions	9	16%
No. nodal lesions	13	23%
No. osseous lesions	9	16%
No. adrenal lesions	6	11%
No. soft tissue masses	1	2%
Mean no. sites per patients	2	(1-5)
No. exposed to systemic therapy before protocol radiotherapy	24	81%
Mean no. courses of systemic therapy	1.7	(0-9)
Mean no. systemic agents exposed to	2.5	(0-11)

*Numbers do not add to 100% due to rounding.

Table 2. Control of targeted tumors

Dose	Ultimate control of targeted tumors		Total
	Yes	No	
24 Gy	12 (39%)	19 (61%)	31
30 Gy	15 (79%)	4 (21%)	19
36 Gy	5 (83%)	1 (17%)	6
Total	32 (57%)	24 (43%)	56 (100%)

Each metastatic lesion was considered a target lesion and independently assessed for response. Initial response was defined at the time of first follow-up imaging usually 1 mo after the completion of radiotherapy. Axial unidimensional measurements were used to assess response per Response Evaluation Criteria in Solid Tumors criteria (21). A complete response was defined as the complete disappearance of the target lesion radiographically or metabolically (standardized uptake value = 0, if a positron emission tomography scan had been done before radiotherapy and the target lesion had previously been metabolically active). A partial response was defined as greater than a 30% reduction in the radiographic size of disease. Stable disease was defined as <30% reduction to 20% growth of tumor. Progression of disease was defined as >20% increase in size or intensity on clinical examination, or radiographic or metabolic imaging. Patterns of progression were determined by following all target and nontarget lesions (primary tumors as well as all metastatic sites) on all follow-up imaging studies.

Progression-free survival was calculated using the method of Kaplan and Meier (23). Cumulative patterns of progression were tabulated. Progression was classified as occurring within a radiated field, outside a radiated field but confined to previously identified sites of cancer, or progression in a previously uninvolved site. When analyzing patterns of progression, lymph node regions were considered one site of failure.

Results

Since the study began in November 2004, additional data about dosing at the lung and liver sites (16, 18) have become available, suggesting that significant changes in the original dosing schema need to be considered for patients with single metastases to the liver and lung. This interim report has thus been generated despite the fact that patient accrual continues. This report includes all the 29 enrolled patients (56 radiated lesions) with follow-up imaging through February 2008, with a median follow-up of 14.9 months (range, 5.3-27).

Patient characteristics, sites of initial disease presentation, histology, and sites of metastasis are detailed in Table 1. The median time to metastasis from initial diagnosis was 3 months (range, 0-299 months). The median time from diagnosis of metastasis to protocol enrollment was 11 months (range, 1-85 months). Twenty-four patients received systemic therapy before treatment on our protocol. The median time from completion of the last cycle of chemotherapy to enrollment was 3 months (range, 1-71 months). As shown in Table 1, most patients were treated with one line of systemic therapy consisting of two agents before enrollment. Five patients did not receive systemic therapy due to a known lack of response (three), patient perceived marginal benefit (one), and presentation with synchronous brain and lung metastases (one).

Toxicity. Acute toxicity was limited, with two patients experiencing acute grade ≥3 toxicity. In the lung cohort, one patient experienced a cough interfering with activities of daily living, and radiographic findings consistent with pneumonitis 2 months after the completion of radiotherapy, which improved on nonsteroidal anti-inflammatory medication. This was scored as grade 3 pneumonitis. In the liver cohort, one patient experienced grade 3 vomiting, which required hospital admission, and one patient experienced grade 2 transient transaminase elevation. In the extremity cohort, two patients experienced grade 2 desquamation (dry-patchy moist). Fatigue was common in all cohorts following treatment but did not interfere with activities of daily living.

Chronic toxicity has been limited. Three months following the completion of therapy, one patient in the lowest abdominal dose level (24 Gy in three 8 Gy fractions) with tumors adjacent to the small intestine experienced grade 3 gastrointestinal hemorrhage, which required blood transfusion and eventual laser photocoagulation. No other chronic complications were noted.

Dose escalation. The planned dose-escalation schedule is ongoing. The extremity cohort remains to be escalated, although two patients have been treated at 24 Gy without complication. The liver cohort has been escalated to 30 Gy. The lung cohort has been escalated to 42 Gy. The abdominal cohort has been escalated to 36 Gy. Due to competing protocols, no patients in the head and neck site have been accrued.

