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Original Article

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Impact of Liver Metastasis on First-Line Immunotherapy in Stage IV Non-Small Cell Lung Cancer

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Abstract

Background: Immunotherapy has become a key component of systemic therapy in stage IV non-small cell lung cancer (NSCLC). However, there have been conflicting reports of its efficacy in patients with liver metastasis (LM).

Methods: Using National Cancer Database (NCDB), patients who have been diagnosed and treated at Commission on Cancer- participating US institutions were screened for analysis. Selection criteria included clinical stage IV NSCLC, available cTNM stage information, overall survival (OS) with at least 1 month, and diagnosis between 2015 and 2017. They were grouped based on status of LM as well as use of immunotherapy. Clinical characteristics were collected and their association with LM/immunotherapy was analyzed. Impact of immunotherapy on OS was examined according to LM status. Propensity score matching (PSM) analysis was also conducted.

Results: A total of 83,479 including 18,497 LM-positive and 64,982 LM-negative patients met the study criteria. Presence of LM was associated with a number of clinical variables such as younger age, male sex, and chemotherapy. OS in patients with LM was significantly worse than that in those without LM (median OS, 5.0 vs. 8.8 months; hazard ratio (HR), 1.46; log-rank, $P < 0.0001$). Significant OS benefit from immunotherapy was observed in both LM-positive (median OS, 4.1 vs. 9.0 months; HR, 0.62; $P < 0.0001$) and negative groups (median OS, 7.2 vs. 15.6 months; HR, 0.64; $P < 0.0001$).

Conclusion: Immunotherapy benefited similarly to the survival of metastatic NSCLC patients regardless of with or without LM. Further research to validate the result would be warranted.

Keywords: Non-small cell lung cancer; Overall survival; Liver metastasis; Immunotherapy

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Introduction

Although overall outcome of lung cancer has been improving over the last few decades, it remains one of the deadliest adult cancers worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and often presents with metastatic or advanced disease which is generally incurable [1]. Recent development of novel systemic therapies such as targeted and immunotherapy dramatically changed the landscape in the management; however, NSCLC cases with advanced stages have rarely been cured despite all the progresses. Continuing effort is needed for further therapeutic improvement.

Since the discovery of immune checkpoints and their therapeutic implication as immunotherapy, a majority of human cancer types with advanced stage and at least those with high tumor mutational burden can be treated with inhibitors of programmed cell death-1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis such as pembrolizumab [2]. These agents have been tested in numerous clinical trials primarily for advanced stage, achieving regulatory approvals in various settings. They typically do not cause bone marrow toxicity which significantly limits the number and duration of treatment, resulting in shorter duration of disease control. Better efficacy and tolerability attracted clinicians and researchers to further investigate in early-stage settings [3, 4].

However, we face therapeutic resistance as *de-novo* or acquired phenomenon in almost all patients with advanced disease. Previous studies showed that presence of liver metastasis (LM) is associated with a poor survival and resistance to immunotherapy [5-7]. Increased immune tolerance was observed in LM due to a lower infiltration of cytotoxic T cells as compared to other metastatic sites [8]. These findings have been debated with recent contradictory reports, where similar magnitude of survival benefit from the use of immunotherapy has been observed in those with LM [9].

To address relatively small sample sizes in previous studies, we decided to investigate impact of LM on efficacy of immunotherapy using one of the largest cancer databases in the world.

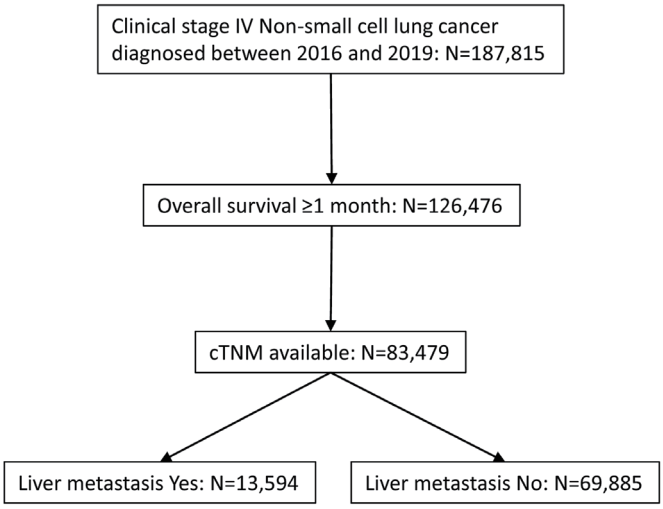


Figure 1. CONSORT diagram for case selection. De-identified cases were released from National Cancer Database.

