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Single-arm multicenter phase II study on aggressive local consolidative therapy in combination with systemic chemotherapy for stage IV non-small cell lung carcinoma with oligometastases: CURE-OLIGO (TORG1529)

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Abstract

Introduction Stage IV non-small cell lung carcinoma (NSCLC) with oligometastases is potentially curable by radical treatment. This study aimed to evaluate the efficacy and safety of chemoradiotherapy (CRT) for thoracic disease, including the primary lesion and lymph node metastases, combined with local consolidative therapy (LCT) for oligometastases.

Methods This was a multicenter Phase II trial for patients with Stage IV NSCLC with oligometastases for whom CRT for thoracic disease was feasible. The treatment procedures included CRT containing platinum-doublet for thoracic disease and LCT for oligometastases within 8 weeks of starting or completing CRT. The primary endpoint was the 2-year survival rate.

Results We enrolled 19 patients between June 2016 and May 2020. The median age was 68 (range: 51–74) years. Twelve patients had adenocarcinoma, and 6 had squamous cell carcinoma. The metastasis sites included the brain, bone, adrenal gland, lung, and cervical lymph node (n = 9, 7, 2, 1, and 1, respectively). All patients completed CRT concurrently with LCT for all oligometastases. There were 11 partial responses, resulting in a response rate of 58% (95% confidence interval [CI] 33.5–79.7%). Median progression-free survival and overall survival were 8.6 (95% CI 7.0–10.2) and 42.1 (80% CI 13.6–not reached) months, respectively. The 2-year survival rate was 68.4% (80% CI 52.6%–79.9%). Fourteen patients (74%) showed progression with newly observed lesions. There were no severe adverse events, and toxicities were tolerable.

Conclusion Chemotherapy in combination with aggressive LCT for NSCLC with oligometastases might extend survival and achieve local control.

Clinical trial registration: University Hospital Medical Information Network, Japan (protocol identification number: UMIN000022431, first registration date: 01/JUN/2016).

Keywords Oligometastasis, Local consolidative therapy, Non-small cell lung cancer

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Introduction

Some preclinical and translational analyses have suggested that Stage IV disease that is limited to only a small number of sites (oligometastatic disease) represents an indolent phenotype that could benefit from local consolidative therapy (LCT; e.g., surgery or radiotherapy) [1–4]. The clinical practice guidelines of the European Society for Medical Oncology recommend imaging for oligometastases [5]. Although uncertainty remains regarding the exact definition of limited metastases, current trial design and clinical practice are fairly consistent in limiting oligometastatic disease to a maximum of three to five sites [6].

A single extrathoracic metastasis was newly categorized as M1b by the eighth edition of the American Joint Committee on Cancer (AJCC) TNM Staging of Lung Cancer. Several single-arm prospective studies and a meta-analysis of many retrospective studies revealed that patients with non-small cell lung carcinoma (NSCLC) with solitary and synchronous oligometastasis who received LCT and/or systemic chemotherapy showed a trend toward prolonged survival in subgroup analyses [7–10]. However, no prospective data have been available on this patient population.

Thus, we launched a multicenter, single-arm Phase II study of aggressive LCT in combination with systemic chemotherapy for Stage IV NSCLC with solitary and synchronous oligometastasis: CURE-OLIGO (TORG1529). Here we report the final analysis results, including efficacy and safety data.

Materials and methods

Study design

This was an open-label, multicenter, single-arm Phase II study. The primary endpoint was the 2-year survival rate. Secondary endpoints were progression-free survival (PFS) as assessed by the investigator, overall survival (OS), and safety.

Eligibility and exclusion criteria

Eligible patients were pathologically confirmed as having NSCLC with solitary oligometastasis. As an exception, brain metastases that could be controlled by stereotactic radiosurgery (SRS) and/or surgery, and less than 4 were eligible. Additionally, eligible patients had to be treatment-naive with Stage IV disease (as per the seventh edition of the AJCC TNM Staging of Lung Cancer) regardless of whether the target lesions were assessable using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria. Those patients with pleural effusion, pleural dissemination, ascites, peritoneal dissemination, bilateral adrenal gland metastases, and activating *EGFR* mutations or *ALK* rearrangement were excluded. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and adequate organ function. Before treatment initiation, mandatory chest and abdomen computed tomography (CT) scans, brain magnetic resonance imaging (MRI) or CT scans, and positron emission tomography (PET) scans or bone scans were performed.

