Patterns of Recurrence After Curative-Intent Radiation for Oligometastases Confined to One Organ

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Objectives: We sought to characterize and describe the patterns of distant recurrence in patients with macroscopic oligometastases, limited in number (≤5) and confined to one organ, treated with curative-intent stereotactic body radiotherapy (SBRT).

Methods: Seventy-seven patients enrolled on prospective studies of SBRT for oligometastases are included in the present analysis. All available radiography and records were retrospectively reviewed to determine the timing and location of recurrences.

Results: New metastases occurred in 73% of patients. Among these patients, new metastases developed most frequently in the same organ (occurring in 82% of first new metastases after SBRT and 89% of cumulative new metastases). Metastases to other organs were common as well (occurring cumulatively in 79% of patients). In patients with liver oligometastases, common sites of further progression included the liver, other abdominal organs, and lungs. In patients with lung oligometastases, common sites of further progression included the lungs, thoracic lymph nodes, bones, liver, and brain.

Conclusions: Patients receiving SBRT for oligometastases confined to one organ are apt to develop new metastases, most frequently occurring in the initially involved organ, but also commonly in other organs. A subset of patients remains disease free after extended follow-up.

Key Words: stereotactic body radiation therapy, oligometastases, patterns of recurrence

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Oligometastatic disease is defined as a state of limited metastases in which frank widespread metastases have not yet developed. It has been hypothesized that patients with oligometastases are potentially curable with resection or ablative therapy to the clinically detectable disease.[1–4]

We previously published a pilot study in which 121 patients with ≤5 oligometastases received curative-intent stereotactic body radiotherapy (SBRT).[5,6] Though a subset of these patients have enjoyed a prolonged disease-free survival, some >7 years, most eventually succumbed to further metastatic progression.[5]

In the current study, we retrospectively analyzed the patterns of distant recurrence in patients whose oligometastases at the time of enrollment was radiographically confined to one organ. A separate analysis is offered for patients whose oligometastases were confined to the lung parenchyma and thoracic lymph nodes. There are several studies which have examined the patterns of recurrence after resection, radiofrequency ablation, or cryosurgery of oligometastases.[7–14] To our knowledge, no study has examined the patterns of distant recurrence of irradiated oligometastases initially confined (macroscopically) to one organ.

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METHODS AND MATERIALS

Between February of 2001 and December of 2006, 82 patients with oligometastases (defined as ≤5 radiographically apparent metastases) confined to one organ were treated at the University of Rochester with SBRT as described previously.[5] Five of these patients are excluded from the present analysis. One patient died 2 months after SBRT from local progression of a treated liver metastasis (originally 397 mL). Four patients were excluded because they represented the only 1 to 2 patients with oligometastases confined to that organ, and therefore a descriptive analysis would be limited: one patient with brain-only oligometastases who died with brain-only metastases, another patient with an adrenal oligometastasis who developed widespread metastatic disease, and 2 patients with abdominal/pelvic lymph node oligometastases, both of whom developed metastases to the liver, abdomen, and other organs. The remaining 77 patients are described later. An additional 13 patients with oligometastases confined to the lung parenchymal and thoracic lymph nodes are analyzed separately.

Patients routinely underwent whole body CT scanning to detect metastases. Most patients did not undergo a pretreatment PET scan, since this was generally not covered by insurers up until recently.

SBRT Technique

The technique of SBRT employed at the University of Rochester is discussed in detail in previous publications.[5,6,15–17] The Novalis ExacTrac patient positioning platform (BrainLAB, Heimstetten, Germany) was used. Treatment planning was performed using the BrainSCAN (BrainLAB) system. Patients are engaged in a relaxed end-expiratory breath-hold technique or shallow breathing during the recording of sensor positioning at simulation, and during daily set-up and treatment. For liver and lung lesions, the preferred dose-fractionation schedule was 10 fractions of 5 Gy.[6] For bulky lesions or lesions abutting critical structures, smaller fractional doses were generally used.[6]

Follow-Up

Follow-up visits were planned 1 month after completing SBRT and every 3 months (with appropriate imaging to assess tumor control) subsequently for 2 years. Thereafter, intervals ranged from 3 to 6 months, based on physician preference. Patients were followed through March 2008. All available radiography was reviewed to identify distant organ involvement. Survival times are reported from the time of enrolment until last follow-up or death. The term "new metastases" refers to the development of any new, radiographically apparent, metastatic lesion(s). The term "many metastases" refers to the development of >5 metastatic lesions, and implies that this state of disease is not amenable to curative-intent local therapy.

