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Scientific Article

Radioresistant Pulmonary Oligometastatic and Oligoprogressive Lesions From Nonlung Primaries: Impact of Histology and Dose-Fractionation on Local Control After Radiation Therapy

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Purpose: We investigated whether pulmonary metastases from historically considered radioresistant primaries would have inferior local control after radiation therapy than those from nonradioresistant nonlung primaries, and whether higher biologically effective dose assuming alpha/beta=10 (BED10) would be associated with superior local control.

Methods and Materials: We identified patients treated with radiation therapy for oligometastatic or oligoprogressive pulmonary disease to 1 to 5 lung metastases from nonlung primaries in 2013 to 2020 at a single health care system. Radioresistant primary cancers included colorectal carcinoma, endometrial carcinoma, renal cell carcinoma, melanoma, and sarcoma. Nonradioresistant primary cancers included breast, bladder, esophageal, pancreas, and head and neck carcinomas. The Kaplan-Meier estimator, log-rank test, and multivariable Cox proportional hazards regression were used to compare local recurrence-free survival (LRFS), new metastasis-free survival, progression-free survival, and overall survival.

Results: Among 114 patients, 73 had radioresistant primary cancers. The median total dose was 50 Gy (IQR, 50-54 Gy) and the median number of fractions was 5 (IQR, 3-5). Median follow-up time was 59.6 months. One of 41 (2.4%) patients with a nonradioresistant metastasis experienced local failure compared with 18 of 73 (24.7%) patients with radioresistant metastasis (log-rank P = .004). Among radioresistant metastases, 12 of 41 (29.2%) patients with colorectal carcinoma experienced local failure compared with 6 of 32 (18.8%) with other primaries (log-rank P = .018). BED10 ≥100 Gy was associated with decreased risk of local recurrence. On univariable analysis, BED10 ≥100 Gy (hazard ratio [HR], 0.263; 95% CI, 0.105-0.656; P = .004) was associated with higher LRFS, and colorectal primary (HR, 3.060; 95% CI, 1.204-7.777; P = .019) was associated with lower LRFS, though these were not statistically significant on multivariable analysis. Among colorectal primary patients, BED10 ≥100 Gy was associated with higher LRFS (HR, 0.266; 95% CI, 0.072-0.985; P = .047) on multivariable analysis.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: Local control after radiation therapy was encouraging for pulmonary metastases from most nonlung primaries, even for many of those classically considered to be radioresistant. Those from colorectal primaries may benefit from testing additional strategies, such as resection or systemic treatment concurrent with radiation.

Introduction

The lung is a frequent site of cancer metastases, with approximately 20% to 54% of cancer patients developing lung metastases, dependent on the primary site.[1] Traditionally lung metastases were treated with systemic therapy alone; however, the increasing use and availability of imaging combined with advancements in radiation planning and delivery have led to the emergence of metastasis-directed therapy using ablative doses of radiation.[2]

There is a wide spectrum of disease states between locoregionally confined tumors and widespread metastatic disease, with a subset of patients having oligometastatic and oligoprogressive disease. Although there is no universally agreed upon definition of oligometastasis, most prior studies of oligometastatic patients use a cut-off of 3 to 5 metastatic lesions. In contrast to oligometastatic patients, patients with oligoprogressive disease may have polymetastatic disease, but with only a few metastatic lesions progressing while on systemic treatment.[3,4]

For the subset of metastatic patients with oligometastatic and oligoprogressive disease, the efficacy of aggressive metastasis-directed ablative radiation has been demonstrated by several seminal trials that have shown an overall survival (OS) and progression-free survival (PFS) benefit.[5-7] However, the optimal radiation dose-fractionation schedule for the ablative treatment of pulmonary metastases, especially from nonlung primaries, has not been standardized. Radiation schedules used for the treatment of pulmonary metastases have often mimicked the treatment of stage I non-small cell lung cancer. Some prior studies have reported local control rates reaching up to 96%[8] while others, particularly those which focus on colorectal cancer (CRC), have shown poorer local control.[9] However, especially as the number of treated metastases increases, there has been an emphasis on minimizing the risks of toxicity of treatment with dose de-escalation. Several trials are testing the efficacy of stereotactic body radiation therapy (SBRT) biologically effective dose assuming alpha/beta=10 (BED10) well below those used for primary lung tumors for patients with 4 or greater metastases.[10,11]

In this study we investigated whether histologies classically considered radioresistant and/or dose-fractionation were predictors of local recurrence after radiation therapy for pulmonary metastases from nonlung primaries. In addition, we sought to uncover whether there was a subset of radioresistant primary cancers at particularly high risk for local recurrence and could benefit from further treatment escalation.

Methods and Materials

Patient selection and classification

This study was approved by the Yale University Institutional Review Board. We reviewed an institutional database of patients who received lung radiation treatment from February 2013 to June 2020 in the Yale New Haven Hospital System. Of 2571 patients in total, we identified 125 patients with oligometastatic or oligoprogressive pulmonary metastases from nonlung primaries who received lung radiation therapy. Of these patients, 8 were excluded due to incomplete records and 3 were excluded due to low BED for their lung radiation therapy, defined as BED10 <48 Gy, leading to a final cohort of 114 patients.