Materials and Methods

Patient selection

De-identified cases with stage IV NSCLC were obtained through National Cancer Database (NCDB) program, which is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society [10]. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. Its data represent more than 72% of newly diagnosed cancer cases in the US [11].

Those who were diagnosed between 2016 and 2019 for stage IV NSCLC were further investigated to select candidates for analysis (Fig. 1). Candidates must have survived for at least 1 month with available cTNM stage information. Only cases diagnosed through 2017 had available survival data. They were grouped based on status of LM as well as use of immunotherapy. Clinical characteristics including institution (academic vs. other), age (less than 70 vs. 70+), sex (male vs. female), race (white vs. other), Charlson-Deyo (CD) morbidity score (0 - 1 vs. 2+), year of diagnosis (2016 vs. 2017), histology (adenocarcinoma not otherwise specified (NOS) vs. other), clinical T (T3-4 vs. other), clinical N (N2-3 vs. other), clinical M (M1B vs. other), surgery of primary site (yes vs. no/unknown), radiation (yes vs. no/unknown), multi-agent chemotherapy (yes vs. no/unknown), bone metastasis (yes vs. no/unknown), and brain metastasis (yes vs. no/unknown) were collected and their association with LM/immunotherapy was analyzed.

Statistical analysis

Statistical analyses were conducted according to previous publications [12] and as follows: the 5-year overall survival (OS) rates were analyzed on the bases of LM and immunotherapy status (yes vs. no/unknown). The Kaplan-Meier curves were compared using the log-rank test. The associations between LM/immunotherapy and clinical demographics were assessed by Chi-squared test. Univariate and multivariate Cox proportional hazards analyses were performed using JMP version 14 (SAS Institute, Cary, NC, USA). Propensity score matching (PSM) analysis was performed according to XLSTAT software guideline. The propensity scores included the following variables: institution, age, sex, race, CD score, histology, cT, cM1B, multi-agent chemotherapy, and bone metastasis. A propensity score difference of 0.001 was adopted as the maximum caliper width for matching.

A two-tailed P-value less than 0.05 was considered as statistically significant.

This is a hospital-based (NCDB) study that involves no identifiable information for individuals throughout the analyses. This study was reviewed by the institutional review board at University at Buffalo and was designated exempt from human subject research.

Results

A total of 83,479 patients, which include 18,497 and 64,982 patients with or without use of immunotherapy, respectively, met the criteria for further analysis (Table 1). LM was present in 2,944 and 10,650 patients with or without immunotherapy, respectively, and was not associated with the use of immunotherapy (P = 0.1241). Presence of LM was significantly associated with several clinical factors such as academic institution, younger age, male sex, white race, year 2017, other histology, T3-4, N2-3, M1B, lack of surgery, lack of radiation, multi-agent chemotherapy, bone metastasis, and brain metastasis (Table 2). The use of immunotherapy was associated with several factors in both LM-positive and negative groups (Table 3). The highly significantly associated factors include young age (< 70 years old), white race, low CD score, diagnosis year of 2017, adenocarcinoma NOS histology, N2-3 status, no use of multi-agent chemotherapy, and lack of brain or bone metastases.

Survival analysis demonstrated that those with LM had a shorter OS than those without LM: median OS 5.0 vs. 8.8 months, respectively (Fig. 2).

Those with immunotherapy had a longer OS than those without immunotherapy in both univariate and multivariate analyses, regardless of LM status. Median OS was 9.0 and 4.1 months with and without immunotherapy, respectively, for those with LM, and 15.6 and 7.2 months, respectively, for those without LM (Fig. 3). Univariate hazard ratios (HRs) were 0.62 and 0.64 for LM-positive and LM-negative groups, respectively (Tables 4 and 5). Further analysis using PSM procedures was conducted. PSM has not perfectly matched both groups due to many independent factors significant in univariate and multivariate analyses (Table 6); however, it has still validated our findings with univariate HRs of 0.62 and 0.63, respectively, and P-values of < 0.0001 for both LM-positive