RESULTS

Table 1 summarizes patient characteristics. Of the 77 patients with oligometastases confined to one organ, 62 received systemic

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TABLE 1. Patient Characteristics

	Treated Oligometastases: Lesions Isolated to One Organ					Two Organs: Thorax Thoracic LNs + Lungs
	All Patients	Liver	Lungs	Thoracic LNs	Bones	
Number	77	42	21	5	9	13
Age range (yr)	36–88	36–88	41–83	46–66	39–74	43–85
Median	60	61	61	56	43	60
Female:Male	50:27	22:20	14:7	5:0	9:0	6:7
Primary cancer						
Breast	30 (39%)	10 (24%)	7 (33%)	5 (100%)	8 (89%)	2 (15%)
Colorectal	20 (26%)	16 (38%)	4 (19%)	0	0	2 (15%)
Lung, head and neck or esophagus	7 (9%)	4 (10%)	3 (14%)	0	0	5 (38%)
Pancreas/biliary or hepatic	7 (9%)	7 (17%)	0	0	0	0
Sarcoma	4 (5%)	0	4 (19%)	0	0	1 (8%)
Other	9* (11%)	5 (12%)	3 (14%)	0	1 (11%)	3† (23%)
No. lesions						
1	32 (42%)	13 (31%)	9 (43%)	3 (60%)	7 (78%)	—
2	17 (22%)	10 (24%)	4 (19%)	1 (20%)	2 (22%)	4 (31%)
3	16 (21%)	14 (33%)	1 (5%)	1 (20%)	0	5 (38%)
4	5 (6%)	1 (2%)	4 (19%)	0	0	2 (15%)
5	7 (9%)	4 (10%)	3 (14%)	0	0	2 (15%)
Sum of GTVs						
Range (mL)	1.8–422	3.8–422	1.8–73	2.1–64	4.8–50	7.1–125
Median	23	34	11	42	23	35
Follow-up						
Range (mo)	5–85	6–67	5–85	18–82	16–83	6–66
Median	23	21	24	31	40	21
Follow-up (living patients)						
Range (mo)	14–95	35–61	14–85	28–82	16–83	42–66
Median	45	48	40	72	41	54

*Other cancer types include carcinoid (n = 3), renal cancer (n = 2), melanoma, bladder cancer, endocervical cancer, and adrenal cortical carcinoma.
†Other cancer types include renal cancer, bladder cancer, and endometrial cancer.

therapy for metastatic disease before SBRT. A total of 58 patients received systemic therapy at some point after SBRT; in 1 patient, data regarding systemic therapy after SBRT were unavailable. Of the remaining 18 patients who did not receive systemic therapy after SBRT, 4 died 4 to 6 months after radiation, and 6 remain alive at 14 to 64 months (median: 47 months), 5 of whom have developed no new metastases, and 1 of whom has developed new oligometastases only. Of the 13 patients with oligometastases confined to the lungs and thoracic lymph nodes, 11 received systemic therapy for metastatic disease before SBRT. Seven patients received systemic therapy at some point after SBRT. Of the remaining 6 patients who did not receive systemic therapy after SBRT, 4 died 5 to 7 months after SBRT and 1 remain alive at 42 months.

Figure 1 depicts the Kaplan-Meier actuarial overall survival by site of metastases. Figure 2 depicts the Kaplan-Meier actuarial freedom from many metastases. Table 2 summarizes the pattern of new metastases.

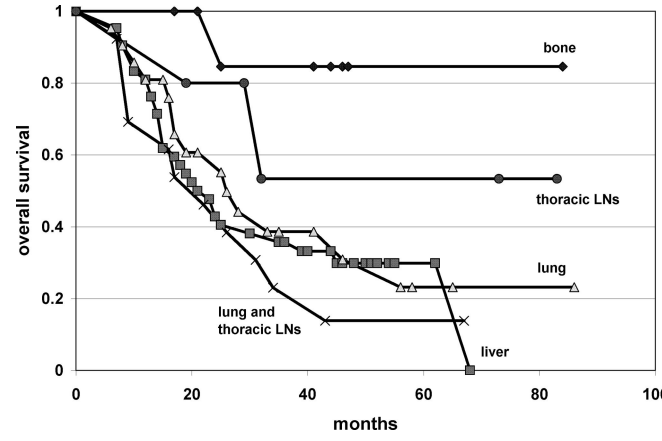

FIGURE 1. Kaplan-Meier actuarial overall survival by site of metastases.

