

ORIGINAL ARTICLE

Efficacy of local therapy for oligoprogressive disease after programmed cell death 1 blockade in advanced non-small cell lung cancer

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Abstract

Immune checkpoint inhibitors (ICIs) have dramatically changed the strategy used to treat patients with non-small-cell lung cancer (NSCLC); however, the vast majority of patients eventually develop progressive disease (PD) and acquire resistance to ICIs. Some patients experience oligoprogressive disease. Few retrospective studies have evaluated clinical efficacy in patients with oligometastatic progression who received local therapy after ICI treatment. We conducted a retrospective analysis of advanced NSCLC patients who received PD-1 inhibitor monotherapy with nivolumab or pembrolizumab to evaluate the effects of ICIs on the patterns of progression and the efficacy of local therapy for oligoprogressive disease. Of the 307 patients treated with ICIs, 148 were evaluated in our study; 42 were treated with pembrolizumab, and 106 were treated with nivolumab. Thirty-eight patients showed oligoprogression. Male sex, a lack of driver mutations, and smoking history were significantly correlated with the risk of oligoprogression. Primary lesions were most frequently detected at oligoprogression sites (15 patients), and 6 patients experienced abdominal lymph node (LN) oligoprogression. Four patients showed evidence of new abdominal LN oligometastases. There was no significant difference in overall survival (OS) between the local therapy group and the switch therapy group (reached vs. not reached, $P = .456$). We summarized clinical data on the response of oligoprogressive NSCLC to ICI therapy. The results may help to elucidate the causes of ICI resistance and indicate that the use of local therapy as the initial treatment in this setting is feasible treatment option.

Abbreviations: ALK, anaplastic lymphoma kinase; AR, acquired resistance; B2M, beta 2 microglobulin; BRAF, B-RAF proto-oncogene, serine/threonine kinase; CT, computed tomography; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer Lung Cancer Group; HE, hematoxylin-eosin; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; KRASv-Ki-ras2, Kirsten rat sarcoma viral oncogene homolog; LAT, local ablative therapy; LN, lymph node; MET, mesenchymal-to-epithelial transition; NSCLC, non-small-cell lung cancer; OS, overall survival; PD, progressive disease; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PET, positron emission tomography; PFS, progression-free survival; PS, performance status; QOL, quality of life; RESIST, Response Evaluation Criteria in Solid Tumors; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TTF, time to treatment failure.

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KEYWORDS

local therapy, nivolumab, oligometastasis, oligoprogression, pembrolizumab

1 | INTRODUCTION

A treatment strategy that blocks the pathway that involves PD-1 and PD-L1 proteins has shown marked efficacy in the treatment of patients with various kinds of solid tumors, especially NSCLC.¹⁻³ Among the anti-PD-1 protein antibodies, nivolumab resulted in significantly longer OS than docetaxel among patients with advanced NSCLC who showed disease progression after platinum-based chemotherapy.⁴⁻⁷ Pembrolizumab resulted in significantly longer PFS and OS than platinum-based chemotherapy among patients with previously untreated advanced NSCLC and high PD-L1 expression.^{8,9} The anti-PD-L1 antibody atezolizumab has been shown to prolong OS in patients with previously treated advanced NSCLC.¹⁰ The addition of pembrolizumab and atezolizumab to platinum-based chemotherapy also improved PFS and OS among patients with advanced NSCLC who did not have driver gene alterations.¹¹⁻¹⁴ As described above, nivolumab, pembrolizumab, and atezolizumab have been approved as the standard treatment for advanced NSCLC. The TTF of these ICIs in patients with advanced NSCLC ranges from 12 to 25 mo, which is 2-3 times greater than that of cytotoxic chemotherapy^{4,5,15,16} and, in some cases, the tumor response has been reported to last for more than 5 y.¹⁷ Moreover, ICI responders with NSCLC who experience prolonged PFS also experience prolonged OS.¹⁸

In 1995, Hellman and Weichselbaum described the concept of the oligometastatic state, in which metastases are limited in number and location (which enables local radical treatment).¹⁹ In some oligometastatic patients, it is possible that the LAT of all metastatic lesions may result in a substantial survival advantage and even a cure. After the concept of "oligometastasis" was first described in 2002, the first molecular targeting agent gefitinib was introduced into clinical practice with NSCLC patients, and multiple actionable oncogenic drivers and the corresponding targeted agents were identified. Most patients treated with these agents will experience some degree of tumor shrinkage, however almost all patients eventually experience tumor progression. Oligoprogressive disease describes the situation in which a patient develops disease progression in a limited number of sites after a targeted therapy has resulted in some degree of response.²⁰ Similar to that observed in an oligometastatic state, the LAT of lesions resulting in progression could contribute to an increase in disease control by targeted agents, and the results of several retrospective studies regarding the outcomes of patients who developed oligoprogressive disease have been reported.²¹⁻²⁴

Various local therapies have been used for the treatment of limited metastases, including surgery, SBRT, and RFA, and various factors, such as the site of metastasis and PS, determine which treatments are optimal. The most robust randomized data that are favorable toward the treatment of oligometastatic cancers are derived from patients with limited brain metastases.²⁵ Both surgery and

SBRT are efficacious, but no large prospective trial has compared the 2 techniques in the treatment of oligometastases confined to the adrenals.^{26,27} Radiotherapy-induced cell death can be immunogenic via various mechanisms²⁸⁻³⁰, however the effects of radiotherapy on tumor immunogenicity are not well known, and this is an exciting area currently under study. There have also been few reports that have described the progression patterns in patients treated with ICIs and the clinical outcomes in the course of subsequent treatment, including local therapies.