Table 1. Clinical Characteristics of Eligible Cases

Factors	Immunotherapy			P-value
	Yes (%)	No (%)	Total (%)	
Total	18,497 (22)	64,982 (78)	83,479 (100)	
Institution				
Academic	6,024 (23)	20,348 (77)	26,372 (100)	0.0012
Other	12,473 (22)	44,634 (78)	57,107 (100)	
Age				
≥ 70	7,416 (20)	30,145 (80)	37,561 (100)	< 0.00001
< 70	11,081 (24)	34,837 (76)	45,918 (100)	
Sex				
Male	9,655 (22)	34,482 (78)	44,137 (100)	0.0373
Female	8,842 (22)	30,500 (78)	39,342 (100)	
Race				
White	15,560 (23)	52,594 (77)	68,154 (100)	< 0.00001
Other	2,937 (19)	12,388 (81)	15,325 (100)	
CD score				
0 - 1	16,150 (23)	54,740 (77)	70,890 (100)	< 0.00001
2 - 3	2,347 (19)	10,242 (81)	12,589 (100)	
Year of diagnosis				
2016	6,523 (16)	35,142 (84)	41,665 (100)	< 0.00001
2017	11,974 (29)	29,840 (71)	41,814 (100)	
Histology				
AdNOS	13,130 (25)	40,242 (75)	53,372 (100)	< 0.00001
Other	5,367 (18)	24,740 (82)	30,107 (100)	
Clinical T stage				
cT3-4	8,825 (22)	31,198 (78)	40,023 (100)	0.4715
Other	9,672 (22)	33,784 (78)	43,456 (100)	
Clinical N stage				
cN2-3	12,169 (24)	39,097 (76)	51,266 (100)	< 0.00001
Other	6,328 (20)	25,885 (80)	32,213 (100)	
Clinical M stage				
cM1B	12,604 (23)	41,983 (77)	54,587 (100)	< 0.00001
Other	5,893 (20)	22,999 (80)	28,892 (100)	
Surgery				
Yes	407 (19)	1,719 (81)	2,126 (100)	0.0007
No	18,090 (22)	63,263 (78)	81,353 (100)	
Radiation				
Yes	8,911 (23)	30,389 (77)	39,300 (100)	0.0007
No	9,586 (22)	34,593 (78)	44,179 (100)	
Multi-agent chemotherapy				
Yes	9,807 (27)	26,418 (73)	36,225 (100)	< 0.00001
No	8,690 (18)	38,564 (82)	47,254 (100)	
Bone metastasis				
Yes	8,187 (23)	26,701 (77)	34,888 (100)	< 0.00001
No	10,310 (21)	38,281 (79)	48,591 (100)	
Brain metastasis				
Yes	5,254 (21)	20,322 (79)	25,576 (100)	< 0.00001
No	13,243 (23)	44,660 (77)	57,903 (100)	
Liver metastasis				
Yes	2,944 (22)	10,650 (78)	13,594 (100)	0.1242
No	15,553 (22)	54,332 (78)	69,885 (100)	

CD: Charlson-Deyo; AdNOS: adenocarcinoma not otherwise specified.

