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Association between clinical outcomes and local treatment in stage IV non-small cell lung cancer patients with single extrathoracic metastasis

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Abstract

Background: Local treatment (LT) such as radiotherapy and metastasectomy on metastatic sites may improve outcomes in oligometastatic NSCLC patients, but more data are necessary to support LT in oligometastatic diseases. Patients with single extrathoracic metastatic lesion are more likely to benefit from local therapy. In this study, we evaluated the impact of LT in NSCLC patients with a single extrathoracic metastatic lesion.

Methods: Data were obtained from the Korean Association for Lung Cancer Registry (KALC-R), a database created using a retrospective sampling survey by the Korean Central Cancer Registry (KCCR) and the Lung Cancer Registration Committee.

Results: A total of 787 NSCLC patients with a single extrathoracic metastatic lesion were evaluated. In the multivariate analysis for OS, age, female sex, poor performance score, squamous histological subtype, LT, and initial treatment modality showed significant associations. Regarding LT, groups that underwent curative LT were significantly associated with better OS compared to groups that did not undergo LT ($p = 0.011$, HR 0.448, 95% CI: 0.242–0.829). In the multivariate analysis of patients who underwent LT, poor performance score, initial treatment modality, and T stage were independently associated with poor OS. Compared to the T1 stage, T3 stage showed an HR of 2.470 (95% CI: 1.309–4.663; $p = 0.005$) and T4 stage showed an HR of 2.063 (95% CI: 1.093–3.904; $p = 0.026$).

Conclusion: In NSCLC with a single extrathoracic metastatic lesion, LT, especially for curative purposes, has an independent association with OS. Moreover, among the patients who received LT, factors such as T stage, poor performance score, and initial treatment modality were significantly associated with OS.

[Correction added on 20 April 2022, after first online publication: in author byline, 'South Korea Central Cancer Registry' has been amended to 'Korea Central Cancer Registry.']

KEYWORDS
metastasectomy, non-small cell lung cancer, oligometastasis, radiotherapy, survival

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. Among NSCLC cases, stage IV cancer comprises 35%–40% of all newly diagnosed NSCLC cases.[1–3] In the past two decades, advances in targeted therapy and immunotherapy have improved clinical outcomes in stage IV NSCLC.[4–10] Despite the advent of treatment modalities, the 5-year survival rate of patients with metastatic NSCLC remains poor.[11]

In stage IV cancer, oligometastasis is usually used to describe patients with ≤5 extrathoracic metastatic lesions in ≤3 organs,[12,13] and they comprise 20%–50% of all patients with locally advanced and metastatic NSCLC.[14,15] According to Hellmann and Weichselbaum, oligometastasis is the state in which the progressing tumor cells are confined to a single or a few organs owing to the relatively limited number of seeding tumor cells and receptivity of the host organ. Furthermore, oligometastatic cancer is clinically more indolent than disseminated diseases[12,16] and shows better outcomes than the more advanced disseminated stage IV cancers.[17,18]

In addition to systemic treatment for NSCLC, local treatment (LT) for intrathoracic lesions and oligometastatic sites can be considered in treatment of oligometastatic patients. Treatment modalities mainly include radiotherapy, and several studies have shown association with overall survival (OS) or progression-free survival (PFS) in the patient groups after radiotherapy to the metastatic sites.[19–22] Nevertheless, the majority of study patients with oligometastatic diseases are heterogeneous in terms of the tumor burden and treatment modalities, and only few studies have a large number of patients enrolled. Furthermore, questions of which clinical factors are related to the benefit of LT in oligometastatic patients remain.

In terms of tumor burden, patients with a single extrathoracic distant metastasis are more likely to benefit from local therapy than patients with more metastatic lesions. Patients with multiple metastatic lesions show worse prognosis than those with a single metastatic lesion.[23] In addition, a study showed that a small number of metastatic lesions was associated with a good prognosis in patients with oligometastatic/oligoprogressive NSCLC who underwent radiotherapy.[24] We assume that the impact of LT is maximized in oligometastatic patients with a small number of metastatic lesions, and patients with a single distant metastatic lesion can be a good study population in which to evaluate the impact of LT.

In this study, we analyzed a nationwide database in Korea to evaluate the impact of LT in NSCLC with a single extrathoracic metastatic lesion.

METHODS

Patient selection

Data from the Korean Association for Lung Cancer Registry, a database created using a retrospective sampling survey by the Korean Central Cancer Registry (KCCR) and the Lung Cancer Registration Committee, were used for the present study.[25] During 2014–2016 period, the Korean Central Cancer Registry (KCCR) registered the data of patients newly diagnosed with lung cancer (24 354 patients in 2014, 24 502 patients in 2015, and 25 780 patients in 2016). From the eligible patients, about 10% of the overall patients that are representative of the whole population, were selected for more detailed survey after stratified random sampling. The patients with lung cancer were randomly selected from certified 13 regional cancer centers and 39 hospitals in Korea from which a significant number of registrations were made.[26] Patients were stratified by the date of diagnosis, sex, age, and extent of cancer spread.[25] After excluding multiple primary cancer patients, 2621 patients in 2014, 2660 patients in 2015, and 2829 patients in 2016 were selected from the 52 centers through systematic sampling methods.[27] Of the 8110 patients registered between 2014 and 2016, 1059 SCLC patients were excluded, and a total of 7051 patients with NSCLC were selected. Among the selected patients, 2909 patients with stage IV cancer were enrolled in this study. According to the data on extrathoracic metastatic sites, 787 patients with a single extrathoracic metastatic lesion were finally included in the evaluation (Figure S1). All patients were confirmed as having a single site of synchronous extrathoracic metastasis at the time of diagnosis by imaging investigations according to national protocols that include routine positron emission tomography computed tomography (PET/CT), bone scan and brain magnetic resonance imaging.