Metastatic disease state was defined according the European Organization for the Research and Treatment of Cancer and European Society for Radiotherapy and Oncology consensus recommendations. To simplify disease state categories, patients were classified as having oligometastatic disease (those with synchronous oligometastatic disease, metachronous oligorecurrence and repeat oligorecurrence), or having oligoprogressive disease (those with repeat oligoprogression, induced oligoprogression, repeat oligopersistence, and induced oligopersistence). All oligometastatic patients had 1 to 5 lesions within the lung at the time of diagnosis of oligometastatic pulmonary disease. Four of the 74 oligometastatic patients also had additional metastatic disease outside of the lung which was confined to 1 to 2 other organs and with 3 or fewer lesions in each organ. Seventy patients were identified as oligoprogressive. Oligoprogressive patients received systemic treatment after diagnosis of metastatic pulmonary disease and were found to have growth or persistence of 1 to 5 lung lesions after systemic treatment. Patients who initially responded to systemic treatment but then had growth of 1 to 3 lung lesions while off systemic treatment were defined as oligometastatic.

Radioresistant primary cancers included CRC, endometrial carcinoma, renal cell carcinoma, melanoma, and sarcoma. Nonradioresistant primary cancers included breast, bladder, esophageal, pancreas, and head and neck carcinomas. Renal cell carcinoma, melanoma, and sarcoma were classified as radioresistant based on prior studies of SRS for brain metastases.[12-21] The classification of CRC metastases as radioresistant was based on prior studies of SBRT for lung metastases.[22-25] Finally, the

classification of endometrial as radioresistant was based on the fact that 2 of the 4 patients had a histology (serous or leiomyosarcoma) for which adjuvant radiation has shown limited benefit.[26-30]

High-dose radiation therapy technique

SBRT techniques used at our institution have been previously described in detail.[31] In brief, a 4-dimensional CT simulation is done in a full-body vacuum cushion. Next, an internal gross tumor volume (IGTV) is constructed on the average intensity projection scan and includes the full extent of tumor movement during the respiratory cycle. Finally, a 0.5 to 0.7 cm expansion on the IGTV volume is done to generate the planning target volume (PTV). Normal tissues including the heart, lungs, esophagus, proximal tracheobronchial tree, spinal cord, chest wall, and brachial plexus were also contoured as needed. Patients were treated with 7 to 13 nonopposed, noncoplanar 6 MV photon beams that conformed to the PTV using multileaf collimator leaves, dynamic conformal arcs, or volumetric-modulated arc therapy. Cone beam CT was used for image guidance and verification before each treatment delivery.

For hypofractionated and standard fractionation, intensity modulated RT was used. The clinical target volume was defined to be the IGTV plus a 0.5 to 0.7 cm margin as appropriate to account for microscopic tumor extension. The PTV was the clinical target volume plus a margin (0.3-0.5 cm).

Follow-up

Patients were typically scheduled for their first follow-up 1 month after RT. After this, follow-ups and chest CT scans were scheduled subsequently every 3 to 6 months for 1 year and every 4 to 6 months thereafter until 5 years had elapsed. Five years after radiation treatment the patient would typically only follow-up with their primary medical oncologist, who would arrange their annual surveillance imaging. PET-CT was performed if follow-up CT imaging findings were suspicious for recurrence.

Definition of local recurrence

Local recurrence was defined as recurrence within or immediately adjacent to the radiation field or progressive growth of the treated lesion after RT as seen on 2 consecutive follow-up imaging scans and/or documented in an oncology follow-up note. In addition to using the CT report, the images from each CT chest scan were also individually reviewed. Progressive growth on 2 consecutive scans allowed us to differentiate recurrence from posttreatment pneumonitis or fibrosis.

Statistical analyses

The Pearson χ^2 test was used to assess for associations between patient, tumor, and treatment characteristics and radioresistant and nonradioresistant histology. Time to develop pulmonary metastases was defined as time from initial diagnosis to identification of pulmonary metastasis on imaging. Time to local failure was defined as time from RT treatment to development of local progression or recurrence. Overall survival time was defined from time from RT treatment to last follow-up or death. Kaplan-Meier method was used for analysis of local recurrence-free survival (LRFS), OS, new metastasis-free survival (NMFS), and PFS. Median follow-up was determined by the reverse Kaplan-Meier method. These outcomes were calculated based on time from the date of last fraction of RT treatment.

Univariable Cox proportional hazard analysis was used to evaluate patient, tumor, and treatment characteristics as prognostic factors for LRFS and OS. The following characteristics were included in univariable analysis: age at diagnosis (<70 or ≥70 years), sex (male or female), Eastern Cooperative Oncology Group (ECOG) (<2 or ≥2), smoking history (<10 or ≥10 pack-years), initial M stage (M0 or M1), time to development of pulmonary metastases (<12 or ≥12 months), biologically effective dose assuming α/β of 10 (BED10 <100 or ≥100 Gy), number of lung lesions treated (1 or >1 lesion), radioresistance of primary tumor (nonradioresistant or radioresistant), and disease state (oligometastatic or oligoprogressive). For CRC primaries, univariable Cox proportional hazard analysis was used to evaluate whether the following variables were prognostic for LRFS: age at diagnosis (<70 or ≥70 years), sex (male or female), ECOG (<2 or ≥2), smoking history (<10 or ≥10 pack-years), disease state (oligometastasis or oligoprogression), time to lung metastasis (≤12 or >12 months), number of lung lesions treated (1 or >1 lesion), grade (low-grade or high-grade), KRAS status (no mutation or mutation present), IGTV volume (≤30 or >30 cm^3), BED10 to lung metastasis (<100 or ≥100), and systemic treatment after SBRT (systemic treatment or no systemic treatment). Multivariable analysis was then performed by including all variables with $P < .05$ on univariate regression, BED10 was included on multivariable analysis a priori. We used IBM SPSS Statistics for Mac Version 25.0 (IBM Corp) for all statistical analyses. Hypothesis testing was 2-sided with a 5% level of significance.