Table 2. Patient Characteristics: Overall Population

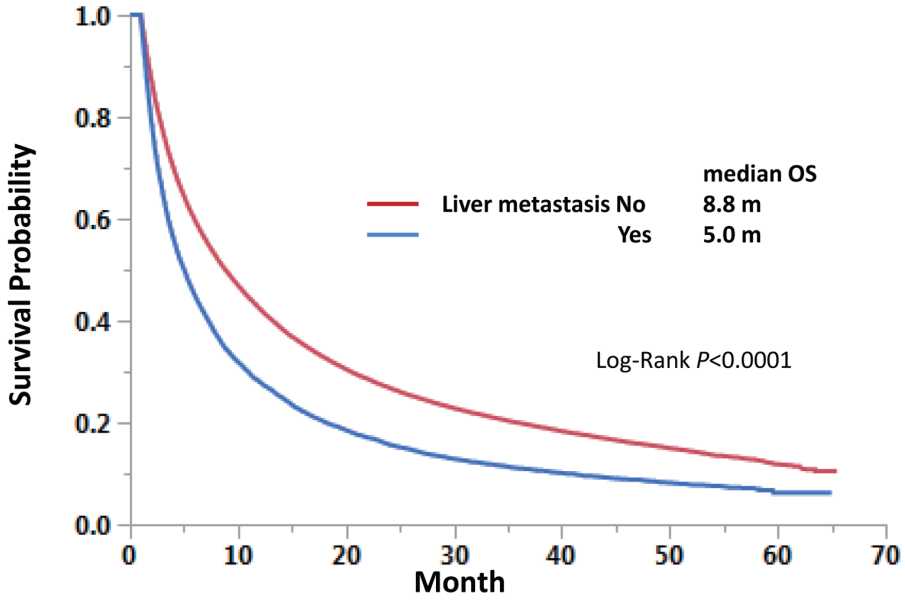
Factors	Liver metastasis			P-value
	Yes (%)	No (%)	Total (%)	
Total	13,594 (16)	69,885 (84)	83,479 (100)	
Institution				
Academic	4,174 (16)	22,198 (84)	26,372 (100)	0.0151
Other	9,420 (16)	47,687 (84)	57,107 (100)	
Age				
≥ 70	5,828 (16)	31,733 (84)	37,561 (100)	< 0.00001
< 70	7,766 (17)	38,152 (83)	45,918 (100)	
Sex				
Male	7,341 (17)	36,796 (83)	44,137 (100)	0.0039
Female	6,253 (16)	33,089 (84)	39,342 (100)	
Race				
White	11,251 (17)	56,903 (83)	68,154 (100)	0.0002
Other	2,343 (15)	12,982 (85)	15,325 (100)	
CD score				
≥ 2	2,041 (16)	10,548 (84)	12,589 (100)	0.8129
0 - 1	11,553 (16)	59,337 (84)	70,890 (100)	
Year of diagnosis				
2016	6,635 (16)	35,030 (84)	41,665 (100)	0.0050
2017	6,959 (17)	34,855 (83)	41,814 (100)	
Histology				
AdNOS	8,266 (15)	45,106 (85)	53,372 (100)	< 0.00001
Other	5,328 (18)	24,779 (82)	30,107 (100)	
Clinical T stage				
T3-4	6,614 (17)	33,409 (83)	40,023 (100)	0.0701
Other	6,980 (16)	36,476 (84)	43,456 (100)	
Clinical N stage				
N2-3	9,267 (18)	41,999 (82)	51,266 (100)	< 0.00001
Other	4,327 (13)	27,886 (87)	32,213 (100)	
Clinical M stage				
cM1B	11,781 (22)	42,806 (78)	54,587 (100)	< 0.00001
Other	1,813 (6)	27,079 (94)	28,892 (100)	
Surgery				
Yes	160 (8)	1,966 (92)	2,126 (100)	< 0.00001
No	13,434 (17)	67,919 (83)	81,353 (100)	
Radiation				
Yes	5,973 (15)	33,327 (85)	39,300 (100)	< 0.00001
No	7,621 (17)	36,558 (83)	44,179 (100)	
Multi-agent chemotherapy				
Yes	7,806 (20)	30,437 (80)	38,243 (100)	< 0.00001
No	5,788 (13)	39,448 (87)	45,236 (100)	
Bone metastasis				
Yes	5,550 (17)	26,844 (83)	32,394 (100)	< 0.00001
No	8,044 (16)	43,041 (84)	51,085 (100)	
Brain metastasis				
Yes	4,044 (16)	21,532 (84)	25,576 (100)	0.0140
No	9,550 (16)	48,353 (84)	57,903 (100)	

CD: Charlson-Deyo; AdNOS: adenocarcinoma not otherwise specified.

Table 3. Patient Characteristics With or Without Liver Metastasis

	With liver metastasis (N = 13,594)			Without liver metastasis (N = 69,885)		
	IO (%)	No IO (%)	P-value	IO (%)	No IO (%)	P-value
Total	2,944 (22)	10,650 (78)		15,553 (22)	54,332 (78)	
Institution						
Academic	934 (22)	3,240 (78)	0.1749	5,090 (23)	17,108 (77)	0.0034
Other	2,010 (21)	7,410 (79)		10,463 (22)	37,224 (78)	
Age						
≥ 70	1,145 (20)	4,683 (80)	< 0.00001	6,271 (20)	25,462 (80)	< 0.00001
< 70	1,799 (23)	5,967 (77)		9,282 (24)	28,870 (76)	
Sex						
Male	1,528 (21)	5,813 (79)	0.0098	8,127 (22)	28,669 (78)	0.2588
Female	1,416 (23)	4,837 (77)		7,426 (22)	25,663 (78)	
Race						
White	2,498 (22)	8,753 (78)	0.0007	13,062 (23)	43,841 (77)	< 0.00001
Other	446 (19)	1,897 (81)		2,491 (19)	10,491 (81)	
CD score						
≥ 2	374 (18)	1,667 (82)	0.0001	1,973 (19)	8,575 (81)	< 0.00001
0 - 1	2,570 (22)	8,983 (78)		13,580 (23)	45,757 (77)	
Year of diagnosis						
2016	1,011 (15)	5,624 (85)	< 0.00001	5,512 (16)	29,518 (84)	< 0.00001
2017	1,933 (28)	5,026 (72)		10,041 (29)	24,814 (81)	
Histology						
AdNOS	1,988 (24)	6,278 (76)	< 0.00001	11,142 (25)	33,964 (75)	< 0.00001
Other	956 (18)	4,372 (82)		4,411 (18)	20,368 (82)	
Clinical T stage						
T3-4	1,432 (22)	5,182 (78)	0.9878	7,393 (22)	26,016 (78)	0.4421
Other	1,512 (22)	5,468 (78)		8,160 (22)	28,316 (78)	
Clinical N stage						
N2-3	2,121 (23)	7,146 (77)	< 0.00001	1,951 (76)	10,048 (24)	< 0.00001
Other	823 (19)	3,504 (81)		5,505 (20)	22,381 (80)	
Clinical M stage						
cM1B	2,587 (22)	9,194 (78)	0.0291	10,017 (23)	32,789 (77)	< 0.00001
Other	357 (20)	1,456 (80)		5,536 (20)	21,543 (80)	
Surgery						
Yes	33 (21)	127 (79)	0.75	374 (19)	1,592 (81)	0.0005
No	2,911 (22)	10,523 (78)		15,179 (22)	52,740 (78)	
Radiation						
Yes	1,339 (22)	4,634 (78)	0.0565	7,572 (23)	25,755 (77)	0.0048
No	1,605 (21)	6,016 (79)		7,981 (22)	28,577 (78)	
Multi-agent chemotherapy						
Yes	1,363 (17)	6,443 (83)	< 0.00001	8,226 (27)	22,211 (73)	< 0.00001
No	1,581 (27)	4,207 (73)		7,327 (19)	32,121 (81)	
Bone metastasis						
Yes	1,118 (20)	4,432 (80)	0.0004	6,361 (24)	20,483 (76)	< 0.00001
No	1,826 (23)	6,218 (73)		9,192 (21)	33,849 (79)	
Brain metastasis						
Yes	819 (20)	3,225 (80)	0.0097	4,435 (21)	17,097 (79)	< 0.00001
No	2,125 (22)	7,425 (80)		11,118 (23)	37,235 (77)	