In this study, we retrospectively reviewed the progression patterns resulting from treatment with ICIs according to different TTFs and evaluated the clinical outcomes in the course of treatment with subsequent local therapies.

2 | MATERIALS AND METHODS

2.1 | Patients and data analysis

At our institute, we retrospectively evaluated 307 patients treated with anti-PD-1 antibodies (nivolumab or pembrolizumab) between May 2013 and September 2018. Patients who were not evaluated according to the RECIST criteria or who had been previously treated with ICIs were excluded from the analysis. In total, 148 patients were included in this study, all of whom had progressed after treatment with ICIs. We analyzed detailed information regarding the progressive organ sites and lesions resulting from ICI progression. This retrospective study was approved by the Institutional Review Board of the Aichi Cancer Center (IRB number: 2018-1-205).

2.2 | PD-1 inhibitor treatment and response

Patients received at least 1 course of nivolumab (3 mg/kg every 2 wk) or pembrolizumab (2 mg/kg every 3 wk) as monotherapy. The ICI treatments were continued until patients developed PD or experienced unacceptable adverse events. In general, patients who underwent radiographic imaging 3 mo before the initiation of ICI treatment were evaluated for tumor response according to the RECIST, version 1.1.³¹ In this study, oligoprogression and oligometastasis were defined as the presence of 1 progressive/metastatic organ site within 3 lesions after PD-1 blockade, and oligometastasis was defined as the presence of 1 metastatic organ site within 3 lesions. Of the 3 to 6 lesions of oligoprogressive disease that have been reported,³²⁻³⁴ we used the smallest number in this study. The imaging evaluations were performed mostly during the therapeutic period with CT scan, however in 9 of 10 cases (90.0%) of oligoprogression and oligometastasis the details of metastasis before or soon after LAT intervention were evaluated by PET-CT.

2.3 | Statistical analysis

Differences in the categorical variables were evaluated using chi-square (χ^2) test or Fisher exact test, as appropriate. PFS was measured from the start of ICI therapy (nivolumab or pembrolizumab) until the date of RECIST-defined PD. OS was measured from the initiation of ICI treatment until death and was censored at the date of the last visit or telephone contact for patients whose death could not be confirmed. The survival probabilities were estimated using the Kaplan-Meier method, in which differences in the variables were calculated using the log-rank test. All reported *P*-values are two-sided and a *P*-value < .05 was considered statistically significant unless stated otherwise. We analyzed the data using GraphPad Prism software version 7 for Windows (GraphPad Software Inc) or the JMP statistical software package for Windows version 9 (SAS Institute).

3 | RESULTS

3.1 | Patient clinicopathological characteristics

Baseline patient demographics and disease characteristics are listed in Table 1. The majority of patients (59%) had adenocarcinoma. Forty-three patients (29%) had driver mutations, 23 patients harbored EGFR mutations, 7 patients had Kirsten rat sarcoma (*KRAS*) mutations, 4 patients had MET exon 14 skipping variants, 3 patients had ALK rearrangements, and 3 patients had v-RAF murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutations. The overall response rate was 22.3%. PFS and OS were 3.02 mo (95% CI: 2.67-3.87) and 18.4 mo (95% CI: 15.2-23.0), respectively (Figure 1A,B). Forty-nine patients presented with the exacerbation of lesion(s) in a single organ at the time of PD, and among these 49 patients, 38 showed oligoprogression (Figure 2).

	n	Oligo n = 38	Non-oligo n = 110	P-value
Age, median (range)	65 (37-87)	68 (48-87)	64 (37-82)	
Sex, female/male	41/107	5/33	36/74	.021
ECOG performance status, 0/1/2	52/91/5	17/20/1	35/71/4	.35
Driver mutation				
Positive (%)	43 ^a (29%)	8(21%)	35 (32%)	.300
Histology				
Ad/Sq/other	87/41/20	15/15/8	72/26/12	.019
Smoking history				
Yes/No	118/30	35/3	83/27	.034
Stage				
Postoperative recurrence/III/IV	16/29/103	6/6/26	10/23/77	.458
ICI treatment				
Nivolumab/ Pembrolizumab	106/42	25/13	81/29	.406
ICI line				
1/2/3 or later	20/76/52	9/20/9	11/56/43	.054
Response to PD-1 blockade				
PR	33	20	13	
SD	20	7	13	
PD	95	11	84	
ORR	22.3%	52.6%	11.8%	<.0001
PFS				
Within 6 mo/over 6 mo	104/44	14/24	90/20	<.0001

TABLE 1 Characteristics of patients who received ICI treatment (n = 148)

Abbreviations: Ad, adenocarcinoma; ECOG, Eastern Cooperative Group; ICI, immune checkpoint inhibitor; Non-oligo, non-oligoprogression; Oligo, oligoprogression; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; Sq, squamous cell carcinoma.