Owing to the slow accrual of participants, we amended the protocol twice. First, the locoregional lymph node range was increased from N0–1 to N0–3. Second, the upper age limit was changed from ≤ 75 years to no limit, and the number of metastases was changed from only 1 to ≤ 3 within 2 organs, except for brain metastases,

Table 1 Patient characteristics

Characteristic	N = 19
Age (years)	
Median	68
Range	51–74
Sex	
Male	13
Female	6
Smoking status	
Never-smoker	17
Smoker	2
Performance status	
0–1	19
Histology	
Adenocarcinoma	12
Squamous	6
NOS	1
*T**	
T1a/T1b	2/5
T2a/T2b	4/1
T3/T4	4/3
N	
0/1/2/3	7/3/5/4
M	
M1a/M1b (ver7)	0/19
M1a/M1b/M1c (ver8)	0/17/2
Number metastasis	
1/2	17/2
Metastatic site	
Brain	9
Bone	7
Adrenal grand	2
Lung	1
Cervical lymph node	1

*TNM version 7

where ≥ 4 were allowed if it was possible to treat all lesions with SRS.

Study treatment

All patients were administered platinum-doublet chemotherapy and radiotherapy for thoracic disease and LCT for distant disease within 8 weeks of starting or completing thoracic radiotherapy. Treatment was composed of concurrent chemoradiotherapy (CCRT) and subsequent consolidation chemotherapy and LCT. Investigators could choose the regimen of systemic chemotherapy: either cisplatin plus vinorelbine or cisplatin plus docetaxel.

Thoracic radiotherapy was started on day 1 and delivered 5 days per week in 2-Gy fractions for a total dose of 60 Gy. Three-dimensional CT planning was mandatory, and involved-field radiotherapy was used. Gross tumor volume included the primary tumor and clinically positive lymph nodes observed during CT planning (> 1 cm short-axis diameter) or pretreatment PET. The clinical target volume included gross tumor volume plus a total margin of ≥ 0.5 cm. The total planning target volume included the clinical target volume plus a total margin of ≥ 0.5 cm. The dose was prescribed at a reference point. The optimal planned target volume coverage was 95%–107% of the prescribed dose. All radiation doses were calculated using heterogeneity corrections (superposition/convolution dose calculation algorithms). The maximum spinal cord dose was limited to 52 Gy, and 1 cm^3 of the spinal cord could not exceed 48 Gy. The volume of both lungs that received ≥ 20 Gy (V20) did not exceed 35% of the total. Brachial plexus doses were maintained at < 66 Gy.

The LCT protocol for oligometastases was administered within 8 weeks of starting or completing systemic treatment. Patients with brain metastases were treated with either resection or SRS, depending on the volume and the location of the brain metastases. Resection for brain metastases followed by whole-brain radiotherapy was not mandatory. When surgery was considered in cases of extracranial metastases, a radical resection was envisaged. The type of LCT was determined in consultation with radiologists. The treating radiotherapist was responsible for the choice of dose-fractionation regimen, with curative intent when possible. Stereotactic body radiotherapy (SBRT) and conventional radiotherapy were allowed.

Table 2 Treatment delivery

	N = 19
Chemotherapy	
Cisplatin + Vinorelbine	18 (94.7%)
3 cycles	2
4 cycles	16
Cisplatin + Docetaxel	1 (5.3%)
4cycles	1
Thoracic radiotherapy	
60 Gy completed	19 (100%)
Without discontinuation	10
With discontinuation	9*
Local consolidative therapy	
Brain	9 (47.4%)
Surgery	1
Surgery + whole-brain radiotherapy	3
Stereotactic irradiation	5
Bone	7 (36.8%)
Radiotherapy	7
Adrenal grand	2 (10.5%)
Surgery	1
Radiotherapy	1
Cervical lymph node	1 (5.3%)
Surgery + radiotherapy	1

*Neutrophil count decreased: 6, Febrile neutropenia: 1, other: 2

Efficacy and safety evaluations

Before treatment initiation, all patients underwent mandatory chest and abdomen CT scans, brain MRI or CT scans, and PET scans or bone scans. Tumor assessments were performed at baseline and every 8–12 weeks for a 2-year follow-up period. The tumor response was evaluated according to RECIST version 1.1. Adverse events (AEs) were recorded using Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

