ORIGINAL ARTICLE

Radiotherapy Improves Survival in NSCLC After Oligoprogression on Immunotherapy: A Cohort Study

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ABSTRACT

Introduction: The patterns of oligoprogression after first-line immune checkpoint inhibitors (ICIs) for metastatic NSCLC are yet to be well established. An increasing volume of data suggests that directed radiotherapy improves survival outcomes in patients with progression after ICIs.

Methods: A retrospective cohort study was performed on patients with metastatic NSCLC who had completed first-line programmed death-(ligand) 1 inhibitor therapy with or without chemotherapy at two high-volume cancer centers. We sought to characterize the frequency and location of oligoprogression and determine the overall survival (OS) after radiotherapy in this population.

Results: A total of 159 patients were included in the study. At first progression, 62 (39.0%) were classified as undergoing oligoprogression. Multivariate analysis confirmed the presence of brain metastases was associated with an increased likelihood of oligoprogression (OR = 2.44, p = 0.04) with most (63.2%) of these patients experiencing progression intracranially. The presence of liver metastases was associated with a decreased likelihood of oligoprogression (OR = 0.17, $p < 0.01$). For patients with oligoprogression, those who received radiotherapy had a longer median progression-free survival-2 (PFS2) (17 versus 11.5 mo, HR = 0.51, p = 0.02) and a longer median OS (23 versus 13 mo, HR = 0.40, $p < 0.001$) compared with those who did not receive radiotherapy. No difference in PFS2 or OS outcomes was observed between patients who received radiotherapy versus those who did not for systemic progression.

Conclusions: In patients with oligoprogressive metastatic NSCLC after treatment with first-line ICIs, radiotherapy significantly improves OS and PFS2 outcomes. Patients with baseline brain metastases are more likely to experience oligoprogression. Further prospective studies in directed, less heterogeneous populations of patients with metastatic NSCLC will be fundamental to optimize management.

Keywords: NSCLC; Immunotherapy; Oligoprogression; Radiotherapy

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Introduction

Immune checkpoint inhibitors (ICIs) have improved survival for patients with metastatic NSCLC without oncogenic drivers. In certain patients with metastatic NSCLC, ICIs have durable efficacy, with 18.4% to 31.9% of patients alive at 5 years.[1–3] However, most patients will experience progression either owing to primary or acquired resistance.

It has become evident that the pattern of progression is an important prognostic factor for patients with metastatic NSCLC. Patients who progress in limited sites, termed oligoprogression, have improved survival outcomes compared with those who progress in multiple sites; systemic progression.[4] Recently, a consensus definition for oligoprogression was formulated as a subclassification of oligometastatic disease.[5,6] Oligometastatic disease is a term initially defined by Hellman and Weichselbaum[7] as metastases to a single or limited number of organs. The ESTRO-ASTRO consensus classification defines oligoprogression as new or enlarging oligometastases in patients undergoing active systemic therapy.[6] However, the definition of "limited metastases" remains somewhat ambiguous and open to interpretation by clinicians. In cases of oligoprogression, contemporary guidelines recommend local ablative therapy with radiotherapy - stereotactic ablative radiation therapy (SABR) or conventional radiotherapy to extend the benefit of the preceding therapy.[8]

Some studies have shown the benefit of local therapy to extend overall survival (OS) and time to tumor progression on next-line treatment (progression-free survival-2 [PFS2]) in patients with oligoprogressive NSCLC.[4,9–11] However, studies in NSCLC describing the benefits of local therapy have generally included patients with multiple tumor types,[12] or those progressing after treatment with second-line ICIs[4,10] or tyrosine kinase inhibitors.[9,11] Therefore, the role of local therapy in oligoprogressive NSCLC without oncogenic drivers for patients treated with first-line ICIs is poorly understood owing to prior heterogeneity in study populations. In addition, there is a paucity of data regarding the management of oligoprogression after programmed death-(ligand) 1 (PD-[L]1) inhibitors and chemotherapy.

In this study, we sought to characterize the frequency and location of oligoprogression and determine the benefit of radiotherapy in patients with metastatic NSCLC treated with first-line PD-(L)1 inhibitors with or without chemotherapy.

Materials and Methods

Patients and Treatment

A retrospective cohort study was performed and data were extracted from the electronic medical records at two Australian tertiary cancer care centers from January 2017 to January 2022. Patients with locally advanced or metastatic NSCLC without a targetable oncogenic driver (EGFR, anaplastic lymphoma kinase, and ROS1 negative) who received at least one dose of first-line anti–PD-1 with or without platinum-doublet chemotherapy (either carboplatin or cisplatin and pemetrexed for non-squamous tumors and taxane or gemcitabine for squamous tumors). Patients who had progressed on first-line therapy were included. Radiological assessments were performed locally. Approval from the Institutional Ethics Review Board (Western Sydney Local Health District Human Research Ethics Committee; 2020/ETH02064) was obtained. A waiver of consent was obtained from the Human Research Ethics Committee for this study, permitting the research to proceed without obtaining individual consent from participants.

Data Collection

Patient demographics, tumor histopathology, systemic therapy details, tumor response, sites of progression, management of progression, and survival outcomes were collected. Details regarding the management of oligoprogression were collected including systemic therapy type, radiotherapy type, site, and dose. The equivalent dose in 2 Gy fractions (EQD2) was calculated and therapy was categorized by low dose ($<$45 Gy EQD2) or high dose ($\geq$45 Gy EQD2) using an α/β ratio of 10.

Management of Progression

Decisions regarding the management of oligoprogression or systemic progression were made by the treating medical oncologist and radiation oncologist with the input of a multidisciplinary team for difficult cases. In general, if the location of oligoprogression was amenable to radiotherapy and patient performance status allowed, radiotherapy to treat disease progression was administered. In patients who had radiotherapy after systemic progression, radiotherapy was often used for symptom control.