Results

Patient, tumor, and treatment characteristics

In the study, 114 patients with 146 treated lesions were included in our cohort; 74 patients (64.9%) had

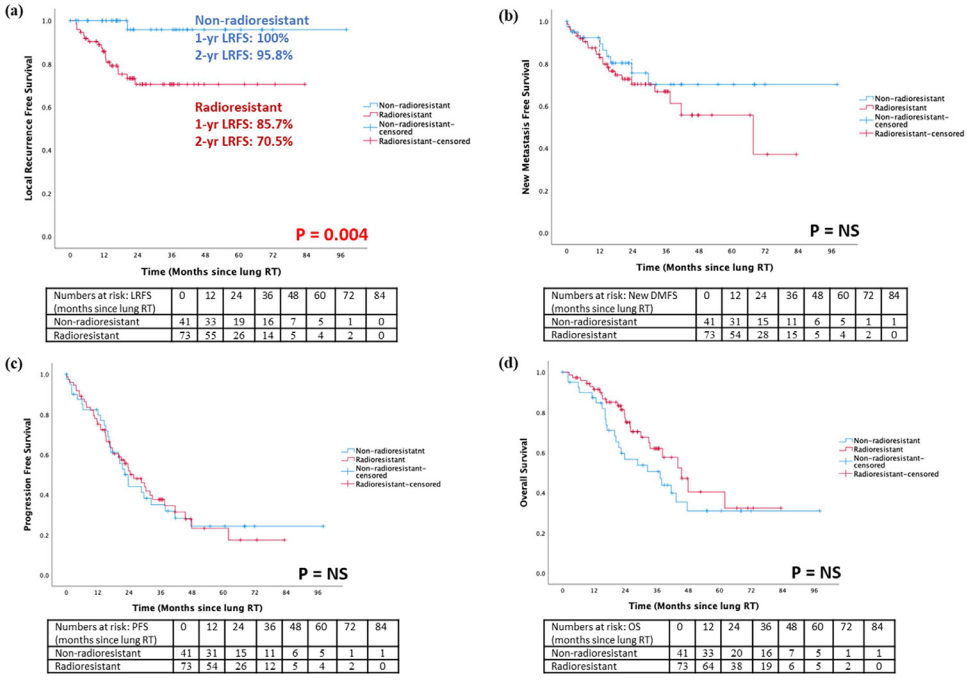


Figure 1 Kaplan-Meier curves for the nonradioresistant and radioresistant subgroups. (a) local recurrence-free survival, (b) new metastasis-free survival, (c) progression-free survival, and (d) overall survival curves for nonradioresistant (blue) and radioresistant (red) subgroups. *P* values (log-rank) and numbers at risk are shown. *Abbreviations*: DMFS = distant metastasis-free survivial; LFRS = local recurrence-free survival; RT = radiation therapy.

oligometastatic pulmonary disease and 40 patients (35.1%) had oligoprogressive lung metastases (Table E1). Based on the histology of their primary cancer, patients were designated as either radioresistant (n = 73) or nonradioresistant (n = 41; Fig. E1). A comparison of baseline demographic, tumor, and treatment characteristics between radioresistant and nonradioresistant patients is shown in Table 1. Notably there was an imbalance between radioresistant and nonradioresistant patients with regards to disease state (radioresistant patients had more oligoprogressive disease rather than oligometastatic) and number of lung lesions treated by SBRT (more radioresistant patients had >1 lung lesion treated than nonradioresistant patients). Two out of the 114 patients (1 radioresistant and 1 nonradioresistant) received systemic treatment during lung radiation treatment, one patient received cetuximab (nonradioresistant patient) and the other patient received nivolumab (radioresistant patient).

Out of 114 patients, 104 (91.2%) received stereotactic body radiation therapy (SBRT), defined as ≤5 fractions with at least 6 Gy per fraction; 8 of 114 patients (7.0%) received hypofractionated radiation therapy to 60 Gy in 15 fractions or 72 Gy in 18 fractions; and 2 of 114 patients (1.8%) received conventionally fractionated radiation therapy to 60 Gy in 30 fractions. The median total dose per lesion was 50 Gy (IQR, 50-54 Gy), and the median number of fractions was 5 (IQR, 3-5). The most common fractionation schedules were 54 Gy in 3 fractions (31.6%, BED10 of 151.2) and 50 Gy in 5 fractions (37.7%, BED10 of 100.0). Ninety-two out of 114 patients (80.7%) were treated with a BED10 ≥100 Gy. A median of 1 lesion was treated (range, 1-5 lesions). Median follow-up time was 36.4 months.

Median LRFS was not reached for radioresistant or nonradioresistant groups. LRFS was poorer among patients with radioresistant histologies than those with nonradioresistant histologies (1-year 85.7% vs 100%, 2-year 70.5% vs 95.8%, log-rank $P = .004$; Fig. 1). Median OS for all patients was 41.5 months. The median OS was 37.2 and 45.4 months for patients with nonradioresistant and radioresistant primaries, respectively ($P = .21$). One-, 2-, and 5-year OS for all patients was 90.0%, 68.9%, and 31.7%, respectively. NMFS and PFS were also not significantly different between the radioresistant and nonradioresistant groups (Fig. 1).