The primary endpoint was the 2-year survival rate. The key secondary endpoints were PFS, OS, and safety. A single-arm Phase II study for NSCLC with oligometastases showed a 2-year survival rate of 16.4–23.3% [7, 10]. The 2-year survival rate of Phase III studies for advanced NSCLC treated with chemotherapy without immune checkpoint inhibitors (ICIs) is typically approximately 30% [11, 12]. Thus, we set the threshold at 30% because we used aggressive LCT for Stage IV patients, so we expected a greater therapeutic effect. In contrast, the 2-year survival rate of stage III NSCLC treated with CCRT without ICI was reported as 60% [13–15]. Assuming a clinically meaningful 20% increase and setting the expected value at 50%, 51 patients were required in this study according to the exact binomial test (one-sided $\alpha = 0.05$, $1 - \beta = 0.9$). Considering patient ineligibility, a sample size of 55 patients was set. In 2018, owing to the slow accrual of participants, we amended the one-sided α-error to 0.10 and the statistical power

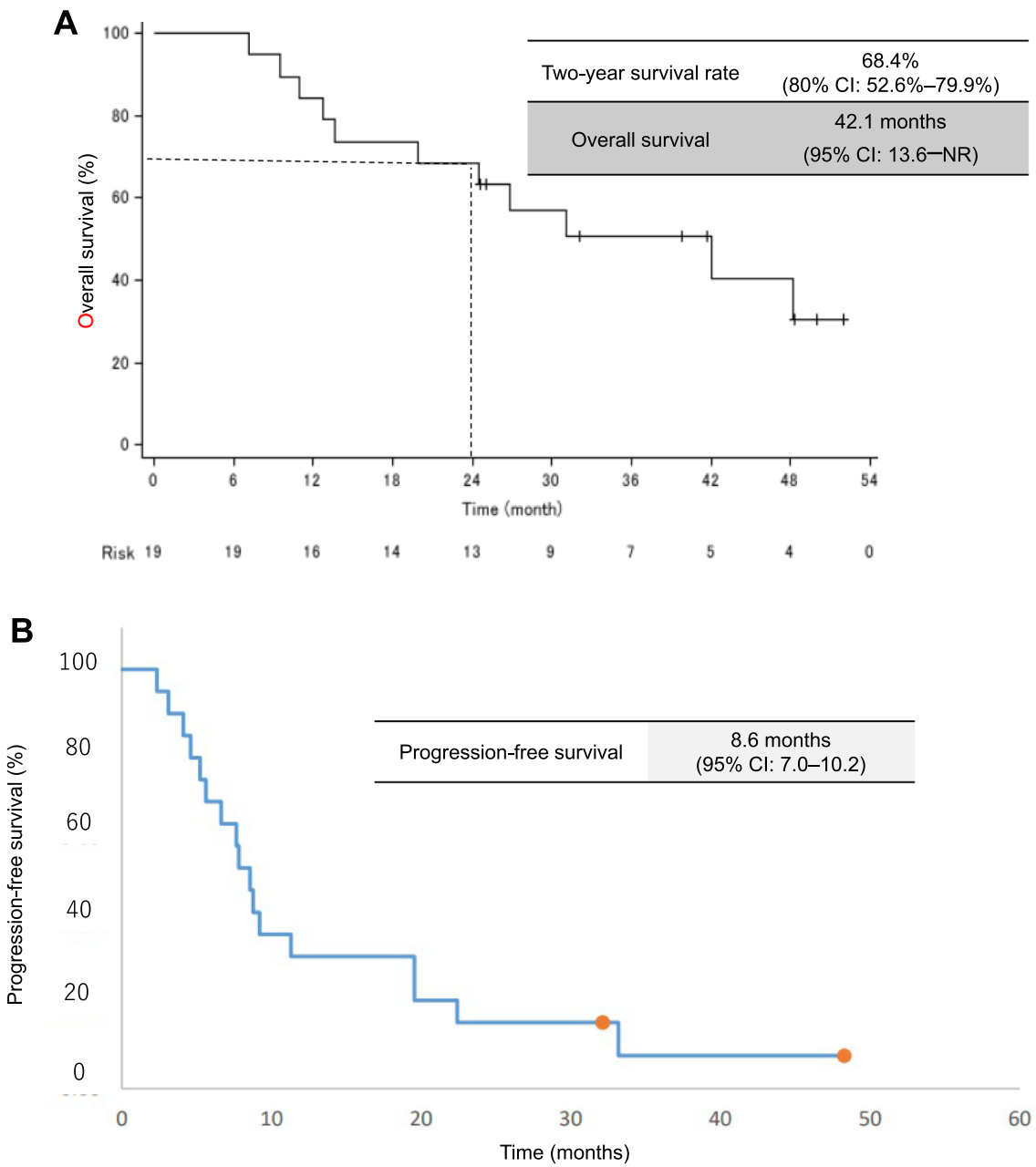


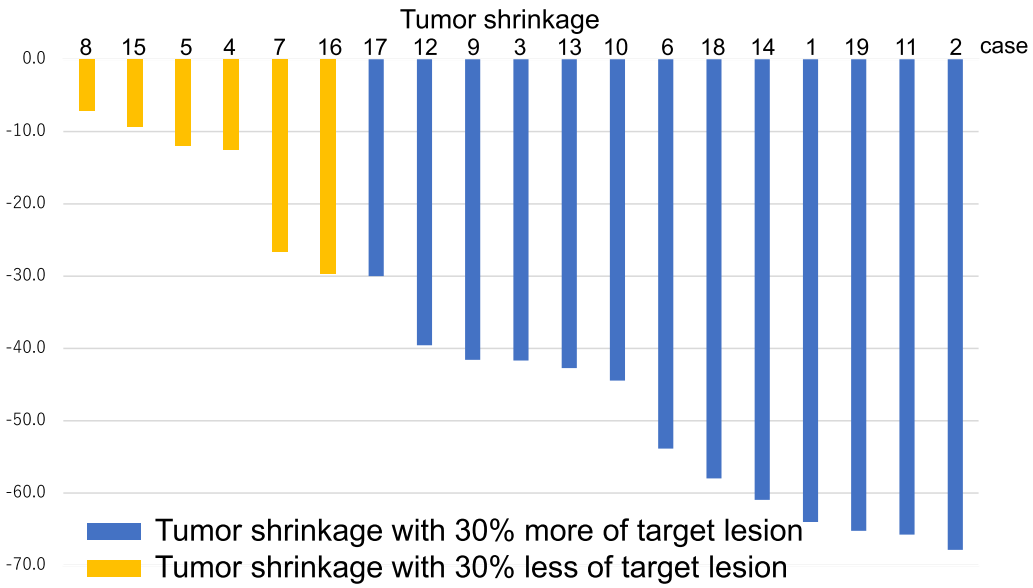
Fig. 1 Kaplan–Meier curves of (**A**) overall survival and (**B**) progression-free survival. Vertical lines show censored events

to 0.70. As a result, the number of required patients was reduced to 20.

Results

Patients' characteristics

We enrolled 19 patients between June 2016 and May 2020. The trial was terminated before completing full enrollment (n = 20) due to slow accrual, and the baseline characteristics of the 19 enrolled patients are summarized in Table 1. The median age was 68 