Disease Assessment

Computed tomography (CT) of the chest, abdomen, and pelvis (3-mm slices) was obtained at baseline (before starting treatment), then every 12 to 16 weeks or more frequently, according to institutional practice. Patients either underwent an additional baseline fluorodeoxyglucose-positron emission tomography scan or whole-body bone scan to assess for bone metastases, if clinically indicated, before systemic therapy. All patients had central nervous system (CNS) imaging before the commencement of systemic therapy, either

with CT or magnetic resonance imaging (MRI). In patients with known brain metastases, patients were followed up with an MRI brain, or CT if the MRI was contraindicated, every 12 to 16 weeks. All patients had repeat CNS imaging at the progression of the disease, either with CT or MRI to confirm CNS involvement at progression.

Initial progression of disease (progression-free survival-1 [PFS1]) after commencement of anti–PD-1 with or without chemotherapy was dichotomized as oligoprogression; defined as progression in $\leq$three sites, within one to two anatomical locations, or systemic progression; defined as progression in greater than three sites. Oligoprogression was further characterized as repeat (oligometastatic disease at original diagnosis) or induced (polymetastatic disease at original diagnosis) in keeping with the European Society for Radiotherapy & Oncology-European Society for Medical Oncology guidelines.[5]

Statistical Analysis

The outcomes assessed included: (1) OS and PFS2 after receipt of radiotherapy for the management of oligoprogression; (2) OS and PFS2 after receipt of radiotherapy in the overall cohort and the systemic progression cohort; (3) OS, PFS1, and PFS2 in the oligoprogression cohort compared with the systemic progression cohort and (4) to determine the clinical predictors of oligoprogression.

Descriptive analysis was used to assess baseline characteristics and management of progression. Continuous variables were summarized using medians and interquartile ranges (IQR) and categorical variables were summarized using proportions. A chi-square test was employed to compare categorical variables between two independent groups. Univariate and multivariate logistic regression was performed to identify factors predictive of oligoprogression. Factors for regression analyses included baseline clinical characteristics, such as age, sex, Eastern Cooperative Oncology Group performance status, tumor histopathology, site of metastases, the volume of disease, and oligometastatic versus polymetastatic disease and size of metastatic deposits. Multicollinearity was assessed using variance inflation factor, variables with a variance inflation factor of approximately 1 were considered independent of the others. Baseline characteristics with a p values $\leq$0.05 from the univariate logistic regression analysis were included in the multivariate model.

OS, PFS1, and PFS2 were calculated from the date of commencement of first-line treatment to the date of an event (either death [OS], first progression event [PFS1], or second progression event after first progression [PFS2]). Patients without a clinical event were censored at the last follow-up date. Kaplan-Meier Curves were formulated and survival differences between groups were compared using Cox proportional hazards tests. Median survival and associated 95% confidence interval (CI) were calculated. All statistical analyses were performed using R (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) and some graphics were created using GraphPad Prism (version 10.0; GraphPad Software, Boston, MA) and BioRender.

Results

Patient Characteristics

Two hundred and two patients were treated with first-line ICI with or without chemotherapy across the two centers. One hundred and fifty-nine (78.7%) of these had progressed at the time of analysis and these patients were included in the final cohort for analysis (Supplementary Fig. 1). At baseline, before the commencement of first-line systemic therapy, the median age was 68 (IQR: 60–75) (Table 1). The Eastern Cooperative Oncology Group performance status was 0 to 1 in 137 patients (86.2%) and $\geq$2 in 22 patients (13.8%). Ninety-three (58.5%) had adenocarcinoma, 44 (27.7%) had squamous cell carcinoma, 18 (11.3%) had undifferentiated large cell carcinoma, two (1.3%) had adenosquamous carcinoma, and two (1.3%) had NSCLC, not otherwise specified. PD-L1 status was $<$1% in 36 (22.6%), 1–49% in 33 (20.8%), $\geq$50% in 76 (47.8%). In 14 patients (8.8%), PD-L1 was not available. Twenty-four patients (15.1%) were never smokers, and 135 (84.9%) had a history of smoking (either current or ex-smokers). Seventy-seven (48.4%) were treated with anti–PD-1 monotherapy and 82 (51.6%) were treated with platinum-doublet chemotherapy plus anti–PD-1 (chemoimmunotherapy). Ninety-two patients (57.9%) received upfront radiotherapy before systemic therapy (Supplementary Table 1).

At baseline, 30 (18.9%) had oligometastatic disease, 129 (81.1%) had polymetastatic disease, 37 (23.3%) had brain metastases, 26 (16.4%) had liver metastases, 29 (18.2%) had adrenal metastases and 52 (32.7%) pleural effusion or metastases.

While all patients were negative for EGFR, anaplastic lymphoma kinase, and ROS1, 105 patients (66.0%) underwent further next-generation sequencing for other mutations (Supplementary Table 2). Forty-two (26.4%) had additional oncogene mutations found including 30 (18.9%) with a KRAS mutation; of which nine had a KRAS G12C mutation.

Of the 37 patients with baseline brain metastases, 32 (76.2%) had local therapy before systemic therapy.