Patients With Initial Liver-Confined Oligometastases

Among 42 patients with initial liver-confined oligometastases, 30 are deceased at 6 to 67 months (median: 20 months), 12 remain alive at last follow-up at 35 to 61 months (median: 48 months), of whom 4 have developed no new metastases at 39 to 53 months (median: 43 months). Two patients died without evidence of multiple metastases: one died of hepatic failure from local progression of liver metastases; another died of unknown causes 13 months after the first of 2 curative-intent SBRT course for liver metastases. Eight of the 12 patients who remained alive at last follow-up developed new metastases, of whom 5 initially developed oligometastases treated with curative-intent. Of these 8 patients, 4 developed oligometastases without developing many metastases (alive at 47–50 months) and 4 developed many metastases, being treated with palliative intent (alive at 35–61 months). Nineteen of 42 patients

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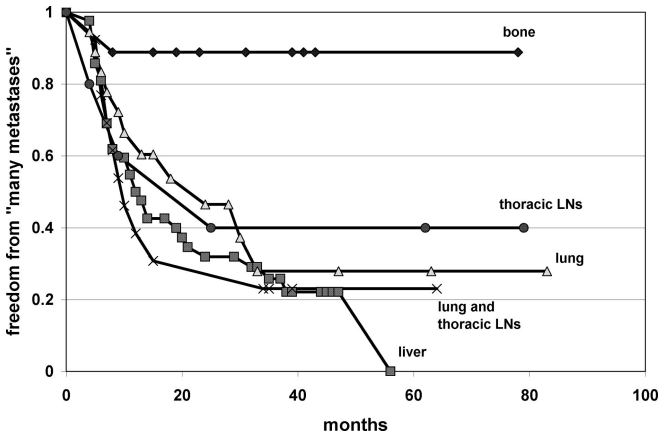

FIGURE 2. Kaplan-Meier actuarial freedom from many metastases.

(45%) developed local recurrence after SBRT (30/99 lesions locally recurred), 1 of whom died with no evidence of new metastases, and 1 who was salvaged with an embolization procedure. Fourteen patients developed local recurrence synchronously with new metastases, whereas 3 developed new metastases after local recurrence. Of the 30 lesions that locally recurred, 2 recurred at the margin of the treatment field.

Tables 3 and 4 summarize the patterns of first new metastases and cumulative new metastases, respectively. As outlined in Table 3, the first new metastases among patients with initial liver-confined oligometastases occurred most commonly in the liver. The lungs and abdominal and pelvic lymph nodes were also common sites of metastatic spread. As shown in Table 4, nearly all patients with initial liver-confined oligometastases, who developed new metastases, eventually recurred in the liver, whereas roughly one-third developed lung metastases. New metastases to abdominal and pelvic lymph nodes and other abdominal organs were also common. Six patients developed new omental/peritoneal metastases. Three of these 6 patients developed synchronous abdominal/pelvic lymphadenopathy and 1 developed new metastases to the spleen and abdominal/pelvic lymph nodes 11 months after having omental/peritoneal metastases. One of these 6 patients developed new adrenal metastases, and one other patient developed new metastases to the spleen (total of 2 of these 6 patients).

Table 5 describes the timing of the development of new metastases. In this Table, metastases to the abdominal/pelvic lymph nodes, omentum/peritoneum, adrenals, and spleen were grouped together. New metastases tended to occur earlier in the liver as opposed to other organs.

Patients With Initial Lung-Confined Oligometastases

Among 21 patients with initial lung-confined oligometastases, 14 are deceased at 5 to 55 months (median: 17 months), 7 remain alive at last follow-up at 14 to 85 months (median: 40 months), of whom 4 have developed no new metastases at 14 to 64 months (median: 34 months). Of the 3 patients alive after developing new metastases, one has developed lung-confined oligometastatic-only disease and is alive at 82 months, another has developed many (innumerable) lung metastases at 28 months and remain alive at 40 months, and another has developed many new liver metastases at 33 months and is alive at 36 months. Three patients died without evidence of many metastases: one died of pneumonia and sepsis-related respiratory and renal failure; another died of unknown causes at 3.8 years, with no appreciable metastases 3 years after SBRT; and another received additional curative-intent radiation for a new lung lesion and a brain metastasis (presumably brain metastases were the cause of death).