Initial response to treatment. The radiographic/metabolic response rate of the radiated lesions (complete response or partial response) treatment was 59% (33 of 56). Thirty-one tumors (55.4%) achieved a complete response, 2 (3.6%) achieved a partial response, 20 (35.7%) maintained stable disease, and 3 tumors (5.4%) progressed. The median duration of response in treated sites was 7.8 months (range, 1-25 months). At last follow-up, 57% (32 of 56) of treated tumors have not progressed. One tumor was salvaged with further local therapy for an ultimate local control rate of 59% (33 of 56). Control of targeted tumors as related to radiation dose is shown in Table 2.

Analyses of patterns of first progression are summarized in Table 3. Following protocol treatment, six patients (21%) with a median follow-up of 14.4 months (range, 10-28 months) have not shown disease progression. Twenty-three patients (79%) have experienced disease progression at a median of 4.4 months. In six patients (21%), first progression was only within treated tumors. Six patients (21%) progressed only in

Table 3. Patterns of first progression

Site of failure	*n* = 29
No progression after hypofractionated radiotherapy	6/29 (21%)
Progression in treated sites only	6/29 (21%)
Progression in treated sites and distant site with known cancer involvement	1/29 (3.5%)
Progression in distant sites	16/29 (55%)
Progression in sites not previously involved with cancer	8/29 (27.6%)
Progression in sites previously involved with cancer	6/29 (21%)
Progression in sites previously involved with cancer and in uninvolved sites	2/29 (7%)

Table 4. Analysis of progression

Cumulative no. sites of progression	All patients		Amenable to further local therapy	
	No. patients	%	No. patients	%
1	5	22	5	22
2	3	13	2	8.7
3	6	26	4	17
4	4	17	2	8.7
5	0	0	0	0
6	2	8.7	1	4.3
7	1	4.3	0	0
≥10	1	4.3	0	0
Total	23	79.3	14	48.3

sites known to have been involved with cancer and treated before protocol therapy and were controlled in the sites treated on protocol. One patient (3.5%) had disease progression noted both within a treated tumor and within a site previously involved with cancer. Eight patients (27.9%) were controlled within the treated tumor but progressed first in sites not known to have cancer.

Cumulative progression was not widespread as shown in Table 4. The median number of cumulative sites of progression was 2 (range, 1-10). Most patients with progressive disease experienced progression in a limited number of organs; five (22%) progressed in one site, three (13%) progressed in two sites, six (26%) progressed in three sites, and four (17%) progressed in four sites. At last follow-up, nine patients (31%) progressed only in organs known to be involved with cancer at the time of protocol enrollment. Progression-free survival by number of metastatic lesions is shown in Fig. 1. Progression in 14 patients (48%) was amenable to further local therapy (limited volume disease confined to limited organs).

Discussion

We tested the hypothesis that patients in a general hospital population with five or less metastasis in one or more organs could be identified using clinical criteria derived from our previous investigations and safely treated with hypofractionated image-guided radiotherapy. We found that patients tolerated the procedure with limited difficulty. Patients had promising response rates and durable (>6-month median) responses. Whereas other studies have reported dose-escalation studies for stereotactic body radiotherapy to one organ (16, 18) or standard doses to two organs (19), our study is unique in that patients with metastases in multiple different organs were included and treated safely.

Acute and chronic toxicity was limited. Only one patient experienced grade 3 pneumonitis and one patient experienced grade 3 nausea/vomiting. Currently, no predictor for radiation pneumonitis in hypofractionated image-guided radiotherapy patients is known (21), and plans for patients with lung lesions followed Radiation Therapy Oncology Group criteria. The patient with grade 3 nausea was prescribed antiemetics but failed to take this before treatment. Subsequently, patients with abdominal lesions have not been treated unless they have taken prescribed antiemetics. The grade 3 hemorrhage was observed in a patient treated to multiple involved lymph nodes about the duodenum. Subsequent to our observation of this toxicity,

other reports in the literature confirmed that the duodenum was a sensitive structure to radiation (22) and we have since avoided high-dose radiation to the small intestine. Alternative radiation fractionation schemes more tolerable to the duodenum should be explored for this anatomic region that may harbor limited metastasis.