Table 1. Baseline Characteristics

Characteristic	All N = 159, n (%)	Oligoprogression n = 62, n (%)	Systemic Progression n = 97, n (%)
PFS1[a]	4 mo (95% CI: 4-6)	7 mo (95% CI: 5-11)	3 mo (95% CI: 2-5)
Age[b]	68 (60-75)	69 (62-74)	67 (59-75)
Tumor type			
Adenocarcinoma	93 (58.5)	34 (54.8)	59 (60.8)
Squamous cell carcinoma	44 (27.7)	17 (27.4)	27 (27.8)
Undifferentiated large cell carcinoma	18 (11.3)	10 (16.1)	8 (8.2)
Adenosquamous carcinoma	2 (1.3)	0 (0)	2 (2.1)
Other	2 (1.3)	1 (1.6)	1 (1.0)
Treatment			
Immunotherapy	77 (48.4)	27 (43.5)	50 (51.5)
Chemoimmunotherapy	82 (51.6)	35 (56.5)	47 (48.5)
Upfront RT			
No upfront RT	92 (57.9)	31 (50.0)	61 (62.9)
Upfront RT	67 (42.1)	31 (50.0)	36 (37.1)
ECOG PS			
0	50 (31.4)	20 (32.3)	30 (30.9)
1	87 (54.7)	37 (59.7)	50 (51.5)
2	17 (10.7)	5 (8.1)	12 (12.4)
3	5 (3.1)	0 (0)	5 (5.2)
Smoking status			
Never-smoker	24 (15.1)	8 (12.9)	16 (16.5)
Ex-smoker	92 (57.9)	37 (59.7)	55 (56.7)
Current smoker	43 (27.0)	17 (27.4)	26 (26.8)
PD-L1 status			
<1%	36 (22.6)	16 (25.8)	20 (20.6)
1-49%	33 (20.8)	8 (12.9)	25 (25.8)
≥50%	76 (47.8)	37 (59.7)	39 (40.2)
Not tested	14 (8.8)	1 (1.6)	13 (13.4)
Oligometastatic at diagnosis			
Oligometastatic	30 (18.9)	16 (25.8)	14 (14.4)
Polymetastatic	129 (81.1)	46 (74.2)	83 (85.6)
Volume of disease			
<5 metastases	30 (18.9)	16 (25.8)	14 (14.4)
5-20 metastases	96 (60.4)	36 (58.1)	60 (61.9)
>20 metastases	33 (20.8)	10 (16.1)	23 (23.7)
Brain metastases			
Not present	122 (76.7)	43 (69.4)	79 (81.4)
Present	37 (23.3)	19 (30.6)	18 (18.6)
Lung metastases			
Not present	82 (51.6)	38 (61.3)	44 (45.4)
Present	77 (48.4)	24 (38.7)	53 (54.6)
Liver metastases			
Not present	133 (83.6)	59 (95.2)	74 (76.3)
Present	26 (16.4)	3 (4.8)	23 (24.7)
Adrenal metastases			
Not present	130 (81.8)	54 (87.1)	76 (78.4)
Present	29 (18.2)	8 (12.9)	21 (21.6)
Pleural effusion/metastases			
Not present	107 (67.3)	45 (72.6)	62 (63.9)
Present	52 (32.7)	17 (27.4)	35 (36.1)
Lymph node metastases			
Not present	27 (17.0)	13 (21.0)	14 (14.4)
Present	132 (83.0)	49 (79.0)	83 (85.6)

[a]Median (95% CI).
[b]Median (IQR).
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PD-L1, programmed death-ligand 1; PFS1, Progression-free survival 1; RT, radiotherapy.

Twelve underwent surgery followed by cavity stereotactic radiosurgery (SRS), 15 underwent SRS alone, three patients had whole brain radiotherapy, two underwent surgery alone and five had no upfront local therapy (Supplementary Table 3). Patients who did not receive upfront local therapy were asymptomatic, did not require steroids, and had lesions ≤1.5 cm.

PFS1

At first progression, 62 (39.0%) were classified as oligoprogression, while 97 (61.0%) experienced systemic progression. With a median follow-up of 41 months (IQR: 31–59), the median PFS1 for patients experiencing oligoprogression was 7 months (95% CI: 5–11 mo) versus 3 months (95% CI: 2–5 mo) for patients who experienced systemic progression (hazard ratio [HR] = 0.61, 95% CI: 0.44–0.85, $p < 0.01$; Fig. 1*A*).

Patients who were classified as oligometastatic at diagnosis had a median PFS1 of 5 months (95% CI: 3–8 mo) versus 4 months (95% CI: 4–6 mo) for patients classified as polymetastatic (HR = 0.86, 95% CI: 0.57–1.28, $p = 0.5$; Supplementary Fig. 2).

Characteristics and Predictors of Oligoprogressive Disease

Of the 62 patients who experienced oligoprogression, 16 (25.8%) had repeat oligoprogression and 46 (74.2%) had induced oligoprogression. The most common sites of oligoprogression were the lung primary (n = 23, 37.1%), brain (n = 13, 20.9%), bone (n = 12, 19.4%), adrenal gland (n = 5, 8.1%) and other sites including lung metastases (n = 2, 3.2%), pleura (n = 3, 4.8%), liver (n = 1, 1.6%) and lymph node metastases (n = 1, 1.6%) (Fig. 2; Supplementary Table 4). Of the patients who had oligoprogression, 40 (64.5%) of these had progression in existing lesions and 22 (35.5%) had progression with the development of new lesions (Fig. 3). Patients with squamous cell carcinoma (17 of 44, 38.6%) experienced similar oligoprogression rates versus those with non-squamous disease (45 of 115, 39.1%, $p = 0.9$).

On univariate analysis, the presence of brain metastases at baseline was associated with an increased likelihood of oligoprogression at PFS1. The presence of bone and liver metastases was associated with an increased likelihood of systemic progression at PFS1. Multivariate analysis including all significant findings on univariate analysis confirmed the presence of brain metastases was