Seven of 21 patients (33%) developed local recurrence after SBRT (12/51 lesions locally recurred), 1 of whom died with no evidence of new metastases and 2 who underwent salvage therapy for local recurrence, and have not developed new metastases. Three patients developed local recurrence synchronously with new metastases, whereas 1 developed new metastases after local recurrence. Of the 12 lesions that locally recurred, 1 recurred at the margin of the treatment field.

As outlined in Table 3, the first new metastases in patients with oligometastases initially lung-confined occurred most commonly in the lungs, whereas thoracic lymph nodes and liver were also common sites of metastatic spread. As shown in Table 4, over three-quarters of patients with initial lung-confined oligometastases, who developed new metastases, developed new lung metastases, whereas over one-third developed new thoracic nodal metastases. Distant spread to bones, liver, and brain was also common.

As shown in Table 5, new metastases in the lungs, thoracic lymph nodes, and brain tended to occur sooner than those in the bones, liver, and abdomen/pelvis.

Patients With Initial Thoracic Lymph Node-Confined Oligometastases

Of the 5 patients with initial thoracic lymph node-confined oligometastases, 3 remain alive at last follow-up, of whom 2 have developed no new metastases (alive at 72–82 months). Two patients (40%) developed local recurrence (2/8 lesions locally recurred), one of whom was salvaged with resection and the other developed new metastases after local recurrence. In 3 patients, the first sites of new

TABLE 2. Patterns of Recurrence

Number Patients	Distantly Recurred/Total	First New Metastases				Cumulative New Metastases			
		OM	SO	DO	Both	OM Only	SO	DO	Both
All patients*	56/77 (73%)	18 (32%)	23 (41%)	10 (18%)	23 (41%)	7 (13%)	12 (21%)	6 (11%)	38 (68%)
Liver metastases	37/42 (88%)	12 (32%)	16 (43%)	5 (14%)	16 (43%)	5 (14%)	8 (22%)	2 (5%)	27 (73%)
Lung metastases	15/21 (71%)	5 (33%)	6 (40%)	4 (27%)	5 (33%)	2 (13%)	4 (27%)	3 (20%)	8 (53%)
Lung and thoracic LN metastases	13/13 (100%)	5 (38%)	5† (38%)	5 (38%)	3 (23%)	2 (15%)	4† (31%)	4 (31%)	5 (38%)
Lung and/or thoracic LN metastases	31/39 (79%)	11 (35%)	18† (58%)	10 (32%)	3 (10%)	4 (13%)	12† (39%)	8 (26%)	11 (35%)

*All patients with oligometastases confined to one organ (i.e. excluding patients with lung and thoracic LN metastases).
†New metastases to lung and/or thoracic lymph nodes.
OM, indicate oligometastatic disease amenable to curative-intent therapy (without widespread distant metastases); SO, same organ only; DO, distant organ only; Both, SO and DO; %, percent of patients who experienced new metastases.

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TABLE 3. Pattern of First Distant Recurrence

		Metastasized Organ									
	No. Recurred	Brain	Lungs	Thoracic LNs	Bones	Liver	Abdominal/Pelvic LNs	Adrenals	Omentum/ Peritoneum	Spleen	Muscle/SQ Soft Tissue
Initial organ involved											
Liver	37	3%	27%	8%	8%	86%	16%	—	8%	—	3%
Lungs	15	13%	73%	33%	7%	20%	—	—	—	—	—
Initial organs involved											
Lungs and thoracic LNs	13	23%	54%	38%	15%	23%	—	—	—	—	—
Lungs and/or thoracic LNs	31	19%	61%	39%	10%	19%	—	—	—	—	—

The reported percentage represents percentage of patients who recurred at that organ among all patients who recurred distantly.
LN indicates lymph nodes; SQ, subcutaneous.