Based on a standardized protocol, data on age, sex, body mass index (BMI), smoking history, results of radiological findings, Eastern Corporative Oncology Group (ECOG) performance status (PS) at the time of diagnosis, clinical stage, treatment modalities, tumor burden, metastatic sites, and survival status were collected. The registered patients were followed up until December 09, 2020.[27] All the data in the study are from the registered database and no additional review of individual patient data was performed.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (range) values and categorical variables are expressed as percentages. Continuous variables were

compared using the Mann–Whitney U test, and categorical variables were compared using the chi-square test. Risk factors for mortality were analyzed using the Cox proportional hazards model. Survival was analyzed using the Kaplan–Meier method and compared using log-rank tests. All *p*-values were two-tailed, with statistical significance set at $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (IBM Corp.,).

Definition of LT

In the present study, LT included local radiotherapy or metastasectomy. Local radiotherapy on both intra- and extrathoracic lesions or metastasectomy was regarded as LT.[28] Patients were categorized according to the objectives of LT as curative or other purposes and according to the treatment site as intra- or extrathoracic. Curative intent LT include stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) to metastatic lesions; however, other radiotherapy modalities were also categorized as curative if multidisciplinary teams approved the treatment for curative purpose. In addition, metastasectomy for solitary extrathoracic metastatic lesion was categorized as curative LT. Extrathoracic sites included the bone, brain, liver, adrenal gland, extrathoracic lymph nodes, and other sites. The sites termed as "other sites" included the eye, intestine, spleen, skin, scalp, etc. Patients who underwent RT for lung parenchymal lesions were categorized as those receiving intrathoracic LT.[29,30] However, concurrent intrathoracic metastatic lesions such as malignant pleural effusion or pericardial effusion were not the target of LT.

RESULTS

Clinical characteristics of patients

A total of 787 NSCLC patients with a single extrathoracic metastatic lesion were evaluated in this study. All patients were clinically diagnosed with stage IV cancer. Their mean age was 68.1, and 202 (25.7%) patients were female. Median OS was 8.8 months (95% confidence interval [CI]: 7.7–9.9 months). The mean BMI was 22.3. Adenocarcinoma accounted for the highest proportion (54.0%), followed by the squamous cell type (23.3%) and unspecified NSCLC type (8.6%). Regarding the performance data, 515 (91.3%) patients had an ECOG score of 0–2. Among the patients with *EGFR* mutation status data, 171 of 532 (32.1%) patients had positive *EGFR* mutations.

A total of 218 (27.7%) patients had concurrent intrathoracic metastatic lesions: malignant pleural effusion in 123 (15.6%), malignant pericardial effusion in 20 (2.5%), pleural nodules in 50 (6.4%), and contralateral lung in 89 (11.3%). Regarding the sites of extrathoracic metastasis, bones were the most common, followed by brain.

TABLE 1 Clinical characteristics of patients

	Patients
Number	787
Age	68.1 ± 11.8
Sex (female)	202 (25.7)
BMI	22.3 ± 3.4
Ever smokers	505 (65.1)
OS (months) (median, 95% CI)	8.8 (7.7–9.9)
Pathology	
Squamous	183 (23.3)
Adenocarcinoma	425 (54.0)
Large cell	8 (1.0)
NSCLC NOS	68 (8.6)
Other	103 (13.1)
ECOG	
0–1	449 (79.6)
2 or more	115 (20.4)
EGFR mutation	171/532 (32.1)
T stage (T1/T2/T3/T4)	76 (11.9)/189 (29.7)/155 (24.3)/217 (34.1)
N stage (N0/N1/N2/N3)	126 (16.7)/56 (7.4)/218 (29.0)/353 (46.9)
Concurrent intrathoracic metastatic lesions	218 (27.7)
MPE	123 (15.6)
Contralateral lung	89 (11.3)
Pleural nodule	50 (6.4)
Malignant pericardial effusion	20 (2.5)
M1b, extrathoracic site	
Bone	330 (41.9)
Brain	214 (27.2)
Adrenal	76 (9.7)
Liver	74 (9.4)
Extrathoracic LN	67 (8.5)
Other sites	30 (3.8)
Initial treatment	
Chemotherapy	292 (39.8)
Best supportive care	201 (27.4)
Radiotherapy	93 (12.7)
CCRT	91 (12.4)
Surgery	26 (3.5)
Unknown	30 (4.1)
LT performed	301 (38.2)
LT objectives ($n = 301$)	
Curative	32 (10.6)
Noncurative	269 (89.4)
LT modality	
Metastasectomy	17 (2.2)
RT	297 (37.7)