^aMajor driver gene alterations were not evaluated in 4 patients because of the presence of pure squamous cell carcinoma histology.

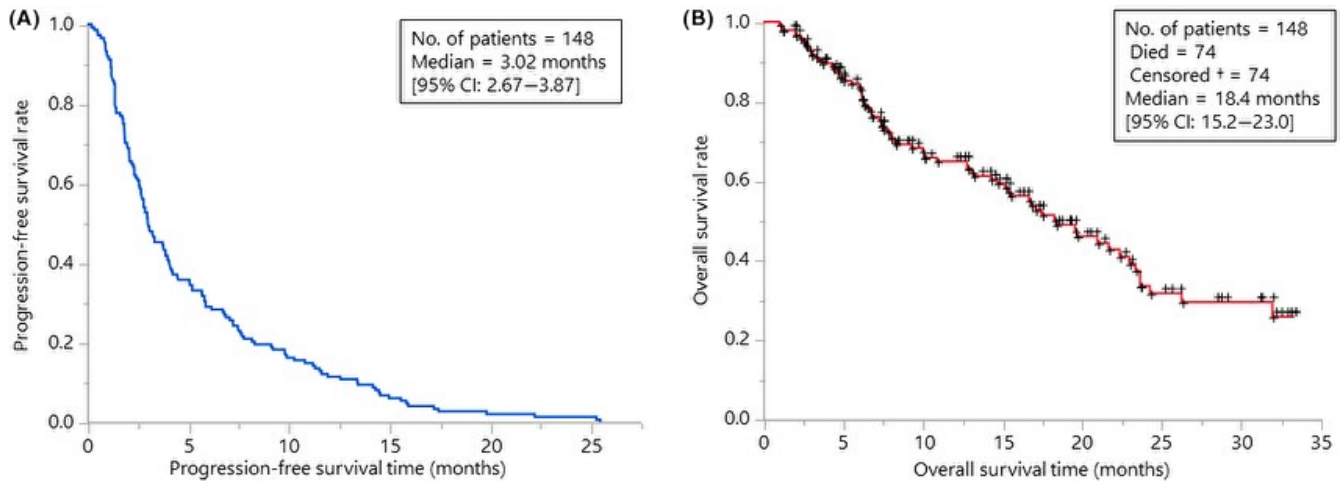


FIGURE 1 Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) among the patients treated with ICIs in our cohort ($n = 148$) are shown