IO: immunotherapy; CD: Charlson-Deyo; AdNOS: adenocarcinoma not otherwise specified.



At risk (month)	0	12	24	36	48
Liver metastasis Yes	13,594	3,462	1,772	1,011	343
No	69,885	27,533	16,119	9,768	3,424

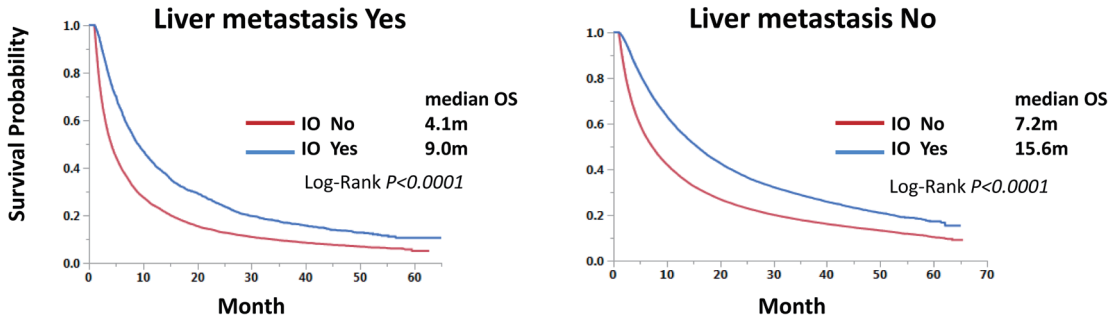
Figure 2. Impact of liver metastasis on overall survival in stage IV non-small cell lung cancer. Kaplan-Meier curves were compared according to the liver metastasis status. Median survival months and log-rank P-values are shown.

and LM-negative groups (Figs. 4 and 5).

Discussion

To address the controversy regarding the efficacy of immunotherapy in LM, we have conducted the current study using the largest cancer databases publicly available in the US. Presence of LM in stage IV NSCLC was associated with worse OS; however, both groups with and without LM achieved almost identical OS HRs around 0.63 when treated with immunotherapy. It indicates that although LM is a prognostic factor for poor survival, its presence does not necessarily relate to poor response to immunotherapy. It rather suggests that immunotherapy similarly benefits those with LM in survival as to those without LM. Although this is a retrospective analysis of existing data, we believe that it is certainly a useful information to be added to the literature.

Modern immunotherapy especially immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 axis has been rapidly developed primarily by multinational industries. Recently, Xia et al reported their meta-analysis focusing on randomized con-



At Risk (Month)	0	12	24	36	48
IO No	10,650	2,313	1,142	673	243
IO Yes	2,944	1,152	630	340	101

At Risk (Month)	0	12	24	36	48
IO No	54,332	19,065	10,922	6,633	2,568
IO Yes	15,553	8,510	5,202	3,135	856

Figure 3. Immunotherapy improves overall survival of stage IV non-small cell lung cancer regardless of liver metastasis status. Kaplan-Meier curves were compared according to the immunotherapy status. Median survival months and log-rank P-values are shown.