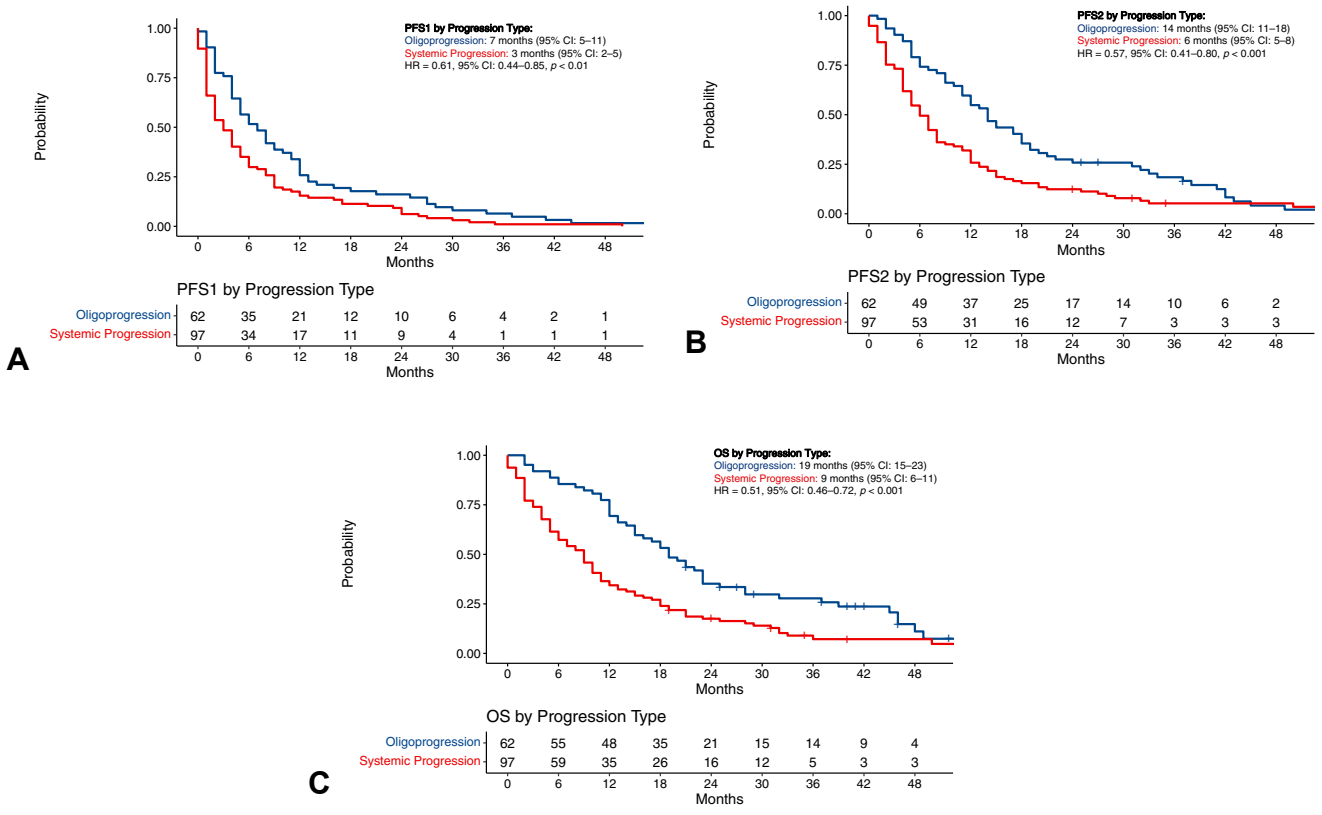

Figure 1. Survival outcomes by progression type. *(A)* PFS1 by oligoprogression versus systemic progression; *(B)* PFS2 by oligoprogression versus systemic progression; *(C)* OS by oligoprogression versus systemic progression. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS1, progression-free survival-1; PFS2, progression-free survival-2.

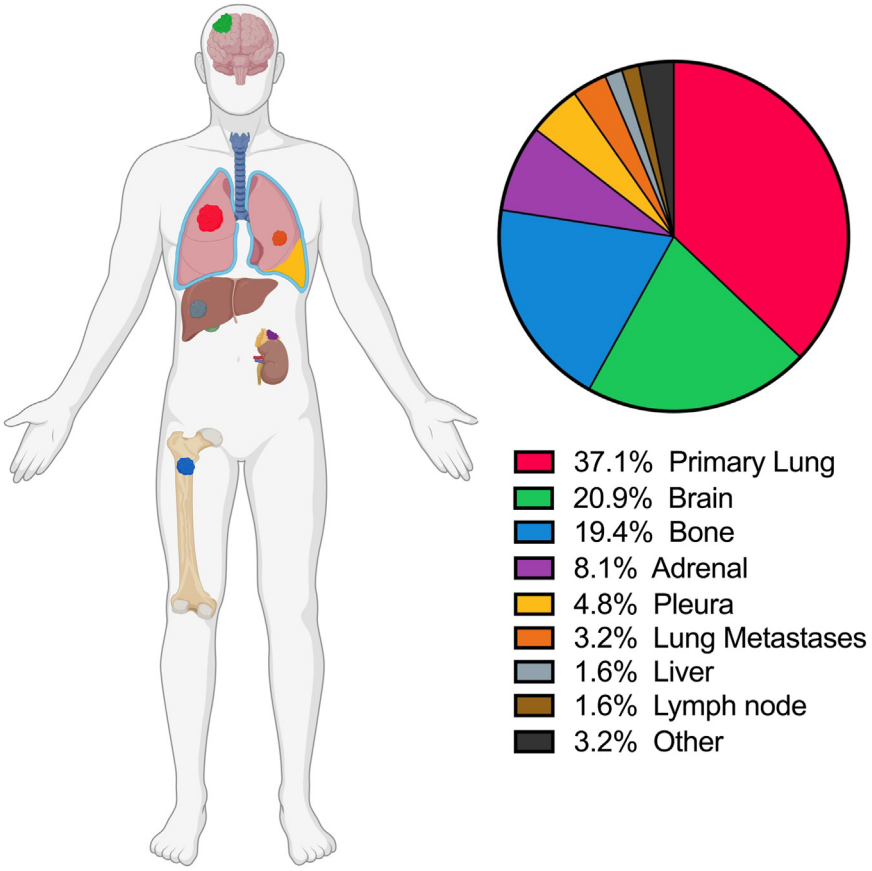

Figure 2. Sites of oligoprogression.

associated with an increased likelihood of oligoprogression at PFS1 (OR = 2.44, 95% CI: 1.06–3.90, $p = 0.04$) and the presence of liver metastases was associated with increased likelihood of systemic progression at PFS1 (OR = 0.17, 95% CI: 0.04–0.54, $p < 0.01$) (Table 2).