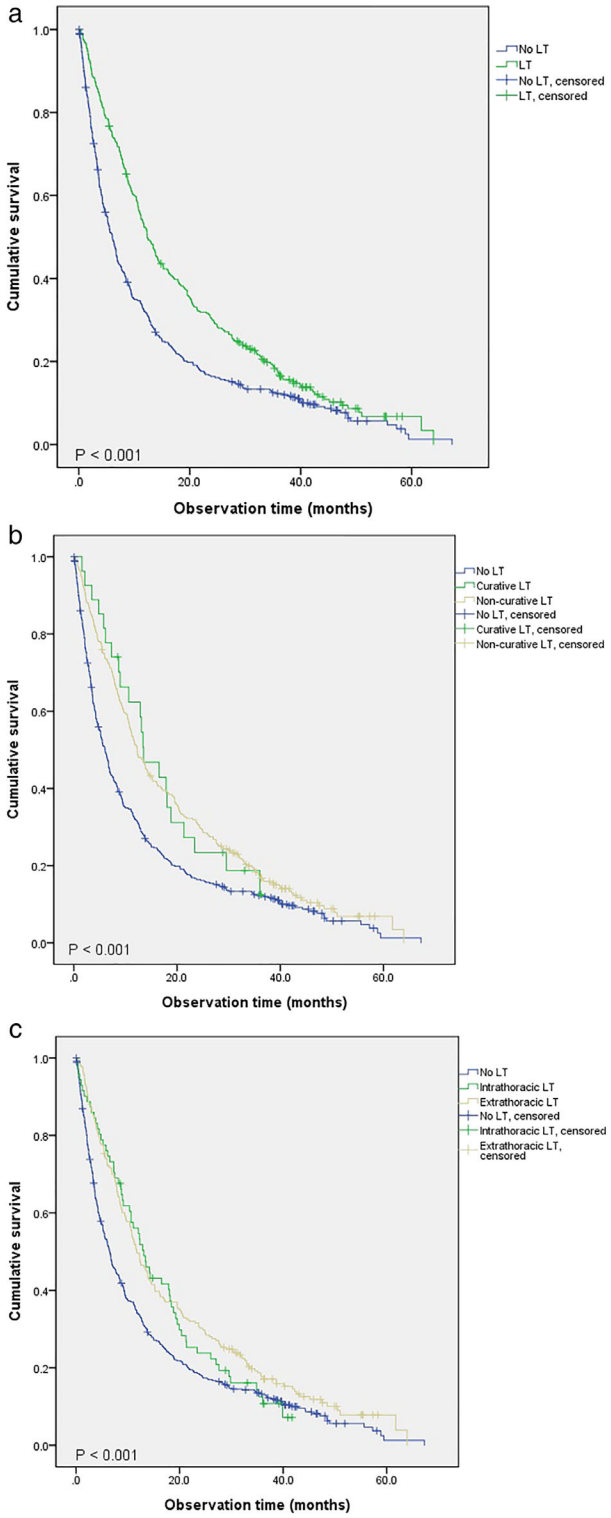
Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LN, lymph node; LT, local treatment; MPE, malignant pleural effusion; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OS, overall survival; RT, radiotherapy.

TABLE 2 Comparison between short- and long-term survivors (740 patients with survival data)

	OS <2 years	OS >2 years	*p*-value
Number	578	162	
Age	69.3 ± 11.5	62.1 ± 10.8	<0.001
Sex			<0.001
Male/female	454 (78.5)/124 (21.5)	101 (62.3)/61 (37.7)	
Body mass index	22.1 ± 3.5	22.3 ± 3.1	<0.001
Pathology			
Squamous	170 (29.4)	13 (8.0)	<0.001
Adenocarcinoma	290 (50.2)	134 (82.7)	<0.001
Large cell	7 (1.2)	1 (0.6)	0.518
NSCLC NOS	56 (9.7)	11 (6.8)	0.256
Other	55 (9.5)	3 (1.9)	0.173
ECOG			<0.001
0–1	322 (77.0)	116 (93.5)	
2 or more	96 (23.0)	8 (6.5)	
EGFR mutation	92/384 (24.0)	79/145 (54.5)	<0.001
Concurrent intrathoracic metastatic lesion			
MPE	95 (16.4)	25 (15.4)	0.759
Pleural nodule	31 (5.4)	17 (10.5)	0.019
Contralateral lung	57 (9.9)	22 (13.6)	0.176
Malignant pericardial effusion	18 (3.1)	2 (1.2)	0.192
M1b, extrathoracic site			
Bone	252 (43.6)	65 (40.1)	0.430
Brain	139 (24.0)	59 (36.4)	0.002
Adrenal	58 (10.0)	15 (9.3)	0.770
Extrathoracic LN	48 (8.3)	16 (9.9)	0.529
Liver	57 (9.9)	6 (3.7)	0.013
Other sites	26 (4.5)	3 (1.9)	0.125
Initial treatment			<0.001
Chemotherapy	201 (37.2)	89 (60.5)	
CCRT	60 (11.1)	30 (20.4)	
Radiotherapy	78 (14.4)	10 (6.8)	
Surgery	14 (2.6)	11 (7.5)	
Best supportive care	168 (31.1)	5 (3.4)	
Unknown	20 (3.7)	2 (1.4)	
LT			0.001
Not performed	367 (63.5)	79 (48.8)	
Performed	211 (36.5)	83 (51.2)	
LT objectives	($n = 211$)	($n = 83$)	0.354
Curative	24 (11.4)	7 (8.4)	
Noncurative	187 (88.6)	76 (91.6)	
LT modality			
Metastasectomy	10 (1.7)	7 (4.3)	0.051
RT	208 (36.0)	82 (50.6)	0.001

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LN, lymph node; LT, local treatment; MPE, malignant pleural effusion; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OS, overall survival; RT, radiotherapy.

There were 292 (39.8%) patients who received systemic chemotherapy as a first-line treatment, followed by the best supportive care (201 [27.4%]), radiotherapy (93 [12.7%]), and concurrent chemoradiation therapy (CCRT) (91 [12.4%]). Regarding the LT modality, 17 (2.2%) patients underwent metastasectomy and 297 (37.7%) underwent radiotherapy (Table 1).