Tumor and treatment factors associated with local failure

One of 41 patients (2.4%) with a nonradioresistant metastasis experienced local failure compared with 18 of 73 (24.7%) patients with radioresistant metastasis (log-rank $P = .004$; Table 2). The only nonradioresistant patient with a local failure received only 30 Gy in 5 fractions (BED10 of 48). Among radioresistant patients, local

Table 1 Patient, tumor, and treatment characteristics based on nonradioresistant and radioresistant primary (N = 73)

Characteristic	Total (N = 114) N (%)	Nonradioresistant (N = 41) N (%)	Radioresistant (N = 73) N (%)	Pearson χ^2 *P* value
Age, y				
<70	55 (48.2)	18 (43.9)	37 (50.7)	.560
≥70	59 (51.8)	23 (56.1)	36 (49.3)	
Sex				.168
Male	66 (57.8)	20 (48.8)	46 (63.0)	
Female	48 (42.2)	21 (51.2)	27 (37.0)	
ECOG				.491
0-1	93 (81.6)	32 (78.0)	61 (83.6)	
≥2	21 (18.4)	9 (22.0)	12 (16.4)	
Smoking history				.378
Never	43 (47.3)	15 (46.9)	28 (47.5)	
<10 pack-years	13 (14.3)	6 (18.8)	7 (11.9)	
≥10 pack-years	35 (38.4)	11 (34.4)	24 (40.7)	
Initial primary M stage				.376
M0	86 (75.4)	33 (80.5)	53 (72.6)	
M1	28 (24.6)	8 (19.5)	20 (27.4)	
Metastatic type				**.004**
Oligometastatic	74 (64.9)	34 (82.9)	40 (54.7)	
Oligoprogressive	40 (35.1)	7 (17.1)	33 (45.3)	
Time to develop lung metastases, mo				.826
<12	29 (25.4)	10 (24.4)	19 (26.0)	
≥12	85 (74.6)	31 (75.6)	54 (74.0)	
Number of lung lesions treated				**.039**
1 lesion	87 (76.3)	36 (87.8)	51 (69.8)	
>1 lesion	27 (23.7)	5 (12.2)	22 (30.1)	
Size of PTV				.530
<50 cc	67 (64.4)	24 (58.5)	43 (58.9)	
>50 cc	37 (35.6)	17 (41.5)	30 (41.1)	
BED10 to lung metastasis				.306
<100	23 (20.2)	6 (14.6)	17 (23.3)	
≥100	91 (79.8)	35 (85.4)	56 (76.7)	
Dose-fractionation				.626
SBRT	104 (91.2)	36 (87.8)	68 (93.2)	
*Hypofractionation†	8 (7.0)	4 (9.8)	4 (5.5)	
Conventional fractionation‡	2 (1.8)	1 (2.4)	1 (1.4)	

Abbreviations: BED = biologically effective dose; ECOG = eastern cooperative oncology group; PTV = planning target volume; SBRT = stereotactic body radiation therapy.
*SBRT regimens: 54/3 (n = 37); 48/4 (n = 1); 30/3 (n = 1); 60/5 (n = 1); 55/5 (n = 7); 50/5 (n = 43); 40/5 (n = 4); 35/5 (n = 1); 30/5 (n = 9).
†Hypofractionation regimens: 72/18 (n = 2); 60/8 (n = 2); 60/15 (n = 4).
‡Conventional fractionation regimen: 60/30 (n = 2).

failure occurred among patients with CRC (12 of 41 patients, 29.2%), endometrial cancer (3 of 4 patients, 75.0%), renal cell carcinoma (2 of 10 patients, 20.0%), and melanoma (1 of 12 patients, 8.3%; Table 3). None of the patients with sarcoma experienced local failure (0 of 6, 0%). Of note, among the 4 patients with endometrial

Table 2 Primary site of patients who experienced LF after lung RT

	Total no. of patients	No. of patients with LF	Percentage of patients with LF	Percentage of total LF
Total	114	19		
Nonradioresistant	41	1	2.4%	5.3%
Bladder	5	0	0	0
Breast	9	0	0	0
Cervix	1	0	0	0
Duodenal	1	0	0	0
Esophagus	4	0	0	0
HCC	2	0	0	0
Head and neck	12	1	8.3%	5.3%
Pancreas	6	0	0	0
Prostate	1	0	0	0
Radioresistant	73	18	24.7%	94.7%
Colorectal	41	12	29.3%	63.2%
Endometrial	4	3	75.0%	15.8%
Melanoma	12	1	8.3%	5.3%
Sarcoma	6	0	0	0
RCC	10	2	20.0%	10.5%

Abbreviations: HCC = hepatocellular carcinoma; LF = local failure; RCC = renal cell carcinoma; RT = radiation therapy.

cancer, 2 had endometrioid histology, 1 had serous histology, and 1 patient had a leiomyosarcoma. Both serous and leiomyosarcoma patients experienced a local failure.

Prior studies of SBRT regimens for stage I non-small cell lung cancer, have recommended biologically effective doses (BED) ≥100 Gy.[32-34] Based on this we divided radiation regimens into BED10 <100 Gy and BED10 ≥100 Gy. For patients with radioresistant primaries, BED10 ≥100 was associated with higher LRFS than BED10 <100 (1-year 90.8% vs 66.7%, 2-year 77.4% vs 38.1%, log-rank P = .01; Fig. 2). When treated with BED10 ≥100, 2-year LRFS for radioresistant and nonradioresistant patients were 77.4% and 100.0%, respectively (log-rank P = .01; Fig. 2, Fig. E2). Escalating BED10 above 100 Gy or 120 Gy did not lead to improved LRFS among radioresistant patients (Fig. E3).

On univariable Cox analysis, BED10 ≥100 was associated with improved LRFS compared with BED10 <100 (HR, 0.263; 95% CI, 0.105-0.656; P = .004). CRC primary site was associated with poorer LRFS compared with all other primary sites (HR, 3.060; 95% CI, 1.204-7.777; P = .019; Table 4). Radioresistant histology was not associated with OS (Table E2), NMFS (data available upon request), or PFS (data available upon request). Notably, systemic treatment after lung SBRT was associated with a statistically significant survival benefit (Table E2).