TABLE 4. Pattern of Cumulative Distant Recurrence

		Metastasized Organ									
	No. Recurred	Brain	Lungs	Thoracic LNs	Bones	Liver	Abdominal/Pelvic LNs	Adrenals	Omentum/ Peritoneum	Spleen	Muscle/SQ Soft Tissue
Initial organ involved											
Liver	37	8%	32%	16%	19%	95%	32%	3%	16%	5%	5%
Lungs	15	20%	80%	40%	27%	33%	7%	7%	7%	—	—
Initial organs involved											
Lungs and thoracic LNs	13	31%	62%	46%	15%	38%	8%	—	8%	—	—
Lungs and/or thoracic LNs	31	26%	71%	45%	23%	35%	6%	3%	6%	—	—

The reported percentage represents percentage of patients who recurred at that organ among all patients who recurred distantly.
LN indicates lymph nodes; SQ, subcutaneous.

TABLE 5. Timing of the Development of New Metastases

	Metastasized Organ					
	Brain	Lungs	Thoracic LNs	Bone	Liver	Abdomen/Pelvis
Initial organ involved						
Liver	8–28 M median 13 M in 3 patients	1.3–56 M median 12 M in 12 patients	5–56 M median 22 M in 6 patients	4–23 M median 11 M in 7 patients	1.3–46 M median 7 M in 35 patients	3–36 M median 11 M in 14 patients
Lungs	0.5–53 M median 6 M in 3 patients	3–69 M median 6 M in 12 patients	3–30 M median 6 M in 6 patients	3–49 M median 11 M in 4 patients	7–48 M median 29 M in 5 patients	13–29 M in 2 patients
Thoracic LNs	2 M in 1 patient	23–24 M in 2 patients	6–23 M in 2 patients	12 M in 1 patient	26 M in 1 patient	None observed
Initial organs involved						
Lungs and thoracic LNs	3–17 M median 5 M in 4 patients	3–25 mo median 7 M in 8 patients	3–25 M median 6 M in 6 patients	2–13 mo in 2 patients	4–24 M median 9 M in 5 patients	5 M in 1 patient

M, months after completion of radiation.

metastases include: thoracic lymph nodes (n = 2), lungs (n = 2), and brain (n = 1), whereas cumulative sites of new metastases include: thoracic lymph nodes (n = 2), lungs (n = 3), liver (n = 1), brain (n = 1), and bones (n = 1).

Patients With Initial Bone-Confined Oligometastases

All but 1 of the 9 patients with bone-only metastases had breast cancer, all of whom had only 1 to 2 lesions initially treated. Eight patients remain alive with no evidence of new metastases at 16 to 83 months (median: 41 months). One patient developed liver and lung metastases at 7 months, followed by a local recurrence, and died at 24 months.

Patients With Initial Thorax-Confined Oligometastases

Among the 13 patients with oligmetastatic lesions initially in both the lungs and thoracic lymph nodes, 11 are deceased at 8 to 42 months (median: 16 months), and only 2 remain alive at last follow-up (at 42 and 66 months), both of whom developed new oligometastic lesions which were treated with SBRT, without developing many metastases. Four patients (31%) developed a local recurrence. The lungs and thoracic lymph nodes were the most common sites of metastases, though brain, bone, and liver metastases were also common.

In a separate analysis, the 13 patients with lung and thoracic nodal oligometastases were pooled with the patients with initial

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TABLE 6. Patterns of Recurrence After Treatment of Limited Liver Metastases: Literature Summary