years, 13 patients (68.4%) were male, 17 patients (89.5%) had a smoking history, and all patients had an ECOG performance status of 0 or 1. Adenocarcinoma and squamous cell carcinoma were present in 12 (63.2%) and 6 (31.6%) patients, respectively. The primary tumor size was as follows: < 3 cm for T1a/T1b (n = 7, 36.8%), < 5 cm for T2a (n = 4, 21.1%), < 7 cm for T2b (n = 1, 5.3%), and > 7 cm for T3/T4 (n = 7, 36.8%). There were 7 (36.8%) patients without regional lymph node metastasis, 5 (26.3%) with N2, and 4 (21%) with N3 disease. The metastasis



Response	N = 19
CR	0
PR	11
SD	8
PD	0
Response rate	57.9% (95% CI: 33.5%–79.7%)

Fig. 2 Waterfall plot and response rate

sites included the brain, bone, adrenal gland, lung, and cervical lymph node (n = 9, 7, 2, 1, and 1, respectively).

Treatment delivery

All patients received platinum-containing chemotherapy, such as cisplatin plus vinorelbine (n = 18) or cisplatin plus docetaxel (n = 1). Overall, 17 (89.5%) patients completed 4 cycles, and 2 (10.5%) patients terminated treatment after 3 cycles because of disease progression. All patients completed chemoradiotherapy (CRT) during the concurrent phase and LCT for all oligometastases (Table 2). Surgery for oligometastases was performed for 6 (31.5%) cases, including brain, adrenal gland, and cervical lymph node operations in 4,1, and 1 patient, respectively. Among them, radiotherapy was added to 3 cases of brain and the single case of cervical lymph node oligometastases. The remaining 13 (68.4%) patients with oligometastases (brain, 5; bone, 7; and adrenal gland, 1) were treated with radiotherapy only.