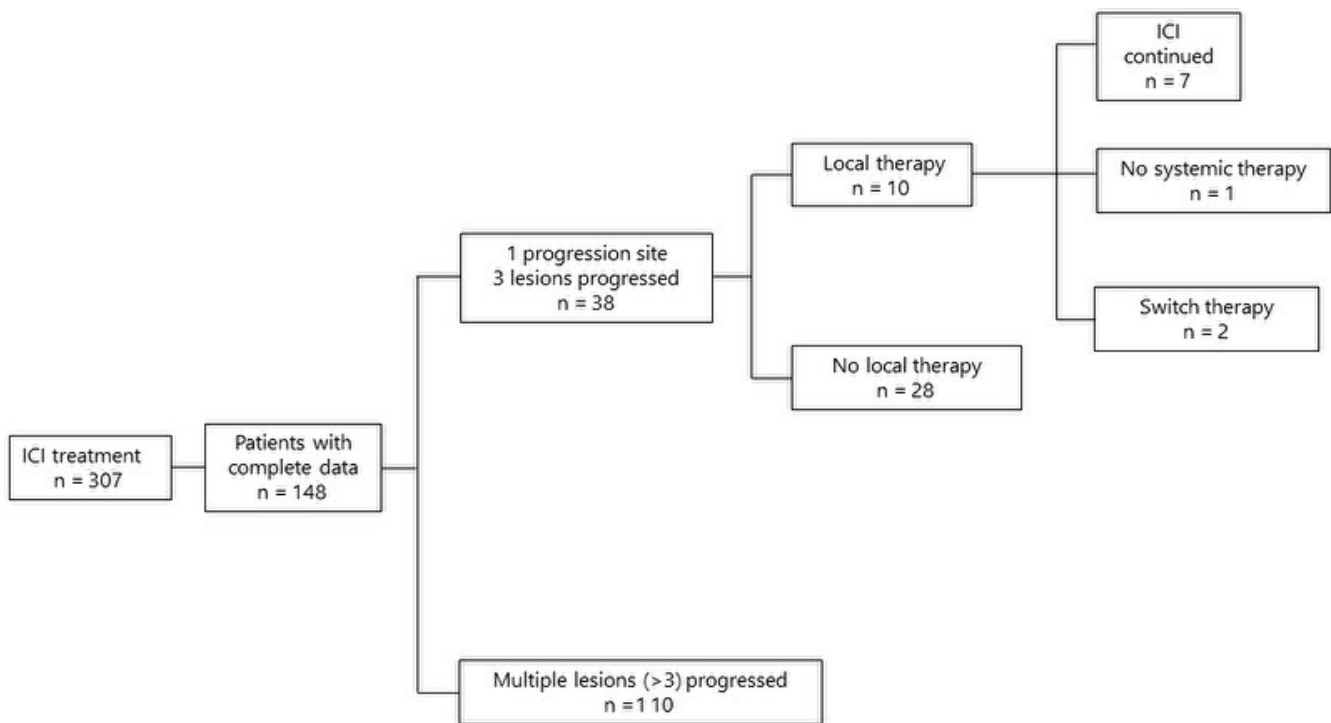


FIGURE 2 Analytical flowchart of this study

Ten patients with oligoprogression underwent LAT, surgery, or radiation. After local therapy, 6 patients continued ICI therapy, and 2 patients received no systemic therapy. The percentages of male patients, patients with adenocarcinoma histology and patients who had never smoked were significantly greater in the non-oligoprogression group than in the oligoprogression group. Patients who developed oligoprogression showed a higher response rate (52.6% vs. 11.8%, $P < .0001$) and a PFS of more than 6 mo (63.2% vs. 18.2%, $P < .0001$) compared with patients who did not develop oligoprogression. The oligoprogression group

showed better PFS (median PFS 7.37 mo vs. 2.50 mo, $P < .0001$) and OS (median OS; not reached vs. 12.94 mo, $P < .0001$) than the non-oligoprogression group (Figure 3).

3.2 | Oligoprogression and oligometastasis sites in organs

The sites of oligoprogression and oligometastasis are shown in Figure 4. Primary lung lesions (15 patients) were the most common

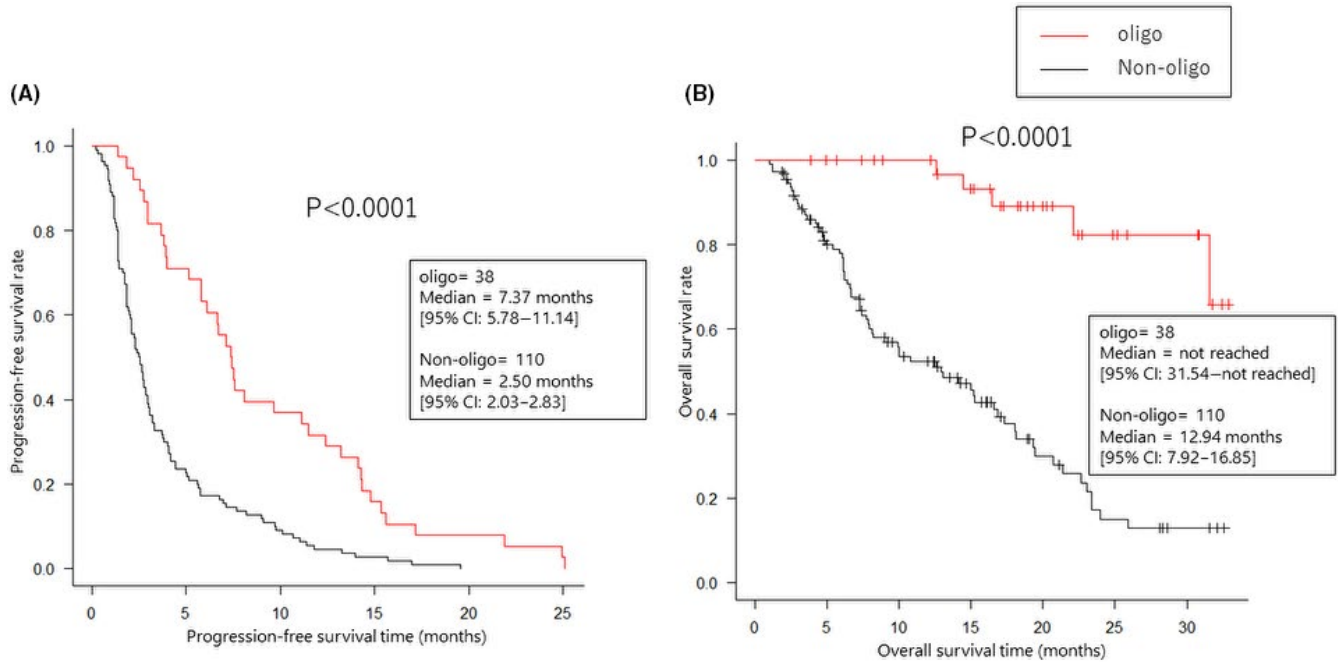


FIGURE 3 Kaplan-Meier estimates of progression-free survival and overall survival among the patients with and without oligoprogression or oligometastasis