First author	Bozzetti et al[7]	Sugihara et al[8]	Lise et al[9]	Topal et al[10]
Institution	Inst. Naz. Tumori	Nat. Cancer Centre Hosp., Tokyo	U. Padova	U. Gasthuisberg
Patient population	Resection of metastases from colorectal cancer	Resection of metastases from colorectal cancer	Resection of metastases from colorectal cancer	Resection of metastases from colorectal cancer
No. recurrences*/no. patient	28/45 (62%)	64/107 (60%)	82/132 (62%)	74/105 (70%)
Follow-up mo	4–45 (median: 18)	6–164 (median: 35)	3–120 (median: 22)	1–100 (mean: 32)
POF among those experiencing recurrence				
Liver recurrence only	39%	—	61%	15%
Extrahepatic recurrence only	43%	—	12%	39%
Liver + extrahepatic recurrence	18%	—	27%	46%
Liver	57%	53%	88%	61%
Lungs	17%	31%	—	54%
CNS	4%	—	—	18%
Bones	—	—	—	14%
Pelvic/intraabdominal	21%	19%	—	—
Retroperitoneal lymph nodes	—	—	—	24%
Portal lymph nodes	—	—	—	7%
Peritoneum	—	—	—	11%
Other	—	9%	—	11%
First author	White et al[11]	Aloia et al[12]	Kosari et al[13]	White et al[11]
Institution	MSKCC†	MDACC	U. Minnesota	MSKCC†
Patient population	Resection of metastases from colorectal cancer	Resection of solitary colorectal liver metastasis	Radiofrequency ablation from various cancers	Radiofrequency ablation from colorectal cancer
No. recurrences*/no. patient	18/27 (67%)	71/150 (57%)	23/45 (51%)	9/21 (43%)
Follow-up mo	3–130	4–138 (median 31)	6–34 (median 19.5)	2–39
POF among those experiencing recurrence				
Liver recurrence only	50%	18%‡	52%	33%
Extrahepatic recurrence only	19%	62%	4%	56%
Liver + extrahepatic recurrence	15%	20%	43%	11%
Liver	65%	38%	96%	44%
Lungs	—	58%	—	—
CNS	—	1%	—	—
Bones	—	6%	—	—
Pelvic/intraabdominal	—	17%	—	—
Retroperitoneal lymph nodes	—	—	—	—
Portal lymph nodes	—	—	—	—
Peritoneum	—	—	—	—
Other	—	—	—	—
First author	Ravi kumar et al[14]	Aloia et al[12]	Present Series	
Institution	Yale	MDACC	U. Rochester	
Patient population	Cryosurgery of metastases from colorectal cancer	Radiofrequency ablation of solitary colorectal met	SBRT of metastases from various cancers	
No. recurrences*/no. patient	17/24 (71%)	19/30 (63%)	37/42 (88%)	
Follow-up mo	5–60 (median 24)	2–70	6–67 (median 21)	
POF among those experiencing recurrence				
Liver recurrence only	35%	26%	22%	
Extrahepatic recurrence only	6%	53%	5%	
Liver + extrahepatic recurrence	59%	21%	73%	

(*Continued*)

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TABLE 6. (*Continued*)

Liver	94%		95%
Lungs	—	42%	32%
CNS	—		8%
Bones	—	5%	19%
Pelvic/intraabdominal	—	26%	32%
Retroperitoneal lymph nodes	—	—	—
Portal lymph nodes	—	—	—
Peritoneum	—	16%	—
Other	—	—	—

*Reported recurrences are distant recurrences. However, the surgical series (with the exception of the MDACC and MSKCC studies) in which liver recurrences are reported do not differential local recurrence from distant liver recurrence, though it is expected that most recurrences do indeed represent distant liver recurrences, as the local control after resection tends to be reasonably good (see text).

†MSKCC = Memorial Sloan Kettering Cancer Center. This study reported first distant recurrence (as opposed to cumulative distant recurrence). Patients treated with RFA had a much higher rate of local recurrence rate than those treated with resection (2-yr rate of local recurrence of 59% vs. 12%), which are not accounted for in this table, which describes distant recurrence.

‡MDACC = M. D. Anderson Cancer Center. This study explicitly excluded local liver recurrences from their patterns of recurrence analysis.

LN indicate lymph node.

lung-only oligometastases (n = 20) and initial thoracic lymph node-only oligometastases (n = 5). The lungs and thoracic lymph nodes were considered one organ for this analysis. Of those who experience new metastases, the majority (58%) of first new metastases were initially isolated to the thorax. Ultimately, most patients (61%) developed new metastases at other distant sites.

DISCUSSION

We analyzed the patterns of recurrence after SBRT for oligometastases limited in number (≤5) and confined to one organ. Most patients developed new metastases. Though the protocol required follow-up imaging every 3 to 6 months, the radiography which was obtained for any given patient was generally selected based on known disease and/or new symptoms. Therefore, our analysis is limited to some extent in that asymptomatic lesions may not have been identified if they were not imaged. Also we cannot determine, in every patient, all other organs that harbored macroscopic metastases in the terminal stages of cancer. Nevertheless, our analysis does reflect the extent of metastatic spread anticipated to be detected in routine clinical practice, and provides an understanding of the metastatic recurrence pattern.