Comparison between short- and long-term survivors

Among the 740 patients with survival data, 578 had an OS of less than 2 years and 162 had an OS longer than 2 years. Clinicopathological parameters were compared between the groups (Table 2). There were 124 (21.5%) and 61 (37.7%) female patients classified as short- and long-term survivors, and the mean age was 69.3 and 62.1 years, respectively ($p < 0.001$ and $p < 0.001$). Mean BMI was 22.1 and 22.3 in short- and long-term survivors, respectively ($p < 0.001$).

The long-term survivor group had a significantly higher proportion of adenocarcinoma cases (82.7% vs. 50.2%, $p < 0.001$) and a better PS of ECOG 0–2 (97.6% vs. 90.9%, $p = 0.014$). The proportion of EGFR mutations was higher in the long-term survivors than in the short-term survivors (54.5% vs. 24.0%, $p < 0.001$).

Regarding the concurrent intrathoracic metastatic findings, the long-term survivor group showed a higher proportion of patients with pleural nodules (10.5% vs. 5.4%, $p = 0.019$). For the extrathoracic sites, the percentage of brain metastasis was higher in the long-term survivor group (36.4% vs. 24.0%, $p = 0.002$), while the percentage of liver metastasis was significantly lower (3.7% vs. 9.9%, $p = 0.013$).

Systemic chemotherapy comprised the highest proportion among the initial treatment modalities for the long-term survivor (60.5%) and short-term survivor (37.2%) groups. In addition, the best supportive care accounted for 31.1% for the short-term survivor group, which was higher than that for the long-term survivor group (3.4%). The long-term survivor group showed a higher proportion of patients who received LT than the short-term survivor group (51.2% vs. 36.5%, $p = 0.001$). Patients who underwent LT showed significantly better OS when compared with the patients who did not ($p < 0.001$). Median OS was 6.1 months for no LT group (95% CI: 5.1–7.0 months) and 12.3 months for LT group (95% CI: 10.7–13.9 months) (Figure FIGURE 1a).

FIGURE 1 (a) Comparison of OS between patients who received local treatment (LT) and patients who did not. There was a statistically significant difference in OS in the two groups ($p < 0.001$). Hazard ratio for survival was 1.507 (95% CI: 1.291–1.760) for the no-LT group when compared to the LT group. (b) Comparison of OS between no-LT, LT of curative purpose and LT of other purposes ($p < 0.001$). In pairwise comparisons, there were significant differences in OS between the no-LT and the curative LT groups ($p = 0.041$), and the no-LT and the noncurative LT groups ($p < 0.001$). However, there was no significant difference between the curative LT and noncurative LT groups. The curative LT group showed HR of 0.640 (95% CI: 0.427–0.960) when compared to the no-LT group. The noncurative LT group showed HR of 0.666 (95% CI: 0.568–0.781) when compared to the no-LT group. (c) Comparison of OS between no-LT, intrathoracic LT and extrathoracic LT (<0.001). In pairwise comparisons, there were significant differences in OS between the no-LT and the intrathoracic LT groups ($p = 0.047$), and the no-LT and extrathoracic LT groups ($p < 0.001$). However, there was no significant difference between the intra- and extrathoracic LT groups. The intrathoracic LT group showed HR of 0.759 (95% CI: 0.581–0.993) when compared to the no-LT group. The extrathoracic LT group showed HR of 0.696 (0.587–0.826) when compared to the no-LT group

TABLE 3 Evaluation of clinical parameters associated with OS in patients

		Univariate		Multivariate	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)
Age ($n = 739$)	Year	<0.001	1.031 (1.024–1.038)	<0.001	1.022 (1.011–1.034)
Gender ($n = 740$)	Male (555)	<0.001	1	0.010	1
	Female (185)		0.669 (0.559–0.801)		0.629 (0.443–0.893)
BMI ($n = 682$)	Kg/m^2	<0.001	0.936 (0.912–0.960)	0.440	0.987 (0.954–1.021)
ECOG 01 vs. 2–4 ($n = 541$)	ECOG 01 (438)	<0.001	1	<0.001	1
	ECOG 2–4 (104)		2.033 (1.628–2.538)		1.758 (1.310–2.359)
LT ($n = 740$)	LT not done (446)	<0.001	1	0.033	1
	Curative LT (31)	0.031	0.640 (0.427–0.960)	0.011	0.448 (0.242–0.829)
	LT of other purposes (263)	<0.001	0.666 (0.568–0.781)	0.121	0.767 (0.548–1.072)
Initial treatment ($n = 666$)	Surgery (25)	<0.001	1	<0.001	1
	Chemotherapy (290)	0.027	1.756 (1.067–2.890)	0.014	2.575 (1.211–5.479)
	Radiotherapy (88)	<0.001	3.390 (1.993–5.765)	0.002	3.695 (1.636–8.345)
	CCRT (90)	0.068	1.646 (0.963–2.811)	0.002	3.614 (1.614–8.092)
	Supportive care only (173)	<0.001	5.692 (3.411–9.498)	<0.001	5.550 (2.507–12.286)
Pathology ($n = 740$)	Nonsquamous (557)	<0.001	1	0.002	1
	Squamous (183)		1.814 (1.521–2.164)		1.549 (1.176–2.041)
Never vs. ever smoker ($n = 734$)	Never (252)	<0.001	1	0.969	1
	Ever (482)		1.423		0.994 (0.718–1.374)
Concurrent intrathoracic metastatic lesion ($n = 740$)	No/yes	0.612	0.957 (0.856–1.136)	-	-
Metastatic site (M1b) ($n = 740$)	Bone metastasis (315)	<0.001	1	0.213	1
	Extrathoracic LN (64)	0.109	0.779 (0.573–1.058)	0.083	0.680 (0.440–1.051)
	Brain metastasis (198)	0.001	0.733 (0.606–0.887)	0.429	1.111 (0.856–1.443)
	Adrenal (73)	0.433	1.112 (0.853–1.449)	0.937	0.984 (0.665–1.458)
	Liver (62)	0.003	1.526 (1.154–2.018)	0.963	0.991 (0.662–1.482)
	Other sites (28)	0.327	1.219 (0.821–1.809)	0.102	0.566 (0.286–1.119)
T stage ($n = 607$)	T1 (73)	<0.001	1	0.377	1
	T2 (180)	0.144	1.252 (0.926–1.692)	0.184	1.279 (0.884–1.903)
	T3 (148)	0.003	1.604 (1.176–2.188)	0.082	1.418 (0.956–2.104)
	T4 (206)	<0.001	1.732 (1.289–2.329)	0.135	1.344 (0.912–1.979)
N stage ($n = 714$)	N0 (121)	0.027	1	0.081	1
	N1 (53)	0.896	1.023 (0.723–1.448)	0.368	1.246 (0.772–2.011)
	N2 (203)	0.009	1.375 (1.081–1.748)	0.069	1.381 (0.975–1.955)
	N3 (337)	0.020	1.304 (1.042–1.631)	0.011	1.553 (1.108–2.175)