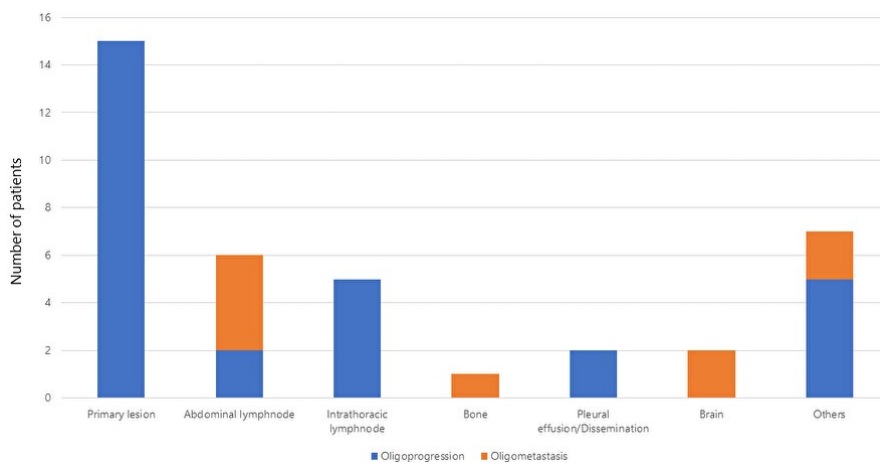


FIGURE 4 Details of oligoprogressive (blue) and oligometastatic (orange) sites

site for oligoprogression; 6 patients experienced abdominal LN oligoprogression, and among these 6 patients, 4 showed evidence of new abdominal LN oligometastasis without other PD sites.

3.3 | Local therapy for oligoprogression and oligometastasis

The characteristics of patients who received or did not receive local therapy for oligoprogression/oligometastasis are shown in Table 2. The details of the clinical course used are shown in Figures 5 and S1, and Tables 3 and S1. There was no difference in characteristics between these 2 groups. Among the 38 patients with oligoprogression, 10 received definitive local therapy at the oligoprogressive site (Figure 5). Six patients continued ICI treatment after progression,

2 patients receive another systemic therapy, and 2 patients had no further systemic treatment. Six of the 10 patients maintained a progression-free status for at least 3 mo; among these 6 patients, 3 received local therapy at the abdominal LNs. The timing to next therapy after LAT was similar in each patient. There was no difference in OS between the groups that received and did not receive local therapy (Figure 6).

3.4 | PD-L1 expression in oligometastatic LNs

PD-L1, PD-1, and HE IHC are shown in Figure 7A,B. Four patients showed evidence of 3 new abdominal LN oligometastases and 1 new chest LN oligometastasis, which were surgically resected. No considerable change was observed in PD-L1 IHC before and after

treatment with ICIs. Tumor cells spread throughout the whole LN, and PD-L1-positive cells seemed to localize within the cortex more than the medulla. PD-1-positive T cells seemed to be relatively sparsely distributed in all patients.

TABLE 2 Characteristics of patients with oligoprogression or oligometastasis who received ICI treatment (n = 38)

	Received LAT n = 10	Did not receive LAT n = 28	P- value
Age, median (range)	63.5 (53-78)	70.0 (48-87)	
Sex, female/male	1/9	4/24	1.00
ECOG P performance status, 0/1/2	3/7/0	14/13/1	.475
Driver mutation			
Positive (%)	1 (10%)	5 (18%)	1.00
Histology			
Ad/Sq/other	2/4/4	13/11/4	.197
Smoking history			
Yes/No	9/1	26/2	1.00
Stage			
Postoperative recurrence/III/IV	3/1/6	3/5/20	.521
ICI treatment			
Nivolumab/ Pembrolizumab	8/2	17/11	.406
ICI line			
1/2/3 or later	1/7/2	8/13/7	.499

Abbreviations: Ad, adenocarcinoma; ECOG, Eastern Cooperative Group; ICI, immune checkpoint inhibitor; LAT, local ablative therapy; Non-oligo, non-oligoprogression; Oligo, oligoprogression; PFS, progression-free survival; Sq, squamous cell carcinoma. Major driver gene alterations were not evaluated in 5 patients because of the presence of pure squamous cell carcinoma histology.

4 | DISCUSSION

Most patients with advanced NSCLC, and who are treated with systemic therapy, relapse at a site of preexisting disease.³⁵ Even after ICI treatment, oligoprogression is observed in existing lesions, including the primary lesion. Regarding cytotoxic chemotherapy, some data suggest that the larger the tumor deposits, the more likely it is that resistant clones will remain and that local control of the lesion will be more beneficial.³⁶ Oligoprogressive disease is believed to be the result of the development of an isolated resistant subclone that usually occurs only at a few metastatic sites.²¹ Theoretically, disease control is attained by the LAT of newly developed oligometastatic sites before the systemic dissemination of resistant clones occurs. In addition to the elimination of resistant subclones, LAT is also beneficial in terms of the prevention of local symptoms and complications from a growing tumor. For example, the LAT of abdominal LN metastases can prevent further neuropathic pain due to the invasion of the peritoneal plexus by metastatic cancer cells.³⁷ As a consequence, currently, the most common method used to treat oligoprogression in NSCLC patients with driver mutations is to continue targeted therapy to suppress the growth of the sensitive clone and to use LAT to eliminate the lesion containing the resistant clone.³⁸