Management of the First Progression Event

At the first progression event, 45 patients (28.3%) were treated with radiotherapy alone, 22 patients (13.8%) were treated with both radiotherapy and continuation of ICI beyond progression, nine (5.7%) continued ICI beyond progression (without receipt of radiotherapy), 56 patients (35.2%) received best supportive care and 25 patients (15.7%) had a change to systemic therapy of whom eight were enrolled on a clinical trial (Table 3). No patients had surgery at progression.

Management of the first progression event was largely dependent on whether the patient experienced oligoprogression or systemic progression. Patients who

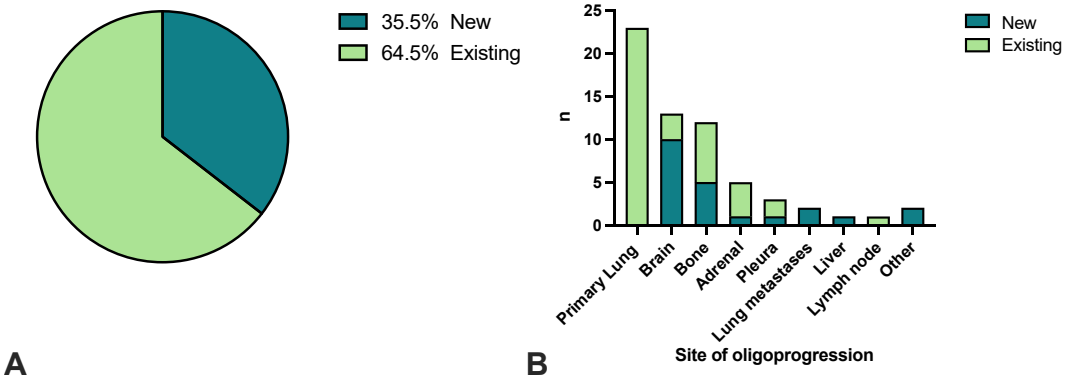

Figure 3. New versus existing lesions by sites of oligoprogression.

Table 2. Univariate and Multivariate Analysis Predictive of Oligoprogression at PFS1

	Univariate[a]			Multivariate[a]			
Characteristics	OR	95% CI	*p* Value	OR	95% CI	*p* Value	VIF
Age, y			0.16				
<65	1.00						
≥65	1.60	0.89-3.16					
ECOG PS			0.86				
0-1	1.00						
≥2	1.06	0.53-2.10					
Sex			0.89				
Female	1.00						
Male	0.95	0.50-1.84					
Tumor type			0.36				
Adenocarcinoma	1.00						
SCC	1.09	0.52-2.28					
Large cell	2.17	0.78-6.19					
Other	1.74	0.07-44.8					
Treatment type			0.32				
Immunotherapy	1.00						
Chemoimmunotherapy	1.38	0.73-2.63					
Upfront radiotherapy			0.11				
No	1.00						
Yes	1.69	0.89-3.25					
Volume of disease			0.16				
<5 metastases	1.00						
5-20 metastases	0.53	0.23-1.20					
>20 metastases	0.38	0.13-1.05					
Size			0.08				
No lesions ≥5 cm	1.00						
One or more lesions ≥5 cm	1.81	0.93-3.53					
Oligometastatic at diagnosis			0.08				
Oligometastatic	1.00						
Polymetastatic	0.48	0.21-1.08					
Adrenal metastases			0.16				
Not present	1.00						
Present	0.54	0.21-1.26					
Bone metastases			**0.02**			0.08	1.007
Not present	1.00						
Present	**0.46**	**0.23-0.89**		0.53	0.26-1.07		
Brain metastases			**0.04**			**0.04**	1.006
Not present	1.00						
Present	**2.31**	**1.04-5.22**		**2.44**	**1.06-3.90**		
Liver metastases			**<0.001**			**<0.01**	1.008
Not present	1.00						
Present	**0.16**	**0.04-0.50**		**0.17**	**0.04-0.54**		
Lymph node metastases			0.29				
Not present	1.00						
Present	0.64	0.27-1.48					
Pleural metastases			0.25				
Not present	1.00						
Present	0.67	0.33-1.33					

[a]Univariate and multivariate analysis using a logistic regression model. Numbers in bold indicate a *p* value ≤0.05.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous cell carcinoma; VIF, variance inflation factor assessing multicollinearity.

experienced oligoprogression were more likely to have radiotherapy than those who had systemic progression (67.7% versus 25.8%, $p < 0.001$), less likely to receive best supportive care (14.5% versus 48.5%, $p < 0.001$) or experience a change in systemic therapy (4.8% versus 22.7%, $p < 0.001$).

Forty-two patients (67.7%) received radiotherapy for the management of oligoprogression, 20 of whom also

Table 3. Management of Oligoprogression and Systemic Progression

Management	Overall N = 159, n (%)	Oligoprogression n = 62, n (%)	Systemic Progression n = 97, n (%)
Best supportive care	56 (35.2)	9 (14.5)	47 (48.5)
Radiotherapy alone	45 (28.3)	22 (35.5)	23 (23.7)
Radiotherapy and ICI continued beyond progression	22 (13.8)	20 (32.3)	2 (2.1)
ICI continued beyond progression	9 (5.7)	6 (9.7)	3 (3.1)
Change to systemic therapy	25 (15.7)	3 (4.8)	22 (22.7)
• Chemotherapy	16	1	15
• Clinical trial	8	2	6
• Other			1 - atezolizumab and bevacizumab

ICI, immune checkpoint inhibitor.

continued ICI beyond progression. The most common sites for treatment with radiotherapy included the brain (11 of 42, 26.2%), bone (11 of 42, 26.2%), and the lung primary (9 of 42, 21.4%; Supplementary Table 5). Thirty patients (30 of 42, 71.4%) received conventionally fractionated radiotherapy, nine (9 of 42, 21.4%) received intracranial SRS and three (3 of 42, 7.1%) received SABR. Eleven (11 of 42, 26.2%) received a high EQD2 dose, 28 (28 of 42, 66.7%) received low EQD2 radiotherapy doses. The exact EQD2 dose was unavailable for three patients.