Table 4. Univariate and Multivariable Analyses of Overall Survival in Patients With Liver Metastasis

Factors	Univariate	Multivariate
	HR (95% CI); P value	HR (95% CI); P value
Institution		
Academic	0.84 (0.81 - 0.87)	0.85 (0.81 - 0.88)
Others (Ref)	< 0.0001	< 0.0001
Age		
< 70	0.85 (0.82 - 0.88)	0.90 (0.87 - 0.94)
≥ 70 (Ref)	< 0.0001	< 0.0001
Sex		
Female	0.84 (0.81 - 0.87)	0.83 (0.80 - 0.86)
Male (Ref)	< 0.0001	< 0.0001
Race		
Others	0.85 (0.81 - 0.89)	0.84 (0.80 - 0.88)
White (Ref)	< 0.0001	<0.0001
CD score		
0 - 1	0.76 (0.73 - 0.80)	0.79 (0.75 - 0.83)
≥ 2 (Ref)	< 0.0001	< 0.0001
Year of diagnosis		
2017	0.98 (0.94 - 1.01)	1.00 (0.96 - 1.04)
2016 (Ref)	0.1784	0.9889
Histology		
Adenocarcinoma NOS	0.84 (0.81 - 0.88)	0.85 (0.81 - 0.88)
Others (Ref)	< 0.0001	< 0.0001
Clinical T stage		
Others	0.91 (0.87 - 0.94)	0.91 (0.88 - 0.95)
T3-4 (Ref)	< 0.0001	< 0.0001
Clinical N stage		
Others	0.96 (0.92 - 1.00)	0.95 (0.91 - 0.99)
N2-3 (Ref)	0.0382	0.0099
Clinical M stage		
Other	0.90 (0.85 - 0.95)	0.91 (0.86 - 0.96)
M1B (Ref)	< 0.0001	0.0004
Surgery		
Yes	0.81 (0.68 - 0.95)	0.82 (0.69 - 0.98)
No (Ref)	0.0137	0.0252
Radiation		
No	0.94 (0.91 - 0.98)	0.98 (0.93 - 1.02)
Yes (Ref)	0.0013	0.2554
Chemotherapy		
Yes	0.70 (0.68 - 0.73)	0.69 (0.67 - 0.72)
No (Ref)	< 0.0001	< 0.0001
Immunotherapy		
Yes	0.62 (0.59 - 0.65)	0.62 (0.60 - 0.65)
No (Ref)	< 0.0001	< 0.0001
Bone metastasis		
No	0.83 (0.80 - 0.86)	0.81 (0.78 - 0.85)
Yes (Ref)	< 0.0001	< 0.0001
Brain metastasis		
No	0.93 (0.89 - 0.96)	0.94 (0.89 - 0.98)
Yes (Ref)	0.0002	0.0031

HR: hazard ratio; CI: confidence interval; Ref: reference; CD: Charlson-Deyo; NOS: not otherwise specified.

Table 5. Univariate and Multivariable Analyses of Overall Survival in Patients Without Liver Metastasis