Efficacy

The data cutoff date was May 31, 2022. The median follow-up time was 42.1 months (95% confidence interval [CI]; 13.6–not reached). The primary endpoint of the study was the 2-year survival rate, which was 68.4% (80% CI 52.6%–79.9%), and the median OS was 42.1 months (95% CI 13.6–not reached) (Fig. 1A). The median PFS was 8.6 months (95% CI 7.0–10.2) (Fig. 1B). Eleven patients (57.9%) showed partial response, 8 (42.1%) had stable disease, and there were no patients with progressive disease (see Fig. 2).

Patterns of recurrence

At the data cutoff date, 2 patients (10.5%) had maintained their status of no disease progression (Fig. 3A, Case No. 08 and 16). Of the 17 patients with disease progression, 14 (73.7%) showed the emergence of new lesions (Fig. 3B). There were 10 (58.8%) who received LCT at the time of progression. The other 3 patients had disease progression such as only LCT lesion (n = 2, brain), and

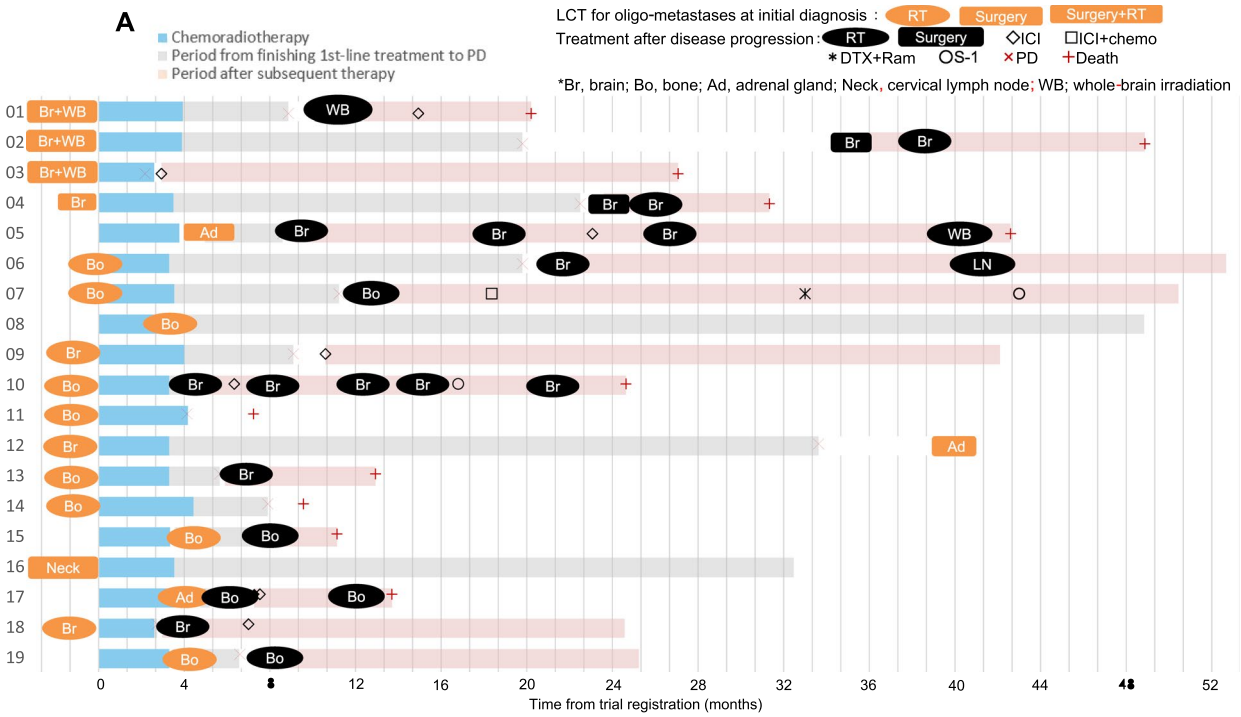


Fig. 3 **A** Swimmer plot shows course of treatment and pattern of recurrence in individual patients. **B** Disease progression at the follow-up cutoff date. LCT, local consolidative therapy; PD, progressive disease

no LCT lesion (contralateral lung metastasis that disappeared following chemotherapy) and a newly observed lesion (n = 1). ICIs were administered to 8 patients as subsequent therapy after progression of the study protocol treatment. There was no statistically significant difference between the patients who did and did not receive subsequent ICIs (see Fig. 4).