To date, the overall irradiated tumor control rate is 57%. Increasing tumor control with higher radiation doses was seen as shown in Table 2. This suggests that the radiation doses used initially were too low. When we initiated our trial, limited data on hypofractionated image-guided radiotherapy doses to sites outside the lung and liver were available. As published phase I data have elucidated organ-specific dosing schedules for small-volume peripheral lung lesions, and limited hepatic metastases with promising local control rates (18, 21), we are modifying our trial to include these schedules for specific situations. However, when tumors are in close proximity with a risk of increased cumulative radiation dose to surrounding uninvolved organs, we are continuing our dose escalation.

We were able to identify patients with limited metastatic disease using systematic clinical criteria based on number of tumors, tumor location, and size of metastatic disease. Response rates were favorable. As shown in Table 3, following treatment, 21% (6 of 29) showed no evidence of disease.
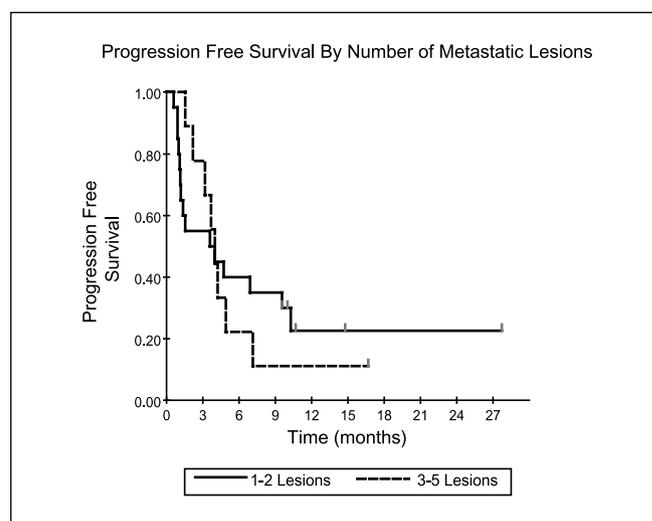

Fig. 1. Progression-free survival by number of metastatic lesions.

However, 21% (6 of 29) progressed first only in sites treated on this protocol. An additional 21% (6 of 29) of patients failed first in distant sites known to be involved with cancer and previously treated before protocol treatment. Potentially, with effective local therapy (e.g., higher radiation doses, surgery, or focused ultrasound ablation), 66% (19 of 29) may have been rendered free of disease. However, long-term follow-up is needed to determine if systematically integrated aggressive local treatment (with radiotherapy or surgery) and systemic therapy may improve disease-free survival in metastatic patients.

Cumulative progression was limited in number and location. As shown in Table 4, of the 23 patients who progressed, 18 (78%) did so in one to four sites. Only five patients (22%) progressed in more than five sites. This indicates that progression of metastasis in patients with limited sites of metastatic disease does not occur widely or randomly. It is possible that aggressive local therapy with concurrent or adjuvant administration of agents known to inhibit metastatic progression, such as matrix metalloprotein inhibitors, epidermal growth factor receptor inhibitors, and cyclooxygenase-2 inhibitors, may help to further halt metastatic progression (24). Additionally, gene signatures (25) may predict sites of failure and allow even more sophisticated tissue-specific biochemical or physical targeting of metastasis.

When we initiated this trial, stereotactic body radiotherapy doses were not standardized, and the need for a trial to determine maximal tolerated doses was needed. Since trial initiation, standard doses for small peripheral lung tumors and limited metastasis to the liver have been established as safe and effective (17, 18). Therefore, we have modified our protocol and are treating patients with limited lung and liver, excluding these patients from further dose escalation, and are treating these patients on protocol at standard doses (60 Gy in three 20 Gy fractions) without dose escalation. However, for patients with more than one metastasis, our dose escalation continues. To the best of our knowledge, no genetic signatures are available to identify patients with oligometastatic disease. The identification of such a signature is one of the end points of a Radiation Therapy Oncology Group protocol under development and may supplant the clinical criteria we used to identify patients with metastatic disease for aggressive local therapy.

In conclusion, these data indicate that a set of clinical criteria derived from published literature and based on the number, location, and size of metastatic foci can select for patients in an oligometastatic state. A small but significant fraction of oligometastatic patients may benefit from local therapy to all known sites of metastatic disease. Disease progression in oligometastatic patients occurs most often in known sites of metastases. Further intensification of local therapy with higher radiation doses and/or radiation sensitizers may improve control of treated lesions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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