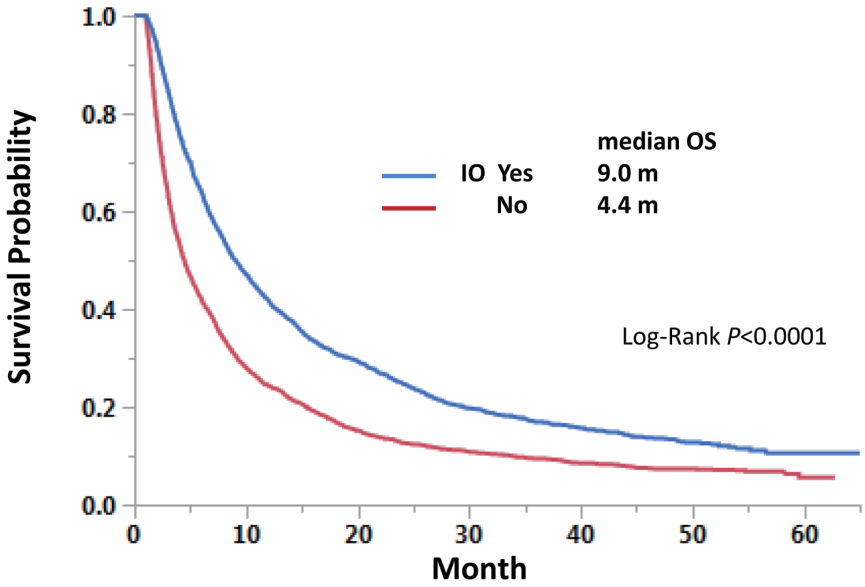
Factors	Univariate	Multivariate
	HR (95% CI); P value	HR (95% CI); P value
Institution		
Academic	0.83 (0.82 - 0.85)	0.84 (0.83 - 0.86)
Others (Ref)	< 0.0001	< 0.0001
Age		
< 70	0.76 (0.75 - 0.78)	0.81 (0.79 - 0.82)
≥ 70 (Ref)	< 0.0001	< 0.0001
Sex		
Female	0.82 (0.81 - 0.84)	0.83 (0.81 - 0.84)
Male (Ref)	< 0.0001	< 0.0001
Race		
Others	0.87 (0.85 - 0.89)	0.86 (0.84 - 0.88)
White (Ref)	< 0.0001	< 0.0001
CD score		
0 - 1	0.72 (0.71 - 0.74)	0.75 (0.73 - 0.77)
≥ 2 (Ref)	< 0.0001	< 0.0001
Year of diagnosis		
2017	0.93 (0.91 - 0.94)	0.95 (0.93 - 0.97)
2016 (Ref)	< 0.0001	< 0.0001
Histology		
Adenocarcinoma NOS	0.81 (0.79 - 0.82)	0.82 (0.81 - 0.84)
Others (Ref)	< 0.0001	< 0.0001
Clinical T stage		
Others	0.90 (0.88 - 0.91)	0.90 (0.89 - 0.92)
T3-4 (Ref)	< 0.0001	< 0.0001
Clinical N stage		
Others	0.87 (0.85 - 0.88)	0.84 (0.83 - 0.86)
N2-3 (Ref)	< 0.0001	< 0.0001
Clinical M stage		
Other	0.88 (0.86 - 0.89)	0.94 (0.92 - 0.96)
M1B (Ref)	< 0.0001	< 0.0001
Surgery		
Yes	0.54 (0.51 - 0.57)	0.57 (0.54 - 0.61)
No (Ref)	< 0.0001	< 0.0001
Radiation		
No	0.97 (0.95 - 0.98)	1.03 (1.01 - 1.05)
Yes (Ref)	< 0.0001	0.0035
Chemotherapy		
Yes	0.72 (0.70 - 0.73)	0.71 (0.70 - 0.72)
No (Ref)	< 0.0001	< 0.0001
Immunotherapy		
Yes	0.64 (0.62 - 0.65)	0.64 (0.63 - 0.65)
No (Ref)	< 0.0001	< 0.0001
Bone metastasis		
No	0.78 (0.77 - 0.79)	0.78 (0.76 - 0.79)
Yes (Ref)	< 0.0001	< 0.0001
Brain metastasis		
No	0.95 (0.94 - 0.97)	0.87 (0.85 - 0.88)
Yes (Ref)	< 0.0001	< 0.0001

HR: hazard ratio; CI: confidence interval; Ref: reference; CD: Charlson-Deyo; NOS: not otherwise specified.

Table 6. Patient Characteristics With or Without Liver Metastasis (Propensity Score-Matched Cases)