Adverse events

Table 3 shows the AEs that occurred during the trial. The most common AEs ≥ grade 3 were a decreased white blood cell count (68%) and decreased neutrophil count (74%). However, febrile neutropenia occurred in 16% of patients (all grade 3). The AEs were generally mild (grades 1–2), and there were no treatment-related deaths. Regarding radiotherapy, common AEs included esophagitis (73.7%), followed by radiation dermatitis

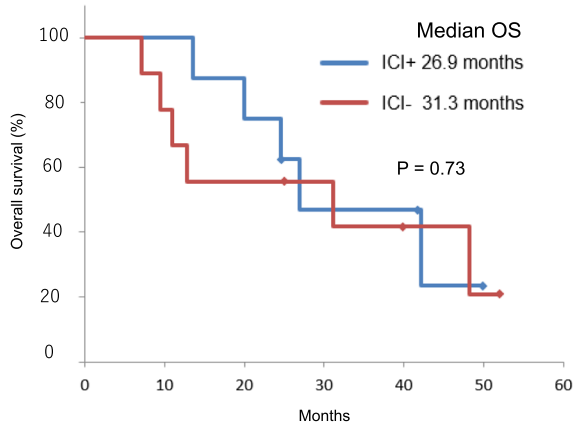


Fig. 4 Kaplan–Meier curves of overall survival with and without immune checkpoint inhibitors after disease progression. Vertical lines show censored events

(68.4%), and pneumonitis (10.5%). No AE related to LCT for oligometastases occurred.

Discussion

The aim of our study was to evaluate the prolongation of survival, including cure following aggressive LCT for both primary lesions with lymph node metastases and all oligometastases combined with systemic chemotherapy for Stage IV NSCLC. Our treatment protocol resulted in a 2-year survival rate of 68.4%, and 2 (10.7%) patients maintained PFS at the end of the 2-year follow-up period. There were 10 (52.6%) patients who developed oligometastatic progression, and all patients received additional LCT. Two of them have maintained a status of no disease progression without systemic treatment after LCT against an oligometastatic progression lesion. Our treatment strategy induced a cure in 10% of patients with advanced NSCLC and 10% of patients with true oligometastases. Notably, although our study did not use ICIs to treat advanced NSCLC, systemic chemotherapy combined with LCT potentiated a promising survival

Table 3 Adverse events

Adverse event	Grade				N = 19	
	1	2	3	4	≧ G3	%
WBC decreased	0	6	8	5	13	68
Neutrophil count decreased	1	3	4	10	14	74
Platelet count decreased	12	1	0	0	0	0
Anemia	7	11	1	0	1	5
Increased ALT	3	1	0	0	0	0
Increased AST	7	1	0	0	0	0
Decrease albumin	12	6	0	0	0	0
Hyponatremia	10	0	1	1	2	11
Hypokalemia	4	0	0	0	0	0
Hyperkalemia	9	0	0	0	0	0
Fever	6	0	0	0	0	0
Fatigue	2	1	1	0	1	5
Malaise	8	3	1	0	1	5
Alopecia	5	3	0	0	0	0
Constipation	7	5	0	0	0	0
Diarrhea	4	0	0	0	0	0
Nausea	5	5	1	0	1	5
Vomiting	2	0	1	0	1	5
Anorexia	8	4	1	0	1	5
Febrile neutropenia	0	0	3	0	3	16
Dysgeusia	2	2	0	0	0	0
Esophagitis	10	4	0	0	0	0
Dermatitis radiation	13	0	0	0	0	0
Pneumonitis	2	0	0	0	0	0
Vasculitis	3	2	0	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

benefit in NSCLC patients with oligometastases, in contrast to data from previous prospective trials using ICIs in NSCLC [16, 17]. However, we could only identify oligometastatic disease using radiological findings in our current study. Only a limited number of studies have addressed the unique biology of oligometastases, and few address potential prognostic or predictive biomarkers that could guide patient selection for specific therapeutic strategies. Thus, further study is warranted to specify an oligometastatic state, including biological findings.