Local control rates and prognostic factors for local failure among CRC versus non-CRC radioresistant patients

There were 41 radioresistant patients with CRC primary cancers, who had a local failure risk of 29.2%. Non-CRC radioresistant patients had a local failure risk of 18.8%, with 3 of the 6 patients with local failures having received 30 to 35 Gy in 5 fractions or 60 Gy in 30 fractions. Compared with non-CRC radioresistant patients, CRC patients were likely to have primaries with metastasis at diagnosis (Table E3). LRFS was poorer among CRC group than the non-CRC radioresistant and nonradioresistant subgroups (1-year 88.0% vs 86.8% and 100%, 2-year 67.6% vs 78.9.% and 95.8%, log-rank P = .018). When treated with BED10 ≥100, 2-year LRFS for CRC and non-CRC radioresistant patients were 75.2% and 85.1%, respectively (P = .041; Fig. E4).

For patients with CRC primaries, BED10 ≥100 was associated with improved LRFS (1-year 94.3% vs 50.0%, 2-year 75.2% vs 33.3%, log-rank P = .016). Analysis with a higher BED10 threshold of 120 Gy did not show an improvement in LRFS among CRC patients (Fig. E5).

Multivariable Cox regression analysis of CRC patients showed that BED10 ≥100 was associated with improved LRFS compared with BED10 <100 (HR, 0.199; 95% CI, 0.060-0.656; P = .008). Greater total IGTV planning volume (>30 cm^3 vs ≤30 cm^3; HR, 3.759; 95% CI, 1.010-14.00;

Table 3 Patient, tumor, and treatment characteristics for patients who experienced local failure after lung RT

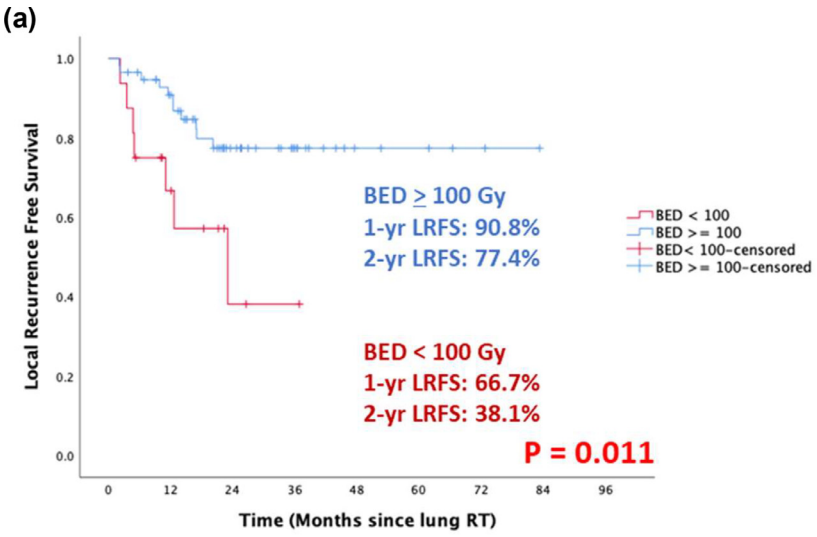
No.	Age	Sex	ECOG	Primary site	Radiation Sensitivity	Time to lung metastasis (mo)*	Lung RT dose and fractionation	BED10	No. of sites treated	Lobes treated	Time to local failure (mo)†	Follow-up time (mo)‡	Overall survival (mo)‡
1	88	M	0	Head and neck	Not resistant	42.1	30 Gy in 5 Fx	48	1	RLL	20.3	23.6	23.6
2	83	M	2	Colon	Resistant	142.1	30 Gy in 5 Fx	48	1	RLL	23.0	47.9	47.9
3	52	M	0	Colon	Resistant	1.7	54 Gy in 3 Fx	151.2	2	LUL, LLL	14.0	29.9	29.9
4	87	F	1	Colon	Resistant	29.5	50 Gy in 5 Fx	100	1	RLL	16.9	16.9	
5	61	F	1	Colon	Resistant	18.7	54 Gy in 3 Fx	151.2	1	LUL	17.0	30.4	
6	79	M	0	Colon	Resistant	39.3	54 Gy in 3 Fx	151.2	2	RML, RLL	7.3	25.9	25.9
7	66	M	0	Colon	Resistant	110.1	40 Gy in 5 Fx	72	1	LLL	3.6	23.7	23.7
8	72	M	1	Colon	Resistant	32.8	54 Gy in 3 Fx	151.2	1	LLL	20.2	28.6	
9	83	F	0	Endometrial (endometrioid)	Resistant	35.9	50 Gy in 5 Fx	100	2	RUL, RLL	12.5	24.4	
10	55	F	0	Endometrial (leiomyosarcoma)	Resistant	27.6	50 Gy in 5 Fx	100	1	RLL	2.1	24.3	
11	66	F	1	Endometrial (serous)	Resistant	51.0	60 Gy in 30 Fx	72	2	RML, RUL	2.2	2.5	2.5
12	56	M	0	Melanoma	Resistant	214.1	30 Gy in 5 Fx	48	1	LLL	11.0	45.4	45.4
13	73	M	0	Renal cell	Resistant	48.0	35 Gy in 5 Fx	59.5	1	Left pleura	12.7	70.6	
14	60	M	1	Renal cell	Resistant	synchronous	50 Gy in 5 Fx	100	2	LLL, LUL	6.3	17.8	
15	55	M	1	Rectal	Resistant	31.9	72 Gy in 18 Fx	100.8	2	LUL, RLL	12.5	36.7	
16	66	M	0	Rectal	Resistant	50.8	40 Gy in 5 Fx	72	1	RLL	4.7	5.0	
17	67	M	2	Rectal	Resistant	0.7	50 Gy in 5 Fx	100	2	RLL	2.2	24.0	24.0
18	67	F	2	Rectal	Resistant	19.8	50 Gy in 5 Fx	100	1	LUL	9.9	14.2	14.2
19	72	M	1	Rectal	Resistant	21.8	60 Gy in 15 Fx	84	1	Right hilum	5.0	34.9	