Nineteen patients with baseline brain metastases had oligoprogression; 12 (63.2%) of these progression events occurred in the brain, and the other seven progression events included two in the bone, four in the lung primary, and one in lung metastasis (Supplementary Table 3). Eleven of the 12 patients (91.7%) who progressed intracranially had received prior local therapy for their CNS disease and were treated with further radiotherapy at oligoprogression. The other patient with baseline brain metastases who experienced oligoprogression intracranially had not received prior local therapy, deteriorated, and thus was treated with the best supportive care. One patient without baseline brain metastases also experienced oligoprogression in the brain.

PFS2 and OS

The median PFS2 for the entire cohort was 8 months (95% CI: 7–12 mo); the median PFS2 was 14 months (95% CI: 11–18 mo) for patients who experienced oligoprogression versus 6 months (95% CI: 5–8 mo) for patients who experienced systemic progression (HR = 0.57, 95% CI: 0.41–0.80, $p < 0.001$; Fig. 1*B*). The landmark PFS2 at 12 months was 54.8% in the oligoprogression group and 25.8% in the systemic progression group.

The median OS for the entire cohort was 12 months (95% CI: 10–15); the median OS was 19 months (95% CI: 15–23) for patients who experienced oligoprogression versus 9 months (95% CI: 6–11) for patients who experienced systemic progression (HR = 0.51, 95% CI: 0.36–0.72, $p < 0.001$; Fig. 1*C*). The landmark OS at 12 months was 69.4% in the oligoprogression group and 34.4% in the systemic progression group.

PFS2 and OS After Radiotherapy

The survival outcomes for patients were compared between patients who received radiotherapy versus those who did not for the management of the progression of the disease (Supplementary Fig. 3). For patients with oligoprogression, those who received radiotherapy had a longer median PFS2 of 17 months (95% CI: 12–31) versus 11.5 months (95% CI: 9–18) (HR = 0.51, 95% CI: 0.29–0.89, $p = 0.02$; Fig. 4*A*). Those who received radiotherapy also had a longer median OS of 23 months (95% CI: 19–45) versus 13 months (95% CI: 11–21) in patients who did not receive radiotherapy (HR = 0.40, 95% CI: 0.22–0.73, $p < 0.001$; Fig. 4*B*).

In the 42 patients treated with radiotherapy for oligoprogression, the best response of the treated region was assessed in 37 patients. Five patients were unable to be assessed for response owing to rapid deterioration and death. Of the treated lesions, 10 (10 of 37, 27.0%) had partial response, 14 (14 of 37, 37.8%) had stable disease and 13 (13 of 37, 35.1%) experienced progressive disease (Supplementary Fig. 4*A*). The best response of the untreated disease regions was also assessed, three (3 of 37, 8.1%) with partial response, 15 (15 of 37, 40.5%) with stable disease, and 19 (19 of 37, 51.4%) with progressive disease (Supplementary Fig. 4*B*). Four (9.5%) remained stable without progression, 11 (26.2%) progressed systemically, six (14.3%) progressed in the radiotherapy-treated lesion or field, 19 (45.2%) progressed in a lesion outside of the radiotherapy field and two (4.8%) died before evaluation of progression location.