The European Organization for Research and Treatment of Cancer and the European Society for Radiotherapy and Oncology proposed an oligometastatic state model in 2020 [18]. Two randomized Phase II trials have reported that LCT with or without maintenance therapy for patients with ≤ 3 oligometastases from NSCLC that did not progress after initial systemic therapy improved PFS and OS compared with maintenance therapy alone [19, 20]. Patients with induced oligometastatic disease were enrolled in these studies. Induced oligometastatic disease is defined as a diagnosis of polymetastatic disease followed by systemic treatment with or without local treatment, and the primary tumor is assumed to be controlled by ongoing or previous treatment. Our study aimed to target de novo oligometastatic disease with synchronous oligometastatic disease without postoperative recurrence. Both treatment goals and treatment strategies have changed with the introduction of the concept of oligometastatic disease. Whereas local treatment aims to eradicate all oligometastases and the potentially uncontrolled primary tumor, the choice of the optimal combination strategy with systemic treatment depends on the oligometastatic disease state and the specific treatment goal.

The general contemporary definition of oligometastatic disease is a malignancy with a limited number of metastases and a limited tumor burden [21]. In our study, 17 (89.5%) patients had solitary metastasis equivalent to M1b in TNM edition 8. However, 12 (63.2%) patients with a tumor ≥ 3 cm (other than T1 in TNM edition 7) were enrolled, including 7 (36.8%) patients with a tumor ≥ 7 cm (T3/T4 in TNM edition 7) and 9 (47.4%) patients with N2/N3 disease. CCRT for unresectable stage III NSCLC patients has been the standard of care for the past decade, with the induction of cure in approximately 20%. Although the response rate has been reported as 60–70%, approximately 50% of patients experienced locoregional recurrence. Our study achieved a good response against thoracic disease treated with CRT, and only 1 patient developed locoregional progression at first recurrence. In other words, 14 (73.7%) patients developed progressive disease in newly observed lesions. Durvalumab maintenance therapy after CCRT for stage III NSCLC has been shown to reduce distant metastases [22]. Furthermore, ICIs in combination with chemotherapy against metastatic NSCLC have been confirmed to confer a better survival benefit than chemotherapy. Moreover, the use of pembrolizumab after SBRT for oligometastatic NSCLC recently showed promising results, with a median PFS of 19.1 months and a 2-year survival rate of 77.5% [23]. Although no clear difference in OS was observed with or without ICI after disease progression in our study, we speculate that ICIs may be a more effective treatment before disease progression, even in cases of oligometastatic disease. Since several studies are currently investigating the use of ICIs in combination with LCT, once these results have been released, we will discuss their implications.

It is necessary to determine whether LCT is tolerable for patients with advanced-stage cancer in addition to systemic treatment. Recently, a single-arm Phase II clinical trial found that the incidence of SBRT toxic effects ≥ grade 3 was < 5%, and the rate of AEs ≥ grade 2 was 18.6% [24]. On the other hand, the rate of AEs ≥ grade 2 was 29% and treatment-related death was 4.5% in a randomized Phase III trial.25 In our study, the main AEs related to CRT were myelosuppression and gastrointestinal symptoms, and the incidence rates of each AE were similar to CRT against stage III NSCLC. In other words, treatment with CRT for thoracic disease combined with LCT was safely performed in 6 patients (31.5%) who underwent surgery for oligometastases.

The limitation of this study is that it was a single-arm Phase II trial with a small number of patients and was prematurely terminated. Therefore, we were unable to draw definitive conclusions about both the safety and efficacy of our treatment protocol from the results of this study alone. Thus, more studies involving a larger number of patients are necessary.

Conclusion

In conclusion, aggressive LCT in combination with systemic chemotherapy for Stage IV NSCLC with solitary and synchronous oligometastasis revealed tolerability and possible efficacy. Further studies incorporating ICIs for treating oligometastatic disease are warranted and could lead to further outcome improvements. Additionally, exploring the optimal administration is also important for the results to be generalizable to clinical practice.

Abbreviations

AE	Adverse events
AJCC	American Joint Committee on Cancer
CI	Confidence interval
CRT	Chemoradiotherapy
CCRT	Concurrent chemoradiotherapy
CT	Computed tomography

ECOG	Eastern Cooperative Oncology Group
ICI	Immune checkpoint inhibitor
LCT	Local consolidative therapy
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung carcinoma
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
RECIST	Response evaluation criteria in solid tumors
SRS	Stereotactic radiosurgery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02577-5.

Additional file 1.

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Author contributions
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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and Japan's Clinical Trials Act. The protocol was registered with the University Hospital Medical Information Network, Japan (protocol identification number: UMIN000022431). All patients provided written informed consent.

Consent for publication
All patients provided consent for publication.

Competing interests
The authors declare no competing interests.