Abbreviations: BED = biologically equivalent dose; ECOG = eastern cooperative oncology group; RT = radiation therapy; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

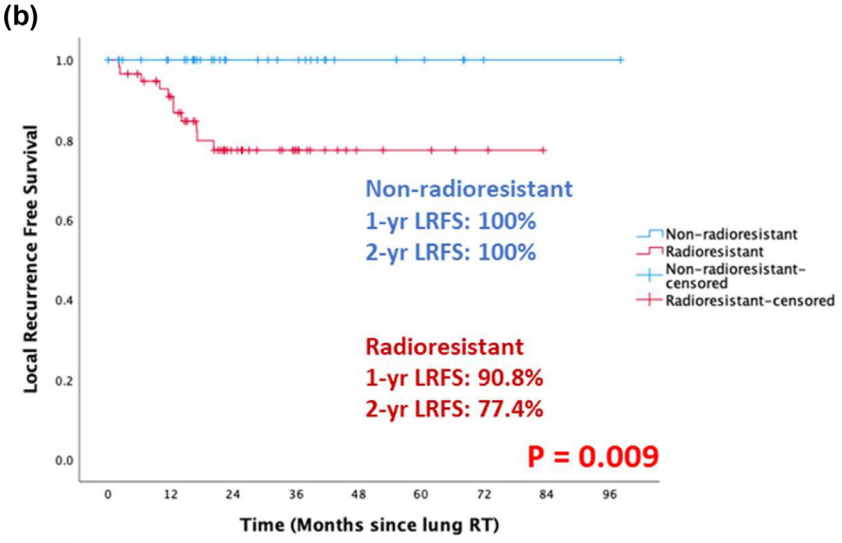
*Time from initial diagnosis to identification of pulmonary metastasis on imaging.

†Time from RT to development of local progression or recurrence.

‡Time from RT to last follow-up or death.



Numbers at risk: LRFS (months since lung RT)	0	12	24	36	48	60	72	84
BED < 100	16	8	2	1	0	0	0	0
BED >= 100	57	46	23	13	5	4	2	0



Numbers at risk: LRFS (months since lung RT)	0	12	24	36	48	60	72	84
Non-radioresistant	35	28	16	13	6	5	1	0
Radioresistant	57	46	23	13	5	4	2	0

Figure 2 (a) Local recurrence-free survival (LRFS) for radioresistant subgroup comparing treatment with biologically effective dose (BED) <100 Gy (red) and BED >100 Gy (blue). (b) LRFS for patients treated with BED >100 Gy comparing non-radioresistant (blue) and radioresistant (red) subgroups. *P* values (log-rank) and 1- and 2-year LRFS are shown on the right.

P = .048) was associated with poorer LRFS (Table E4). Two-year LRFS for IGTV ≤30 cm^3 and IGTV>30 cm^3 were 83.3% and 44.7%, respectively (*P* = .034; Fig. E6).

Discussion

The lung is a common site of metastasis for many solid tumors. RT is a frequently used, noninvasive treatment option that typically provides good local control and acceptable toxicity. It is unclear, however, whether pulmonary metastases from radioresistant primaries have poorer local control after radiation treatment, and whether dose escalation will decrease local failure among higher-risk patients. Within our cohort, we found that radioresistant tumors had poorer LRFS compared with nonradioresistant tumors at all RT doses given. For RT regimens with BED10 <100 Gy, both

Table 4 Associations between baseline characteristics and LF after lung RT

	LF univariable analysis			LF multivariable analysis		
Characteristic	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age, y ≥70 (vs <70)	0.614	0.246-1.527	.294			
Sex Female (vs male)	0.597	0.227-1.571	.296			
ECOG ≥2 (vs <2)	3.804	1.368-10.579	.010	2.917	1.030-8.260	.044
Smoking history (pack-years) ≥ 10 (vs <10)	1.179	0.438-3.173	.745			
Initial primary M stage M1 (vs M0)	0.830	0.275-2.502	.740			
Time to develop lung metastases ≥12 mo (vs <12 mo)	1.934	0.563-6.638	.294			
RT BED dose to lung metastasis ≥100 (vs <100)	0.263	0.105-0.656	.004	0.335	0.105-1.073	.066
No. of lung lesions treated >1 lesion (vs 1 lesion)	1.445	0.549-3.803	.456			
Radioresistance Radioresistance (vs nonradioresistant)	10.830	1.445-81.162	.020			
Primary site Colorectal (vs noncolorectal)	3.060	1.204-7.777	.019	1.952	0.740-5.147	0.176
Disease state Oligoprogression (vs oligometastasis)	3.032	1.217-7.553	.017			
Systemic treatment after SBRT Systemic treatment (vs no systemic treatment)	1.520	0.547-4.220	.422			

Note: Radioresistance and disease state were not included in multivariable analysis given collinearity with primary site.
Abbreviations: BED = biologically equivalent dose; HR = hazard ratio; LF = local failure; ECOG = XXX; SBRT = stereotactic body radiation therapy.

radioresistant and nonradioresistant tumors had poorer local control than when treated with a regimen of BED10 ≥100 Gy. Within our radioresistant group, we identified that patients with CRC primaries experienced high rates of local failure even when using high doses (2-year LRFS 67.6% overall and 75.2% when using BED10 ≥100 Gy). Nonradioresistant tumors (2-year LRFS 95.8% overall and 100% when using BED10 ≥100 Gy, with the only local failure having received 30 Gy in 5 fractions [BED10 of 48 Gy]) and non-CRC radioresistant primaries (2-year LRFS 78.9% overall and 85.1% when using BED10 ≥100 Gy, with 3 of 6 local failures having received only 30 to 35 Gy in 5 fractions or 60 Gy in 30 fractions) fared significantly better. Our results are supported by recently published data of sarcoma-associated pulmonary metastases which found 2-year LRFS of 83% with the use of SBRT regimens with BED10 >100 Gy.[66] Our study demonstrates that not all classically radioresistant primaries are necessarily radioresistant to ablative RT doses to the lung.