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; LT, local treatment; NSCLC, non-small cell lung cancer; OS, overall survival; RT, radiotherapy.

Evaluation of clinical parameters associated with OS in overall patients

Various clinicopathological parameters were entered into the univariate analysis for association with OS (Table 3). In the univariate analysis, age, sex, BMI, ECOG, LT, initial treatment modality, pathologic subtypes, smoking status, metastatic site, T stage, and N stage showed significant association with OS. Factors significant in the univariate analysis were included in the multivariate analysis. Age, female sex, worse ECOG status, squamous subtype, and initial treatment modality showed a significant association. In the multivariate analysis, the group that underwent curative LT showed a significant association with better OS compared to the group that did not undergo treatment ($p = 0.011$, HR 0.448, 95% CI: 0.242–0.829). When three groups of patients who did not undergo LT, curative LT, and LT of other purposes were compared, Kaplan–Meier survival analysis showed a significant difference ($p < 0.001$). Median OS was 6.1 months for no LT group (95% CI: 5.1–7.0 months), 13.5 months for curative LT group (95% CI: 9.0–18.0 months), and 12.3 months for noncurative LT group (95% CI 10.6–14.0 months) (Figure FIGURE 1b).

TABLE 4 Comparison between three groups according to LT status

	Non-LT	Intrathoracic LT	Extrathoracic LT (on initially confirmed metastatic site at diagnosis)	*p*-value
Number	486	73	228	
Age	70.2 ± 11.4	66.8 ± 11.2	64.2 ± 11.7	<0.001[b]
Sex (female)	124 (25.5)	8 (11.0)	70 (30.7)	0.003
BMI	22.1 ± 3.35	22.2 ± 3.6	22.9 ± 3.5	0.021[b]
Pathology				
Squamous	117 (24.1)	34 (46.6)	32 (14.0)	<0.001
Adenocarcinoma	240 (49.4)	28 (38.4)	157 (68.9)	<0.001
Large cell	5 (1.0)	1 (1.4)	2 (0.9)	0.935
NSCLC NOS	37 (7.6)	8 (11.0)	23 (10.1)	0.416
Other	87 (17.9)	2 (2.7)	14 (6.1)	<0.001
ECOG				0.822
0–1	252 (78.8)	47 (79.7)	150 (81.1)	
2 or more	68 (21.2)	12 (20.3)	35 (18.9)	
EGFR mutation	92/294 (31.3)	10/51 (19.6)	69/187 (36.9)	0.058
T stage (T1/T2/T3/T4)	45 (11.8)/101 (26.6)/ 93 (24.5)/141 (37.1)	9 (13.4)/18 (26.9)/17 (25.4)/23 (34.3)	22 (11.6)/70 (36.8)/45 (23.7)/53 (27.9)	0.233
N stage (N0/N1/N2/N3)	69 (14.9)/33 (7.1)/ 128 (27.7)/232 (50.2)	14 (19.2)/5 (6.8)/21 (28.8)/33 (45.2)	43 (19.7)/18 (8.3)/69 (31.7)/88 (40.4)	0.368
Concurrent intrathoracic metastatic lesion	152 (31.3)	9 (12.3)	57 (25.0)	0.002
MPE	86 (17.7)	7 (9.6)	30 (13.2)	0.098
Contralateral lung	61 (12.6)	3 (4.1)	25 (11.0)	0.103
Pleural nodule	34 (7.0)	0 (0.0)	16 (7.0)	0.065
Malignant pericardial effusion	15 (3.1)	2 (2.7)	3 (1.3)	0.372
M1b sites				
Bone	196 (40.3)	28 (38.4)	106 (46.5)	0.241
Brain	81 (16.7)	16 (21.9)	117 (51.3)	<0.001
Liver	68 (14.0)	6 (8.2)	0 (0.0)	<0.001
Adrenal	59 (12.1)	14 (19.2)	3 (1.3)	<0.001
Extrathoracic LN	57 (11.7)	9 (12.3)	1 (0.4)	<0.001
Other sites	28 (5.8)	0 (0.0)	2 (0.9)	0.001
Initial treatment				<0.001
Chemotherapy	218 (46.2)	18 (28.1)	56 (28.4)	
Best supportive care	201 (42.6)	0 (0.0)	0 (0.0)	
Radiotherapy	7 (1.5)	27 (42.2)	59 (29.9)	
CCRT	5 (1.1)	16 (25.0)	70 (35.5)	
Surgery	11 (2.3)	3 (4.7)	12 (6.1)	
Unknown	30 (6.4)	0 (0.0)	0 (0.0)	
LT objectives				<0.001
Curative	0 (0)	29 (39.7)	3 (1.3)	
Noncurative	0 (0)	44 (60.3)	225 (98.7)	
LT modality				
Metastasectomy	0 (0.0)	0 (0.0)	17 (7.5)	-
RT	0 (0.0)	73 (100)	224 (98.2)	<0.001