Some patients treated by immunotherapy show a marked and durable response, similar to that observed in patients with driver mutations treated with suitable targeted agents. Gettinger S et al reported the results of a retrospective analysis regarding the clinical characteristics and outcomes of patients who acquired resistance to PD-1 axis inhibitors.¹⁷ Of the 26 patients who were evaluated, 15 received LAT, and the median survival time after AR was not reached in these 15 patients, who had a 2-y survival rate of 92%. Eleven patients continued PD-1 axis inhibitor therapy after local therapy. In our study, 6 of 10 patients in an oligoprogressive state after ICI therapy were treated with a course of therapy, and successful results were obtained; this finding supports the initial use of LAT except in patients in whom widespread dissemination of the resistant clone has occurred.

FIGURE 5 Development and management of acquired resistance to ICIs. Swimmer plot showing the time to resistance after the initial response to ICIs and local therapy among 10 patients. Each bar represents 1 patient

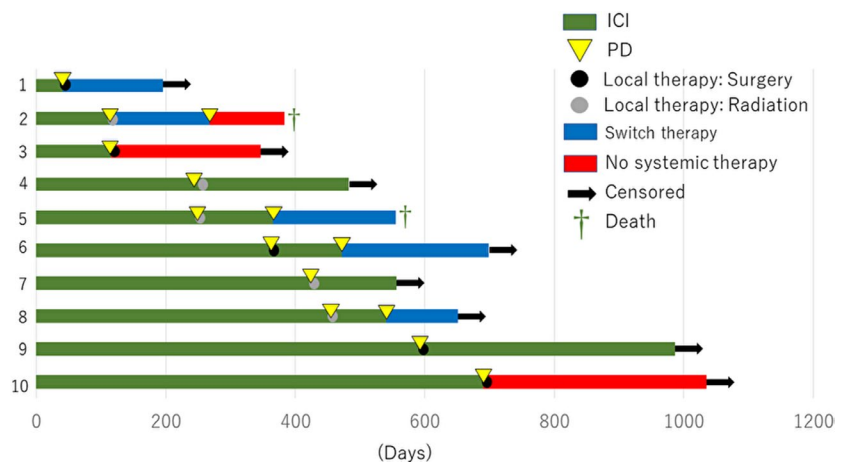
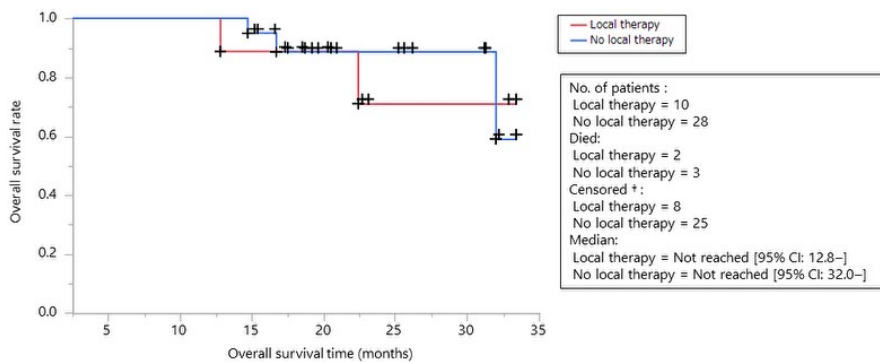


TABLE 3 Clinical outcomes in patients who showed oligoprogressive disease during ICI therapy and who underwent local ablative therapy

No.	Age	Sex	ICI	Histology	Major driver mutation	BI	Treatment lines	PFS (mo)	Progression sites	LAT	Days to next therapy after LAT	Subsequent therapy
1	60	M	PB	NOS	None	720	1	1.4	Abdominal LN	Ope	33	CBDCA + nabPTX
2	58	M	NV	Sq	None	760	2	3.7	Bone	Rad	28	DTX
3	61	M	NV	Pleo	None	800	2	3.9	Abdominal LN	Ope	(no therapy)	No systemic therapy
4	53	M	PB	Sarco	None	600	3	7.5	Gallbladder	Rad	14	PB beyond PD
5	72	M	NV	Sq	None	0	2	8.2	Abdominal LN	Rad	1	NV beyond PD
6	58	M	NV	LCNEC	None	760	2	12.6	Adrenal gland	Ope	16	NV beyond PD
7	74	M	NV	Ad	None	675	2	14.3	Brain	Rad	10	NV beyond PD
8	78	M	NV	Sq	None	1050	4	14.5	Abdominal LN	Rad	64	NV beyond PD
9	72	M	NV	Sq	None	820	2	15.8	Abdominal LN	Ope	34	NV beyond PD
10	66	F	NV	Ad	EGFR Exon 20 insertion	840	2	22.2	Chest wall LN	Ope	(no therapy)	No systemic therapy

Abbreviations: Ad, adenocarcinoma; BI, Brinkman index; CBDCA, carboplatin; DTX, docetaxel; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; LAT, local ablative therapy; LCNEC, large cell neuroendocrine carcinoma; LN, lymph node; nabPTX, nab-paclitaxel; NOS, not otherwise specified; NV, nivolumab; Ope, operation; PB, pembrolizumab; PD, progressive disease; PFS, progression-free survival; Pleo, pleomorphic carcinoma; Rad, radiation; Sarco, sarcomatoid carcinoma; Sq, squamous cell carcinoma.