Previous studies have explored the use of RT for pulmonary metastatic lesions and are shown in Table E5. Overall, these studies have found that higher BED, smaller tumor size, non-CRC primary, and shorter interval between diagnosis and treatment of metastases are favorable prognostic factors influencing local control of lung metastases after RT. In general, a BED10 of 100 Gy was found to serve as a threshold for adequate local control, which is concordant with our results. Kalinauskaite et al suggests that BED10 <100 Gy using single fraction radiosurgery (SFRS; 25-26 Gy median D_{max} of 53 Gy and a median BED_{max} of 81 Gy) might be sufficient for local control in small lung metastases (median PTV ≤ 9.9 cm^3, median diameter 12 mm)[35]; however, this conflicts with the findings of Sharma et al, which noted that SFRS was associated with lower local control than multifraction treatment.[36] SFRS was not investigated in our study, and it is unclear whether comparable local control can be achieved with BED10 <100 as BED10>100 if SFRS is used.

When focusing only on tumors treated with BED10 ≥100 Gy, radioresistant tumors still showed poorer LRFS than nonradioresistant tumors. This prompted us to investigate prognostic factors for local failure

among radioresistant tumors. In addition to BED10 <100 Gy, CRC primary was associated with a greater risk of local failure on univariable Cox regression analysis. A BED10 dose of at least 100 Gy is especially critical for these patients with CRC; when using a dose below 100 Gy their 2-year LRFS drops to 33.3%. Previously, Sulaiman et al[37] and Berkovic et al[38] found that BED10 >110 Gy and >120 Gy, respectively, were associated with improved local control. In a recent meta-analysis Jingu et al showed that LC was significantly inferior for pulmonary metastases derived from a CRC primary, and dose escalation (BED10 >130 Gy) was associated with decreased local recurrence from CRC metastases.[39] However, we did not find that a higher threshold of BED10 (>120 Gy) led to better local control among the CRC subgroup, albeit with a small number of patients.

On univariable Cox regression analysis of prognostic factors for local recurrence among the CRC subgroup, a greater total IGTV planning volume >30 cm^3 was associated with a higher risk of local failure. Our findings bring up the possibility that other forms of treatment escalation may benefit patients with large higher risk radioresistant tumors. Given that the first relapse in the entire cohort was more likely to occur outside the irradiated field than within it, systemic treatment may provide benefit for both local and distant control. Only one of the 73 radioresistant patients in our cohort received concurrent systemic treatment during their radiation treatment. Recent findings also suggest that in addition to local ablation, high-dose RT has the additional benefit of stimulating the immune system through the release of neo-antigens and the activation of host immunity, which may in turn improve local and distant control.[40] Future studies should explore whether patients treated concurrently or sequentially with RT and systemic treatments (chemotherapy, immunotherapy, or targeted therapies) could sustain improved long-term outcomes.

Overall, the major limitation of this study is its retrospective design with heterogeneous primary tumor types and a limited number of patients from a single center. Tumor size and location also varied among patients. Although we excluded patients with RT regimens with BED10 <48 Gy, the included patients did have heterogenous dose-fractionation schedules and other dose metrics besides prescription dose were not considered. Toxicity data was not collected to determine whether these higher-BED treatments for pulmonary metastases were associated with worsened toxicity compared with lower-BED treatments. It will be critical for future studies to include toxicity data as lung SBRT prescription doses are typically limited due to OAR constraints and tumor location. Finally, systemic treatment patterns in relation to RT were not explored within this study.

Conclusion

BED10 ≥100 Gy may be preferred for pulmonary metastases whenever safe and feasible to do so to optimize local control, especially for CRC. When using these high-dose RT regimens, local control is high for metastases from all other nonlung primaries, including classically radioresistant tumors like melanoma, renal cell carcinoma, and sarcoma. In the future, high-quality prospective trials are needed to validate our results and determine the benefit of treatment escalation for radioresistant CRC metastases.

Disclosures

Henry S. Park reports consulting, personal honoraria, and being on an advisory board of AstraZeneca; personal honoraria from Bristol Myers Squibb, Daichii Sankyo, and G1 Therapeutics; being on the advisory board of Galera and Regeneron; institutional research funding from Merck; consulting and institutional research funding from RefleXion.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101500.

References

1. Greelish JP, Friedberg JS. Secondary pulmonary malignancy. *Surg Clin N Am*. 2000;80: 633657.
2. Gutierrez E, et al. Current evidence for stereotactic body radiotherapy in lung metastases. *Curr Oncol*. 2021;28:2560-2578.
3. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol*. 2020;148:157-166.
4. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: A European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21:e18-e28.
5. Gomez D, Tang C, Zhang J, et al. Local consolidative therapy vs maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019;37:1558-1565.
6. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4: e173501.
7. Palma D. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: Long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol*. 2020;38: 2830-2838.