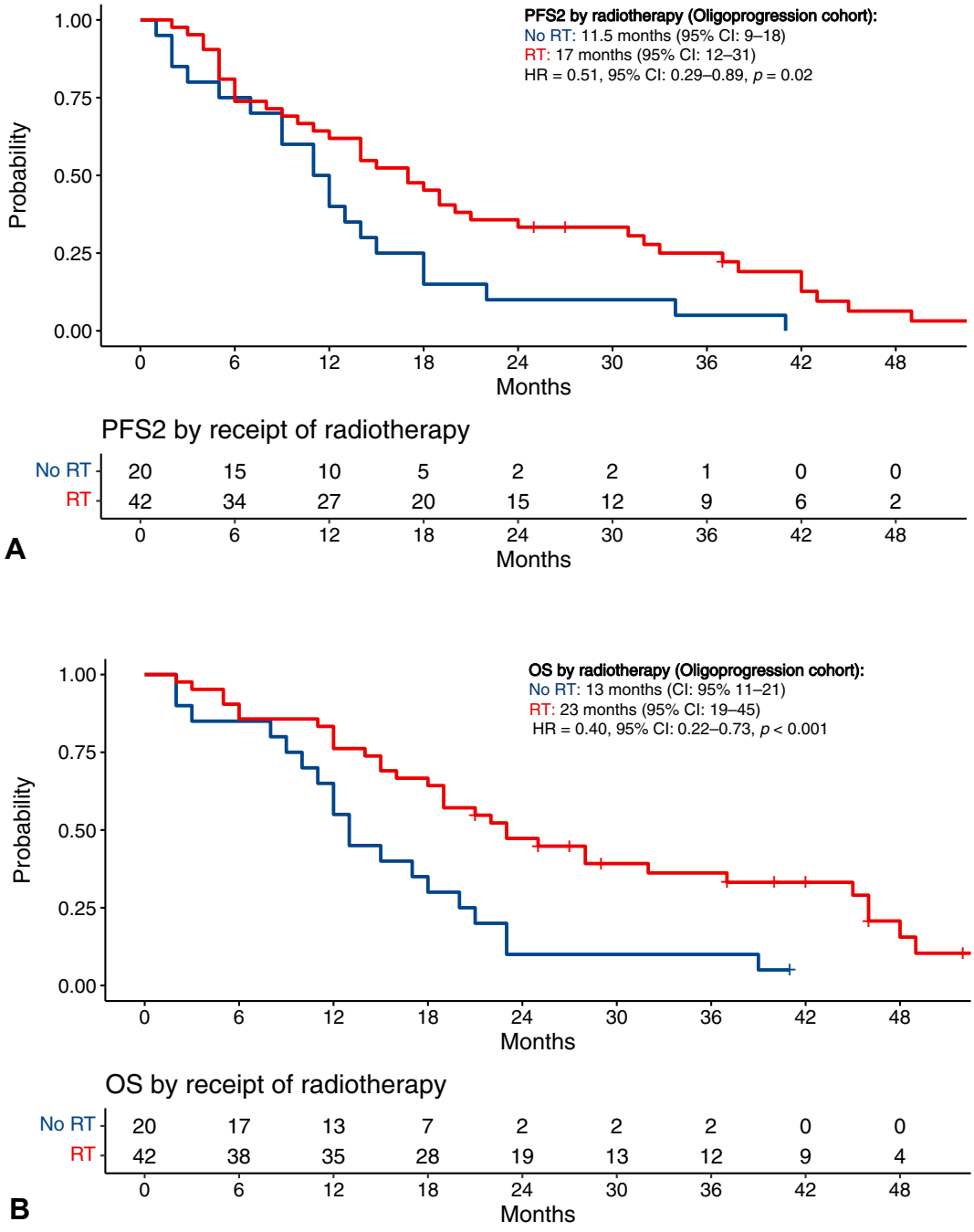

Figure 4. PFS2 and OS after radiotherapy in the oligoprogression cohort. *(A)* PFS2 after radiotherapy for oligoprogression; *(B)* OS after radiotherapy for oligoprogression. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS2, progression-free survival-2; RT, radiotherapy.

For patients with systemic progression, when comparing patients who received radiotherapy versus those who did not, there was no difference in median PFS2 or OS outcomes (Supplementary Fig. 5*A* and *B*).

Discussion

In this large multicenter study assessing progression-dependent survival outcomes of patients with metastatic NSCLC on first-line immunotherapy, we confirm the following findings: (1) oligoprogression correlates with improved survival over systemic progression; (2) in patients who have oligoprogressive disease there is a survival benefit from radiotherapy and (3) patients who have brain metastases at baseline are more likely to experience oligoprogression.

In our study, 39.0% of patients experienced oligoprogression. Patients with oligoprogression after first-line therapy had improved median PFS2 and OS

compared with those who had systemic progression. The rate of oligoprogression in our cohort is similar to a recent study by Friedes et al.[13] who report oligoprogression in 39.9% of patients. Higher rates of oligoprogression, between 10–20%, were reported in a prior study of NSCLC without oncogenic drivers.[4] This may be attributed to our population being limited to patients who progressed on first-line therapy, supporting the observation that oligoprogression is more common after first-line rather than later-line therapy.[4] However, this remains lower than the reported rates in studies of oncogene-addicted NSCLC which are reported as high as 73%.[14,15] The improved survival outcomes in the oligoprogression population compared with systemic progression, support the findings of prior studies within heterogenous NSCLC cohorts.[4,9,11,13]

Patients who had oligoprogression also had a longer PFS1 compared with patients who experienced systemic progression. This suggests that patients who have a prolonged benefit from ICIs are more likely to experience oligoprogression. This has been revealed in the prior retrospective study by Rheinheimer et al.[4] and indicates there may be a biological basis for the development of oligoprogression that also underpins the mechanism behind immunotherapy resistance.

Patients with brain metastases were more likely to experience oligoprogression (OR = 2.44, $p = 0.04$). Studies of oncogene-addicted NSCLC have also revealed an increased proportion of oligoprogression in the brain versus extracranial sites.[14–16] Brain metastases have a unique tumor immune microenvironment which can lead to local adaptive resistance and increased probability of limited intracranial progression.[17–19] In contrast, patients with liver metastases were more likely to experience systemic progression (OR = 0.17, $p < 0.01$). Liver metastases harbor immunotherapy resistance in both lung cancer and melanoma studies.[20,21] Studies have demonstrated the unique tumor microenvironment of liver metastases that explains local immune resistance.[19,22] Immunosuppressive cytokine profiles have also been observed in patients with melanoma liver metastases.[23] This may explain the predisposition of patients with liver metastases to develop progression systemically.

Patients with oligoprogression who received radiotherapy had a longer median OS and PFS2 compared with those who did not receive radiotherapy. This benefit was not seen in patients with systemic progression. In our cohort, 42 patients (67.7%) received radiotherapy for the management of oligoprogression, with 22 (35.5%) receiving radiotherapy alone and 20 (32.3%) continuing ICI post-radiotherapy. Radiotherapy can reinvigorate local immunostimulatory effects or cause direct cell death in immunotherapy-resistant clones. In the 22 patients who received radiotherapy alone, the impact of prior ICI exposure may be enduring, modifying the immune environment to potentially boost subsequent therapies like radiotherapy, and may explain why this population had improved survival outcomes compared with those who did not receive radiotherapy.

Most patients in our oligoprogression cohort received conventionally fractionated radiotherapy, rather than SABR or SRS, and were treated with lower EQD2 doses. It should be noted that most prospective studies assessing radiotherapy in oligoprogression or oligometastatic disease primarily explore the efficacy of SABR. Given the retrospective nature of our cohort, the precise rationale for treatment decisions was not always clear. However, radiotherapy doses and schedules were influenced by several factors, including patient performance status, symptoms, lesion size, location, and prior radiotherapy at the same site. This suggests that specific dosing protocols may not be critically important given the observed survival benefits in patients treated with variable radiotherapy doses for oligoprogression. However, prospective dose-finding studies in this population are warranted.