Abbreviations: #A: No LT versus intrathoracic LT, B: No LT versus extrathoracic LT, C: intrathoracic LT versus extrathoracic LT. Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LN, lymph node; LT, local treatment; MPE, malignant pleural effusion; NOS, not otherwise apecified; NSCLC, non-small cell lung cancer; OS, overall survival; RT, radiotherapy.

TABLE 5 Analysis of association between clinical parameters and OS in patients who received LT ($n = 301$)

		Univariate		Multivariate	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)
Age ($n = 301$)	Year	<0.001	1.024 (1.012–1.036)	0.091	1.015 (0.998–1.034)
Gender ($n = 294$)	Male (218)	0.004	1	0.317	1
	Female (76)		0.655 (0.493–0.871)		0.772 (0.465–1.281)
BMI ($n = 276$)	Kg/m^2	0.009	0.946 (0.908–0.986)	0.164	0.965 (0.917–1.015)
ECOG 0–1 vs 2–4 ($n = 241$)	ECOG 01 (195)	<0.001	1	0.022	1
	ECOG 2–4 (46)		1.908 (1.365–2.668)		1.645 (1.076–2.524)
LT objective ($n = 294$)	Curative LCT (31)	0.827	1	-	
	LCT of other purposes (263)		1.407 (0.692–1.585)	-	
LT site ($n = 294$)	Intrathoacic (71)	0.459	1	-	
	Extrathoracic (223)		0.897 (0.672–1.196)	-	
LT modality ($n = 294$)	RT (277)	0.311	1	-	
	Metastasectomy (17)		0.755 (0.439–1.300)	-	
Initial treatment ($n = 254$)	Surgery (15)	<0.001	1	0.035	1
	Chemotherapy (73)	0.020	2.409 (1.152–5.040)	0.059	2.716 (0.964–7.653)
	Radiotherapy (81)	<0.001	5.788 (2.764–12.122)	0.011	3.975 (1.375–11.494)
	CCRT (85)	0.006	2.825 (1.349–5.916)	0.012	3.750 (1.331–10.566)
Pathology ($n = 294$)	Nonsquamous (228)	<0.001	1	0.289	1
	Squamous (66)		1.963 (1.472–2.620)		1.265 (0.819–1.955)
Never vs ever smoker ($n = 292$)	Never (100)	<0.001	1	0.489	1
	Ever (192)		1.675 (1.285–2.184)		1.175 (0.744–1.856)
Concurrent intrathoracic metastatic lesion ($n = 294$)	No/yes	0.103	0.781 (0.580–1.051)	-	
Metastatic site (M1b) ($n = 294$)	Bone metastasis (131)	0.070	1	-	
	Extrathoracic LN (10)	0.066	0.463 (0.203–1.052)	-	
	Brain metastasis (128)	0.043	0.762 (0.586–0.992)	-	
	Adrenal (17)	0.734	1.095 (0.649–1.847)	-	
	Liver (6)	0.623	1.229 (0.541–2.794)	-	
	Other sites (2)	0.182	2.604 (0.638–10.620)	-	
T stage ($n = 252$)	T1 (29)	0.007	1	0.030	1
	T2 (88)	0.527	1.170 (0.719–1.903)	0.129	1.637 (0.866–3.096)
	T3 (62)	0.015	1.863 (1.126–3.082)	0.005	2.470 (1.309–4.663)
	T4 (73)	0.022	1.774 (1.087–2.897)	0.026	2.063 (1.090–3.904)
N stage ($n = 285$)	N0 (57)	0.109	1	-	
	N1 (22)	0.484	0.820 (0.472–1.427)	-	
	N2 (88)	0.064	1.400 (0.980–1.999)	-	
	N3 (118)	0.222	1.237 (0.879–1.741)	-	

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LN, lymph node; LT, local treatment; MPE, malignant pleural effusion; NSCLC, non-small cell lung cancer; OS, overall survival; RT, radiotherapy.

Comparison between the three groups according to the status of LT

Patients were categorized into three groups according to their LT status and target sites (Table 4). Among the patients, 486 did not receive LT, 73 received LT only on intrathoracic sites, and 228 received LT for extrathoracic lesions. Clinicopathological parameters were compared among the three groups. The non-LT group showed the highest mean age among the three groups ($p < 0.001$). The extrathoracic LT group showed the highest proportion of female patients (30.7%, $p = 0.003$), and the highest mean BMI of 22.9 ($p = 0.021$).

Regarding pathological types, the intrathoracic LT group showed the highest proportion of squamous cell type (46.6%, $p < 0.001$). There were no significant differences in ECOG, *EGFR* mutation, T stage, and N stage among the groups. The intrathoracic LT group showed the lowest percentage of intrathoracic metastatic lesions (12.3%, $p = 0.002$). The extrathoracic LT group showed the highest proportion of brain metastasis (51.3%, $p < 0.001$) and the

lowest percentage of extrathoracic lymph node (0.4%, $p < 0.001$), adrenal gland (1.3%, $p < 0.001$), and liver (0%, $p < 0.001$) metastases. Among the initial treatment modalities, the extrathoracic LT group showed the highest proportion of CCRT (35.5%) and a smaller proportion of radiotherapy (29.9% vs. 42.2%) compared with the intrathoracic LT group.