**FIGURE 6** Kaplan-Meier estimates of progression-free survival among the patients with oligoprogression or oligometastasis according to local therapy intervention are shown (red: with local therapy, blue: without local therapy)

To obtain robust conclusions regarding the clinical benefit of LAT for patients who show oligoprogressive disease during ICI therapy, a formal statistical analysis with established endpoints (eg, OS or PFS) is required, however this is impossible in any retrospective setting, including our study, because of the extremely heterogeneous background of the evaluated patients.²¹ Recently, the idea that local therapy can be used to treat oligoprogressive disease has received increasing attention from the European Organisation for Research and Treatment of Cancer Lung Cancer Group (EORTC).³⁹ It is also difficult to perform prospective clinical trials under these circumstances. There is no consensus concerning the maximum tolerated number of courses of LAT, the optimal timing, and regimen of subsequent systemic therapy, the necessity of the distinction between brain and nonbrain progression, and the independent protocol to be used to determine the positive/negative population for each driver mutation. Currently, LAT in the oligoprogressive state during ICI therapy could be considered in selected patients, and practitioners should pay attention to the following 3 points. First, careful

patient selection, including intensive clinical tumor staging (including PET-CT), is essential before treatment. Second, to shorten the interruption of ICI treatment, suitable treatment modalities should be selected. Finally, a careful and close follow-up of treated patients is strictly required.

Another notable observation in our cohort was that most patients experienced oligoprogressive disease; 56% of patients had a primary site of progression, 21% had LN progression and oligometastatic disease, and 44% had LN metastases. Similar findings were also observed in 26 patients with NSCLC who developed AR to PD-1 axis inhibitor therapy. Gettinger S et al reported that 11 (70%) patients experienced LN-only progression after treatment with a PD-1 axis inhibitor.¹⁷ Previously, it was not reported that the primary site was the most frequent lesion site that AR to ICIs. The presence of liver and lung metastases was reported to be an independent predictor of nivolumab efficacy in patients with advanced NSCLC.¹⁷ In this report, heterogeneity in PD-L1 expression and heterogeneity in the genetic profiles of primary and metastatic sites may have led to