8. Navarria P, Ascolese AM, Cozzi L, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. *Eur J Cancer*. 2015;51:668-674.
9. Pasqualetti F, Montrone S, Vivaldi C, et al. Stereotactic body radiotherapy in patients with lung oligometastases from colorectal cancer. *Anticancer Res*. 2017;37:315-319.
10. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): Study protocol for a randomized phase III trial. *BMC Cancer*. 2019;19:816.
11. Bauman GS, Corkum MT, Fakir H, Nguyen TK, Palma DA. Ablative radiation therapy to restrain everything safely treatable (ARREST): Study protocol for a phase I trial treating polymetastatic cancer with stereotactic radiotherapy. *BMC Cancer*. 2021;21:405.
12. Sheehan JP, Sun M-H, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery in patients with renal cell carcinoma metastasis to the brain: Long-term outcomes and prognostic factors influencing survival and local tumor control. *J Neurosurg*. 2003;98:342-349.
13. Mori Y, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for cerebral metastatic melanoma: Factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys*. 1998;42:581-589.
14. Wowra B, Siebels M, Muacevic A, et al. Repeated GammaKnife surgery for multiple brain metastases from renal cell carcinoma. *J Neurosurg*. 2002;97:785-793.
15. Lavine SD, Petrovich Z, Cohen-Gadol AA, et al. GammaKnife radiosurgery for metastatic melanoma: An analysis of survival, outcome, and complications. *Neurosurgery*. 1999;44:59-66.
16. Lwu S, Goetz P, Monsalves E, et al. Stereotactic radiosurgery for the treatment of melanoma and renal cell carcinoma brain metastases. *Oncol Rep*. 2013;29:407-412.
17. Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL. Stereotactic radiosurgery for patients with "radioresistant" brain metastases. *Neurosurgery*. 2008;62(Suppl 2):790-801.
18. Manon R, O'Neill A, Knisely J, et al. Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: An Eastern Cooperative Oncology Group study (E 6397). *J Clin Oncol*. 2005;23:8870-8876.
19. Chang EL, Selek U, Hassenbusch III SJ, et al. Outcome variation among "radioresistant" brain metastases treated with stereotactic radiosurgery. *Neurosurgery*. 2005;56:936-945. ; discussion 936-945.
20. Grob JJ, Regis J, Laurans R, et al. Radiosurgery without whole brain radiotherapy in melanoma brain metastases: Club de Cancérologie Cutanée. *Eur J Cancer*. 1998;34:1187-1192.
21. McPherson CM, Suki D, Feiz-Erfan I, et al. Adjuvant whole-brain radiation therapy after surgical resection of single brain metastases. *Neuro Oncol*. 2010;12:711-719.
22. Wang X, Zamdborg L, Ye H, et al. A matched-pair analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer versus early stage non-small cell lung cancer. *BMC Cancer*. 2018;18:962.
23. Binkley MS, Trakul N, Jacobs LR, et al. Colorectal histology is associated with an increased risk of local failure in lung metastases treated with stereotactic ablative radiation therapy. *Int J Radiat Oncol Biol Phys*. 2015;92:1044-1052.
24. Ahmed KA, Scott JG, Arrington JA, et al. Radiosensitivity of lung metastases by primary histology and implications for stereotactic body radiation therapy using the genomically adjusted radiation dose. *J Thorac Oncol*. 2018;13:1121-1127.
25. Ahmed KA, Fulp WJ, Berglund AE, et al. Differences between colon cancer primaries and metastases using a molecular assay for tumor radiation sensitivity suggest implications for potential oligometastatic SBRT patient selection. *Int J Radiat Oncol Biol Phys*. 2015;92:837-842.
26. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine sarcoma: Analysis of 13,089 cases based on Surveillance, Epidemiology, and End Results Database. *Int J Gynecol Cancer*. 2016;26:1098-1104.
27. Li Y, Ren H, Wang J. Outcome of adjuvant radiotherapy after total hysterectomy in patients with uterine leiomyosarcoma or carcinosarcoma: A SEER-based study. *BMC Cancer*. 2019;19:697.
28. Huh WK, Powell M, Leath 3rd CA, et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical Stage I patients with and without adjuvant therapy. *Gynecol Oncol*. 2003;91:470-475.
29. Kwon J, Ackerman I, Franssen E. The role of abdominal-pelvic radiotherapy in the management of uterine papillary serous carcinoma. *Int J Radiat Oncol Biol Phys*. 2004;59:1439-1445.
30. Lim P, Al Kushi A, Gilks B, Wong F, Aquino-Parsons C. Early stage uterine papillary serous carcinoma of the endometrium: Effect of adjuvant whole abdominal radiotherapy and pathologic parameters on outcome. *Cancer*. 2001;91:752-757.
31. Mancini BR, Park HS, Harder EM, et al. Elderly patients undergoing SBRT for inoperable early-stage NSCLC achieve similar outcomes to younger patients. *Lung Cancer*. 2016;97:22-27.
32. Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys*. 2005;63:1427-1431.
33. Xia T, Li H, Sun Q, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable stage I/II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2006;66:117-125.
34. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2008;70:685-692.
35. Kalinauskaite GG, Tinhofer II, Kufeld MM, et al. Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases. *BMC Cancer*. 2020;20:404.
36. Sharma A, Duijm M, Oomen-de Hoop E, et al. Factors affecting local control of pulmonary oligometastases treated with stereotactic body radiotherapy. *Acta Oncol*. 2018;57:1031-1037.
37. Sulaiman NS, Fujii O, Demizu Y. Particle beam radiation therapy using carbon ions and protons for oligometastatic lung tumors. *Radiat Oncol*. 2014;9:183.
38. Berkovic P, Gulyban A, et al. Stereotactic robotic body radiotherapy for patients with oligorecurrent pulmonary metastases. *BMC Cancer*. 2020;20:402.
39. Jingu K, Matsushita H, Yamamoto T, et al. Stereotactic radiotherapy for pulmonary oligometastases from colorectal cancer: A systematic review and meta-analysis. *Technol Cancer Res Treat*. 2018;17:1533033818794936.
40. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: A beneficial liaison? *Nat Rev Clin Oncol*. 2017;14:365-379.