The first new metastases and cumulative new metastases occur quite commonly in the same organ (in 82% and 89% of patients who experience new metastases, respectively), though metastases to other organs are common as well (59% of first new metastases and 79% of cumulative new metastases). In patients with liver oligometastases, typical sites of new metastases include the abdominal organs and lungs. In patients with lung and/or thoracic lymph node metastases, typical sites of new metastases include the lungs, thoracic lymph nodes, bones, liver, and brain.

Table 6 summarizes the studies evaluating patterns of recurrence after treatment of hepatic oligometastases. In surgical series, among patients who experience disease recurrence after resection of limited liver metastases, the crude rate of hepatic recurrence ranges from 57% to 88%, and the crude rate of extrahepatic metastatic spread ranges from 39% to 85%. Some of the reported liver recurrences after resection are likely local recurrences (ie, tumor bed recurrences), though at least 2 studies explicitly differentiated local from distant intrahepatic recurrence, and reported local recurrence rates on the order of 10%.[11,12] In a series examining patients treated with cryosurgery, the local recurrence was 8%. In 2 studies of radiofrequency ablation for liver oligometastases, the local recurrence rate was on the order of 40% to 60%,[11,12] whereas in 1 study it was <10%.[13] In our series, local recurrence was 45%, with 90% of these patients also developing distant recurrence. Although it is difficult to compare the outcome from these studies, given the different patient and treatment characteristics as well as different follow-up strategies, it seems that resection of liver oligometastases affords better local control than other local treatment strategies; new metastases to the liver is common with all of the treatment approaches, as is metastases to other organs, and there is a subset of patients who achieve prolonged disease-free survival and perhaps cure.

There are several competing risks which our analysis of new metastases is unable to adequately examine. Patient death competes with subsequent organ recurrence, and thus impacts cumulative organ recurrence. The clinical manifestation of microscopic/subclinical lesions, present at the time of initial presentation competes with the development of new metastases from further metastatic spread. New metastases occurring shortly after completion of radiation presumably represents the growth of initially occult metastatic disease versus rapid metastatic progression, whereas new metastases that occurs after a longer time interval represents more indolent growth of initially occult metastatic disease versus a more remote occurrence of distant spread. Our present study cannot determine a mechanism to account for new metastases.

Variables other than initial organ involvement are presumably important in predicting where subsequent metastases are likely to occur. Though the use of chemotherapy may alter patterns of distant recurrence, at least one study suggests that (after resection of liver oligometastases) chemotherapy does not alter recurrence pattern.[18] Another study has suggested that the local therapy (comparing resection vs. cryotherapy of liver oligometastases) impacts the risk progression beyond organ-confined disease (specifically pulmonary metastases).[19] Primary cancer type, histology, and grade are also expected to be important variables which can impact the pattern of recurrence. Our analysis is limited to some extent, by including heterogeneous types of primary cancers.

The classic seed and soil hypothesis suggests that a given cancer cell population develops a predilection to deposit and grow in a given environment.[20,21] There are likely to be genotypic and phenotypic changes which lead to metastatic potential, specifically the ability for malignant cells to intravasate into and extravasate out of the blood supply, and deposit, and grow in a new environment.[22–27] With some cancers, in some patients, these changes may be inherent to the initial primary cancer, and thus the metastatic potential may be present at the time of cancer inception.[28] Patients

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with metastases confined to one organ have already demonstrated the ability to metastasize and grow in that organ, which is consistent with the finding that new metastases in the same organ is quite common among the patients in this series. New metastases in other organs is also quite common in the patients in this study. Several mechanisms may account for recurrences to other organs: the metastatic cells, which were initially confined to one organ have the capacity to deposit and grow in a different organ; metastatic cells with different phenotypic and genotypic characteristics had already deposited in the other organ(s) but not yet become manifest; or the metastatic cells undergo further phenotypic and genotypic changes, which allow metastases to develop in other organs.

In conclusion, our study describes the patterns of recurrence among a cohort of patients treated with SBRT for metastases confined to one organ. A subset of patients do achieve a disease-free survival on the order of several years or more, and in those patients who do succumb to metastatic disease, arguably a subset achieved a more prolonged survival as a result of treatment of their grossly metastatic disease. The determination of which patients will benefit from curative-intent treatment of oligometastatic disease remains an area for future investigation. Our hypothesis-generating analysis raises several questions about the biomolecular events that lead to the development of oligometastases and the biomolecular events that lead to subsequent new metastases. Although our study cannot attempt to answer these questions, it can serve as a basis for further inquiry and study.

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