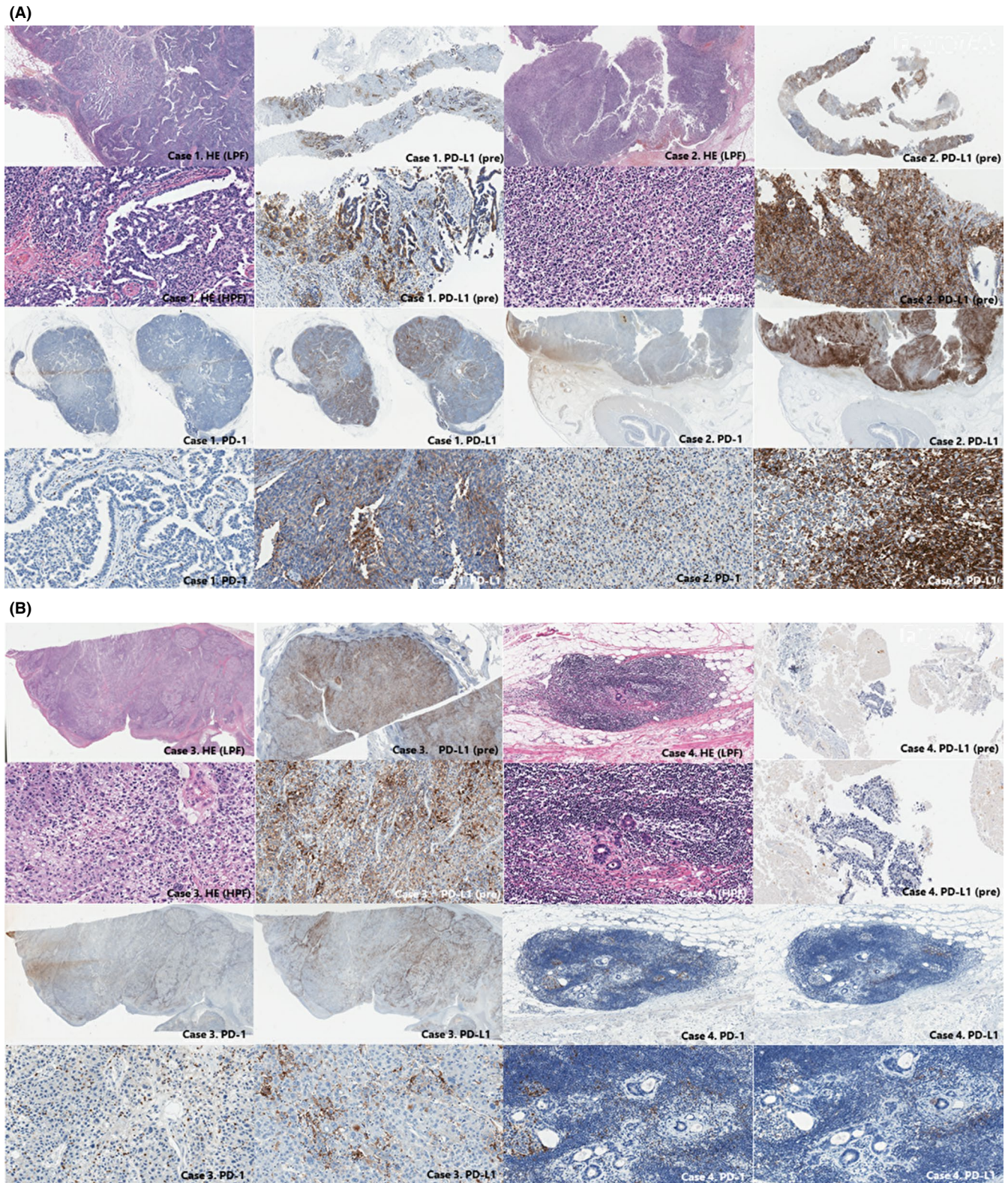


FIGURE 7 Histological sections of resected oligoprogressive lymph nodes with hematoxylin and eosin staining and findings on immunostaining for PD-1 and PD-L1 in (A) cases 1 and 2, and (B) cases 3 and 4. The patient number is the same as Table 3. Findings on immunostaining for PD-L1 is also shown before treatment with ICIs (PD-L1 IHC of cases 2 and 3 were performed with clone 22C3.). PD-L1 TPS is high before and after treatment in cases 1, 2, and 3, negative in case 4. Infiltrating PD-1 positive lymphocyte are sparsely distributed throughout the tumor

AR to ICIs in metastatic lesions. The mechanisms underlying the development of AR to ICIs in NSCLC remain largely unknown. Several of the possible mechanisms of resistance include the upregulation of alternate immune checkpoints,¹⁷ defects in interferon signaling pathways,⁴⁰ the enhanced expression of IL-34,⁴¹ the loss of B2M, which prevents the presentation of tumor antigens by major histocompatibility complex class I,⁴² loss-of-function B2M, JAK1 and JAK2 mutations resulting in insensitivity to interferon gamma,⁴³ and somatic neoantigen loss that compromises immune recognition.⁴⁴ However, a definitive understanding of the mechanism involved in AR has remained elusive.

In our study of patients with AR, similar findings to those of a previous report were observed,¹⁷ which included a tendency for the development of AR within LNs in the case of both oligometastasis and oligoprogression. A potential hypothesis explaining this finding can be offered. Several receptors, including LFA-1 and S1PR1, enable naïve CD8 T cells to enter the LN to search for dendritic cells expressing tumor-specific antigens. When naïve CD8 T cells differentiate into activated effector CD8 T cells, they undergo a dramatic shift in the expression of surface proteins that regulate cellular trafficking. Importantly, effector CD8 T cells lose the expression of both CD62L and CCR7, and prevents these cells from gaining access to LNs through high endothelial venules.⁴⁵ In other words, it may be inherently difficult for tumor-specific CD8 T cells to effectively maintain anatomical localization to secondary LNs (especially sentinel LNs) due to this mechanism.

Among the patients with oligometastases, 4 with abdominal LN metastases had abdominal organ metastases (3 liver and 1 adrenal) before ICI treatment. These LN metastatic lesions showed high PD-L1 expression; according to the proposed hypothesis that heterogeneity in PD-L1 expression may be a possible contributor to resistance, it is difficult to explain this result.⁴⁶ PD-1-positive lymphocyte infiltration appears to have been decreased in an evaluated patient, which may support the explanation that effector CD8 T cells have difficulty infiltrating secondary LNs. In addition, it can be speculated that oligoprogressive and oligometastatic lesions in the central nervous system (CNS) and the pleural fluid may be related to the low penetration of the CNS by ICIs and the fact that this environment is difficult for ICIs to navigate, however this is merely speculation.

This study has limitations. The greatest limitations include the small sample size and the retrospective nature of the study, which prevents the comparison of our findings to nonregional or pretreatment results and causes a selection bias for LAT. A larger prospective study with strict enrollment criteria is urgently needed to overcome these limitations. Specifically, it is necessary to evaluate whether local treatment may improve QOL and prevent complications and to verify whether similar progressive patterns can be reproduced in another larger cohort. It is also important to strictly define the criteria used for the local treatment of these lesions based on definitive results.

In this study, we summarized the clinical data regarding oligoprogressive NSCLC during ICI therapy and showed that the use of

LAT as the initial treatment in this setting is a feasible treatment option.

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DISCLOSURE STATEMENT

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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