As a LT modality, all metastasectomy cases ($n = 17$) were included in the extrathoracic LT group. In the Kaplan–Meier survival analysis, the three groups showed a statistically significant difference ($p < 0.001$). Median OS was 13.1 months for the intrathoracic LT group (95% CI: 10.0–16.2 months) and 11.8 months for the extrathoracic LT group (95% CI: 10.0–13.6 months) (Figure FIGURE 1c).

Patients were also grouped into curative and noncurative LT groups. There were 32 patients in the curative LT group, and 269 patients in the noncurative LT group (Table S1). The curative LT group showed a significantly higher proportion of males, squamous cell cancer, and lower proportion of concurrent intrathoracic metastatic lesion, and brain metastatic lesion when compared to the noncurative LT group.

Analysis of association between clinical parameters and OS in patients who received LT ($n = 301$)

Table 5 shows survival analysis performed in the group that underwent LT. In the univariate analysis, age, sex, BMI, ECOG, initial treatment modality, pathology, smoking status, metastatic site, and T stage were found to be significant factors, which were then entered into the multivariate analysis. Worse ECOG, initial treatment modality, and T stage were independently associated with poor OS. Poor ECOG of 2–4 showed an HR 1.645 (95% CI: 1.076–2.524; $p = 0.022$) when compared to ECOG of 0–1. Compared to surgery as an initial treatment, radiotherapy showed an HR of 3.975 (95% CI: 1.375–11.494; $p = 0.011$) and CCRT showed an HR of 3.750 (95% CI: 1.331–10.566; $p = 0.012$). Compared to T1 stage, T3 stage showed an HR of 2.470 (95% CI: 1.309–4.663; $p = 0.005$) and T4 stage showed an HR of 2.063 (95% CI: 1.093–3.904; $p = 0.026$).

DISCUSSION

The present study showed that LT was independently associated with OS in NSCLC patients with a single extrathoracic metastatic lesion. Furthermore, clinical parameters such as ECOG, initial treatment modality, and T stage were predictive of OS in patients who underwent LT.

Phase II studies performed by Gomez et al.[22] and Iyengar et al.[31] showed that local consolidative therapy may contribute to improvement in outcomes of oligometastatic NSCLC. Other studies also proved that local therapy to metastatic sites were associated with OS and PFS in oligometastatic patients.[19–22] Several prospective studies that evaluated efficacy of local ablative therapy and systemic treatment in oligometastatic NSCLC are reported.[32–34] NCT 01282450 enrolled 40 pathologically proven NSCLC stage IV patients with less than five metastases at initial diagnosis, and median PFS was 12.1 months.[33] The SINDAS study (NCT02893332), a phase III randomized control trial, evaluated the efficacy of upfront concurrent first generation tyrosine kinase inhibitors (TKI) with the addition of stereotactic ablative radiotherapy (SABR) versus without SABR in synchronous oligometastatic NSCLC with *EGFR* mutation. The interim results showed SABR plus TKI was associated with improvement in OS and PFS when compared with TKI alone.[35] Other ongoing studies such as SABR-Comet and "Oligomez" also showed potential clinical benefit of concurrent local radiotherapy in oligometastatic NSCLC.[31,34] Similar to the previous studies, LT, which was comprised of mainly local radiotherapy to either intrathoracic lung lesion or extrathoracic metastatic lesion and a small number of metastasectomies, was shown to have a significant association with OS in our population. Furthermore, patients who underwent LT for curative purposes showed a significantly more favorable survival than those who did not undergo LT in the multivariate analysis. In contrast, the groups that underwent LT for other purposes were not independently associated with OS compared to the no-LT group. It was unexpected that there was no statistically significant difference in OS between noncurative and curative LT groups in the multivariate analysis. This statistical disparity suggests that patients who received curative LT may have other related positive prognostic factors that were not accounted for in the multivariate analysis, and that effect of LT itself should be elucidated in settings that are more accurate. In the present study, a sizable proportion of patients who received LT for purposes other than the curative objective received radiotherapy for palliative objectives. The patients received radiotherapy to relieve associated symptoms or reduce the disease burden of metastatic lesions. We assume that the metastatic disease burden might have been heavier in this group than in the group that underwent curative LT. In the comparison between the curative and noncurative LT groups, the curative LT group showed a significantly lower proportion of concurrent intrathoracic metastatic lesion, and we assume that it contributed to the favorable association with OS in the curative LT group. However, we believe that a further validation study with larger population is necessary to evaluate association between objective of LT and OS, since only 32 patients were allocated to the curative LT group in our study.

Previous studies have shown the clinical impact of LT in oligometastatic NSCLC, which is mostly comprised of local radiotherapy and smaller number of metastasectomies.[36,37] However, several studies had heterogeneous populations in terms of tumor burden. The number of metastatic lesions differed among the study patients.[17,38] In other studies, oligometastatic, oligoprogressive, and oligoresidual sites were all included.[29,39] Thus, to more accurately assess the impact of LT, it was necessary to add homogeneity to the

study populations. The strength of our study is that all patients had a single extrathoracic metastatic lesion at the time of diagnosis and simultaneously had a relatively large number of study patients enrolled from the nationwide database. However, the interpretation of our results requires much caution. There is a possibility that patients who received curative LT had other clinical features related to better prognosis, or relatively less tumor burden. Furthermore, there were other factors such as poor ECOG score, initial treatment modality and T stage that also showed significant association with OS in the present study. The association between LT and OS in our study may not be sufficient to strongly recommend LT in oligometastatic NSCLC, but require further prospective studies which include data about timing and objectives of LT and tumor burden to more accurately evaluate the impact of LT on outcomes.