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References

1. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378–82. https://doi.org/10.1038/nrclinonc.2011.44.
2. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10. https://doi.org/10.1200/JCO.1995.13.1.8.
3. Wong AC, Watson SP, Pitroda SP, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer. 2016;122(14):2242–50. https://doi.org/10.1002/cncr.30058.
4. Lussier YA, Xing HR, Salama JK, et al. MicroRNA Expression.
5. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):192–237. https://doi.org/10.1093/annonc/mdy275.
6. Dingemans AC, Hendriks LEL, Berghmans T, et al. Definition of synchronous oligo-metastatic non-small cell lung cancer—a consensus report. J Thorac Oncol. 2019;14(12):2109–19. https://doi.org/10.1016/j.jtho.2019.07.025.
7. De Ruysscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non–small-cell lung cancer patients with synchronous oligometastases long-term results of a prospective Phase II trial (NCT01282450). J Thorac Oncol. 2012;7(10):1547–55. https://doi.org/10.1097/JTO.0b013e318262caf6.
8. Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. Lung Cancer. 2013;82(2):197–203. https://doi.org/10.1016/j.lungcan.2013.07.026.
9. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic nonsmall-cell lung cancer. Clin Lung Cancer. 2014;15(5):346–55. https://doi.org/10.1016/j.cllc.2014.04.003.
10. Su SF, Hu YX, Ouyang WW, et al. Overall survival and toxicities regarding thoracic three-dimensional radiotherapy with concurrent chemotherapy for stage IV non-small cell lung cancer: results of a prospective single-center study. BMC Cancer. 2013;13:474. https://doi.org/10.1186/1471-2407-13-474.
11. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non–small-cell lung cancer. J Clin Oncol. 2008;26(21):3543–51. https://doi.org/10.1200/JCO.2007.15.0375.
12. Paz-Ares LG, de Marinis F, Dediu M, et al. Paramount: final overall survival results of the Phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non–small-cell lung cancer. J Clin Oncol. 2013;31(23):2895–902. https://doi.org/10.1200/JCO.2012.47.1102.
13. Segawa Y, Kiura K, Takigawa N, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non–small-cell lung cancer: OLCSG 0007. J

Clin Oncol. 2010;28(20):3299–306. https://doi.org/10.1200/JCO.2009.24.7577.
14. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable Stage III non–small-cell lung cancer: West Japan thoracic oncology group WJTOG0105. J Clin Oncol. 2010;28(23):3739–45. https://doi.org/10.1200/JCO.2009.24.5050.
15. Sekine I, Nokihara H, Sumi M, et al. Docetaxel consolidation therapy following cisplatin, vinorelbine, and concurrent thoracic radiotherapy in patients with unresectable Stage III non-small cell lung cancer. J Thorac Oncol. 2006;1(8):810–5.
16. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078–92. https://doi.org/10.1056/NEJMoa1801005.
17. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33. https://doi.org/10.1056/NEJMoa1606774.
18. Guckenberger M, Lievens Y, Bouma AB, et al. Characterization and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organization for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18–28. https://doi.org/10.1016/S1470-2045(19)30718-1.
19. Gomez DR, Blumenschein GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol Xin Shelley Wang. 2016;17(12):1672–82. https://doi.org/10.1016/S1470-2045(16)30532-0.
20. Iyengar P, Zabi W, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non–small-cell lung cancer A Phase 2 randomized clinical trial. JAMA Oncol. 2018;4(1):173501. https://doi.org/10.1001/jamaoncol.2017.3501.
21. Reyes DK, Pienta KJ. The biology and treatment of oligometastatic cancer. Oncotarget. 2015;6(11):8491–524. https://doi.org/10.18632/oncotarget.3455.
22. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in Stage III non–small-cell lung cancer. N Engl J Med. 2017;377(20):1919–29. https://doi.org/10.1056/NEJMoa1709937.
23. Bauml JM, Mick R, Ciunci C, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic non–small cell lung cancer A Phase 2 trial. JAMA Oncol. 2019;5(9):1283–90.
24. Olson R, Jiang W, Liu M, et al. Treatment with stereotactic ablative radiotherapy for UP to 5 oligometastases in patients with cancer primary toxic effect results of the nonrandomized Phase 2 SABR-5 clinical trial. JAMA Oncol. 2022;8(11):1644–50. https://doi.org/10.1001/jamaoncol.2022.4394.
25. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-comet): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051–8. https://doi.org/10.1016/S0140-6736(18)32487-5.

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