However, there are limitations to the effect of radiotherapy on other untreated lesions. In the oligoprogression group, minimal abscopal effect was observed, with only three patients (8.1%) demonstrating a partial response in disease regions not treated with radiotherapy. While preclinical murine and cell models have revealed the induction of abscopal responses when combining radiotherapy and immunotherapy,[24] the results in clinical studies have been variable. The CHEERS study evaluated the value of immunostimulatory radiotherapy by combining the use of low-dose SABR (3×8 Gy) and ICIs for the management of solid organ tumors and failed to reveal an improvement in PFS and OS.[25] In contrast, in the SABR-COMET trial, the use of SABR to all metastatic sites in combination with standard-of-care systemic therapy, with the aim of cytoreduction, revealed an improvement in OS for patients with oligometastatic disease.[26,27] Recently, a pooled analysis of two phase 2 trials has revealed hypofractionated radiotherapy can reinvigorate immunotherapy responses in immunotherapy-resistant NSCLC, leading to ongoing disease control.[28]

While other retrospective trials have shown that management of oligoprogression in metastatic NSCLC with radiotherapy improves survival outcomes,[11,13,29] the results have been variable in prospective clinical trials. The combination of SABR and ICI therapy for oligoprogression in NSCLC and melanoma patients revealed high rates of local and systemic response in a prospective observational study.[30] The Phase II STOP

trial assessing SABR for oligoprogression in multiple cancer types after systemic therapy did not reveal improvement in PFS or OS compared with standard of care.[31] In contrast, the CURB trial revealed an improvement in median PFS after SABR for oligoprogression compared with standard of care (10.0 versus 2.2 mo, $p = 0.002$) for the 59 patients with NSCLC included, with no benefit observed for the breast cancer cohort.[9] The OS data for the CURB trial remains immature. The differential benefit between tumor types suggest mechanistically that, the primary site contributes to the development of and treatment response after oligoprogression. Notably, this study included patients with NSCLC with actionable driver mutations and patients treated with any line of systemic therapy.[9] Radiotherapy for patients with metastatic NSCLC and oligoprogression after first-line ICIs or chemoimmunotherapy is yet to be distinctly examined within trial populations.

It is important to acknowledge that the definition and classification of oligometastatic and oligoprogressive disease has only recently been established by ASTRO and ESTRO,[5,6] with oligoprogression being an umbrella term under oligometastatic disease. It is not yet clear if each state has a differing pathobiology and thus whether management should be the same. Oligoprogressive disease under this umbrella definition refers to the progression of few sites after exposure to systemic therapy, the evolution of which is thought to be complex and dynamic, influenced by alterations of the tumor microenvironment from prior therapies. For patients with de-novo oligometastatic disease, ablation with high-dose therapy may help with long-term disease control.[26,27] However, the oligoprogression paradigm needs to be separately addressed with the aim of treatment of resistant tumor clones, or stimulation of antitumor immunity. Therefore, in this context using immunostimulatory doses of radiotherapy may offer the opportunity to salvage control over metastatic disease and prolong the therapeutic benefits from first-line ICI therapy.

There are several limitations of our study. Firstly, the retrospective nature of the study is associated with an inherent cohort selection bias. Because of the retrospective nature of the study, the aim of radiotherapy was difficult to ascertain and decision-making paradigms were determined by the treating clinicians. Secondly, the small sample size and inclusion of patients from two centers may have limited some detection of clinically meaningful outcomes, particularly in determining the influence of the site of radiotherapy and dosing on the outcomes. Specifically, we observed that 47.8% of patients in our cohort had a PD-L1 $\geq$50%, which is generally higher than the reported rates which are closer to 30%.[32] Thirdly, functional fluorodeoxyglucose-positron emission tomography imaging and brain MRI were not utilized in all cases for initial staging or to confirm progression. Consequently, there is a risk that small metastases at some sites may not have been detected, although this is believed to have had a minimal impact on the results within this population.

Furthermore, the classification of oligoprogression has varied in studies both retrospective and prospective, and thus comparisons between studies are difficult to perform. The definition used in our report encompasses the new consensus definitions of oligoprogression.[5,6] Further study into understanding the natural history and best practice in the management of oligometastatic disease is currently being assessed in the OligoCare cohort of the ESTRO E^{2-}RADIatE study (NCT03818503).

In conclusion, this study provides further insights into the oligoprogression paradigm in metastatic NSCLC after first-line therapy with ICIs with or without chemotherapy. Our study provides clinically meaningful data to support the survival benefits of radiotherapy in this group for the management of oligoprogression. A deeper understanding of the mechanisms behind oligoprogression after immunotherapy in NSCLC is required to understand the biological basis for oligoprogression. Further prospective studies in directed, less heterogeneous populations of patients with metastatic NSCLC treated with first-line ICIs will be fundamental to further optimize management.

CRediT Authorship Contribution Statement

Lauren Brown: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing-Original draft preparation.

Julie Ahn: Methodology, Investigation, Data Curation, Writing- Original draft preparation.

Bo Gao: Writing- reviewing and editing.

Harriet Gee: Writing- reviewing and editing.

Adnan Nagrial: Writing- reviewing and editing.

Ines Pires da Silva: Conceptualization, Methodology, Supervision, Writing- reviewing and editing.

Eric Hau: Conceptualization, Methodology, Supervision, Writing- reviewing and editing.

Disclosure

Dr. Gee received honoraria from AstraZeneca. Dr. Nagrial is an advisory board member for Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, AstraZeneca, Pfizer Merck Serono. Dr. Silva is a consultant advisor for Merck Sharp & Dohme and received honoraria from Roche, Novartis, and Bristol-Myers Squibb. Dr. Eric Hau received honoraria and research funding from

AstraZeneca, and honoraria from Novartis. The remaining authors declare no conflict of interest.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2024.100695].

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