When comparing the intra- and extrathoracic LT groups, the intrathoracic LT group showed a lower proportion of concurrent intrathoracic metastatic lesions, and the extrathoracic LT group included a higher proportion of patients with brain metastasis. We believe that pathological type is relevant to the lower proportion of concurrent intrathoracic metastatic lesions in the intrathoracic LT group. The proportion of squamous cell carcinoma was 46.6% and 14.0% in the intra- and extrathoracic LT groups, respectively. When compared to adenocarcinoma type, squamous cell carcinoma showed a lower proportion of MPE which accounted for the large percentages of intrathoracic metastatic lesions.[40,41] The reason for the higher proportion of brain metastasis in the extrathoracic LT group is possibly due to wider options of local treatment modalities for a solitary metastatic lesion. While metastasectomy, SRS and SBRT are available modalities, strong evidences supporting LT on brain metastasis are also present.[42–44] Furthermore, the intrathoracic LT group showed a significantly higher proportion of patients who underwent radiotherapy as the initial treatment. The majority of patients who underwent intrathoracic LT underwent radiotherapy for primary lung lesions. We assume that the squamous cell type, which was the frequent pathological type in the intrathoracic LT group, is more likely to be centrally located, and in some cases in which invasion of the central airway is present, radiotherapy to the intrathoracic lesion may have been required.[45]

The median OS in our study population was 8.8 months, which may be shorter than the result of a single extrathoracic metastatic NSCLC population from a Japanese study (15.2 months),[46] but is similar to the median OS of the solitary single-organ metastases group from the pooled analysis of the Southwest Oncology Group mNSCLC protocols (8.7 months).[18] It should be taken into consideration that a sizable number of patients from our study did not undergo active anticancer treatment, and after exclusion of this patient group, the median OS increased to 11.7 months.

An interesting finding in our study was that among the groups who underwent LT, T stage was found to be an independent predictor of OS, along with the ECOG and initial treatment modality. T stage has been described as a prognostic factor in several studies on oligometastasis.[29,47] In a retrospective study of 29 patients with single-organ metastatic NSCLC, pathological T stage was shown to be a predictor of survival.[47] Another retrospective study by Zhang et al. showed that smokers with T3/4 oligometastatic NSCLC did not benefit from LT.[48] In the present study, the T3–4 stages showed significantly higher HR than the T1 stage in the multivariate analysis within the subgroup that underwent LT. It is necessary to evaluate the T stage components, whether the tumor size or the pattern of nearby organ invasion has a bigger role in the clinical impact. In a study by Jones et al., in which 11 patients with oligometastatic NSCLC were evaluated, the pathological primary tumor size was significantly associated with event-free survival and OS.[17]

There were notable differences between the long- and short-term survivor groups. The long-term survivor group showed a higher proportions of patients with pleural nodules and brain metastasis than the short-term survivor group. As a concurrent M1a finding, we speculated that pleural nodules are more indolent than other lesions such as MPE or malignant pericardial effusion. Furthermore, the long-term survivor group included a higher proportion of patients with brain metastasis. If untreated, brain metastasis is associated with poor prognosis; however, selected patients who present with synchronous brain-only oligometastatic lesion may have a better prognosis than other patients with brain metastases.[49] In addition, local treatment of brain metastatic lesion with surgery or SRS has been proven effective.[42]

Despite some evidences supporting local treatment for oligometastatic sites in advanced NSCLC, clinicians should first examine several important factors. A meticulous multidisciplinary approach is necessary to determine whether oligometastatic patients will benefit from local treatment rather than suffer from unnecessary risks of possible adverse events. Clinicians should consider timing of the treatment, general conditions of patients, appropriate treatment modality and most importantly, safety issues regarding additional LT. Moreover, the management of oligometastatic NSCLC should be more personalized. Not only distant metastatic lesions, but other factors such as concurrent intrathoracic metastatic lesion should also be considered. Recent studies show diverse clinical approaches in advanced NSCLC such as primary tumor resection, hyperthermic intrathoracic chemotherapy in patients with malignant pleural effusion,[50–52] and future studies that take various host and tumor-related factors into account are vital.

The present study had some limitations. First, PFS data were not described. We utilized a nationwide database that had strength in a number of study participants; however, the analysis of PFS was not possible. Second, due to the retrospective nature of the study, the evaluation of the clinical impact of LT may have been limited. The impact of LT in oligometastatic NSCLC has been discussed in a series of retrospective studies. Several prospective studies have been

conducted,[30,31] but larger population studies are necessary, and they should have matching controls which consider tumor burden, performance scores and concurrent treatment modalities in order to estimate the size of any possible effect of LT on survival. Third, a sizable proportion of local radiotherapy performed in our patients may be palliative or to relieve the symptoms of the patients. Therefore, limitations in terms of assessing the impact are present. Fourth, for patients who repeatedly received LT, only the first-line of LT was described in the study. Finally, patients who underwent surgery as the initial treatment were included in the study. It is likely that patients with pathological upstaging of stage IV cancer after surgery were included.

In conclusion, the present study showed that in advanced NSCLC with a single extrathoracic metastatic lesion, LT, especially for curative purposes, has a significant association with OS. Moreover, among the patients who had undergone LT, factors such as the T stage, poor performance score, and initial treatment modality were significantly associated with OS. Future prospective studies including more detailed data on tumor burden and the treatment modalities are necessary to more actively perform LT in oligometastatic NSCLC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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