	With liver metastasis (N = 5,888)			Without liver metastasis (N = 31,106)		
	IO (%)	No IO (%)	P-value	IO (%)	No IO (%)	P-value
Total	2,944 (50)	2,944 (50)		15,553 (50)	15,553 (50)	
Institution						
Academic	934 (50)	929 (50)	0.8886	5,090 (50)	5,094 (50)	0.9615
Other	2,010 (50)	2,015 (50)		10,463 (50)	10,459 (50)	
Age						
≥ 70	1,145 (50)	1,141 (50)	0.9148	6,271 (50)	6,263 (50)	0.9263
< 70	1,799 (50)	1,803 (50)		9,282 (50)	9,290 (50)	
Sex						
Male	1,528 (50)	1,526 (50)	0.9584	8,127 (50)	8,122 (50)	0.9547
Female	1,416 (50)	1,418 (50)		7,426 (50)	7,431 (50)	
Race						
White	2,498 (50)	2,500 (50)	0.9420	13,062 (50)	13,074 (50)	0.8527
Other	446 (50)	444 (50)		2,491 (50)	2,479 (50)	
CD score						
≥ 2	374 (51)	365 (49)	0.7233	1,973 (50)	1,958 (50)	0.7980
0 - 1	2,570 (50)	2,579 (50)		13,580 (50)	13,595 (50)	
Year of diagnosis						
2016	1,011 (36)	1,801 (64)	< 0.00001	5,512 (36)	9,986 (64)	< 0.00001
2017	1,933 (63)	1,143 (37)		10,041 (64)	5,567 (36)	
Histology						
AdNOS	1,988 (50)	1,994 (50)	0.8673	11,142 (50)	11,136 (50)	0.9399
Other	956 (50)	950 (50)		4,411 (50)	4,417 (50)	
Clinical T stage						
T3-4	1,432 (50)	1,427 (50)	0.8963	7,393 (50)	7,390 (50)	0.9728
Other	1,512 (50)	1,517 (50)		8,160 (50)	8,163 (50)	
Clinical N stage						
N2-3	2,121 (48)	2,311 (52)	< 0.00001	10,048 (46)	11,757 (54)	< 0.00001
Other	823 (57)	633 (43)		5,505 (59)	3,796 (41)	
Clinical M stage						
cM1B	2,587 (50)	2,603 (50)	0.5189	10,017 (50)	10,017 (50)	1.0000
Other	357 (51)	341 (49)		5,536 (50)	5,536 (50)	
Surgery						
Yes	2,911 (50)	2,897 (50)	0.1150	374 (32)	793 (68)	< 0.00001
No	33 (41)	47 (59)		15,179 (51)	14,760 (49)	
Radiation						
Yes	1,339 (37)	2,322 (63)	< 0.00001	7,572 (36)	13,354 (64)	< 0.00001
No	1,605 (72)	622 (38)		7,981 (78)	2,199 (22)	
Multi-agent chemotherapy						
Yes	1,581 (50)	1,571 (50)	0.7939	8,226 (50)	8,225 (50)	0.9909
No	1,363 (50)	1,373 (50)		7,327 (50)	7,328 (50)	
Bone metastasis						
Yes	1,826 (50)	1,822 (50)	0.9145	6,361 (50)	6,357 (50)	0.9632
No	1,118 (50)	1, 122 (50)		9,192 (50)	9,196 (50)	
Brain metastasis						
Yes	819 (28)	2,150 (72)	< 0.00001	4,435 (42)	10,512 (58)	< 0.00001
No	2,125 (73)	794 (28)		11,118 (69)	5,041 (31)	

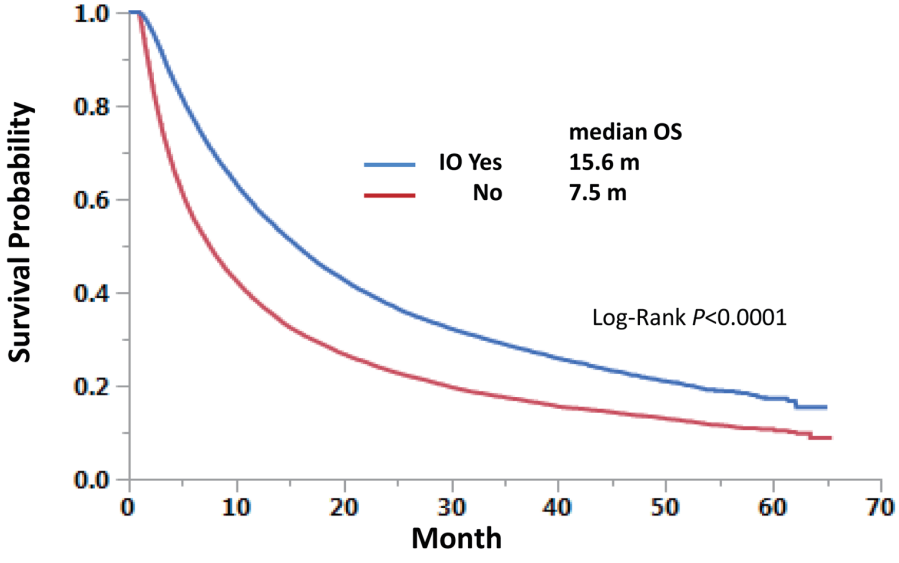
IO: immunotherapy; CD: Charlson-Deyo; AdNOS: adenocarcinoma not otherwise specified.



At risk (month)		0	12	24	36	48
IO	Yes	2,944	666	329	212	94
	No	2,944	1,152	630	340	101

Figure 4. Propensity score-matched cases with liver metastasis. Matched cases among those with liver metastasis were compared for overall survival.

trolled trials (RCTs) in stage IV NSCLC to address survival impact of LM on immunotherapy [13]. Their analysis included 16 RCTs that addressed survival benefit of ICIs. When compared with standard therapies, ICI monotherapy, ICI + chemotherapy, dual ICI therapy, and dual ICI + chemotherapy showed survival advantage for both progression-free survival (PFS) (HR, 0.77; 95% CI, 0.61 - 0.97) and OS (HR, 0.78; 95% CI, 0.68 - 0.90) in patients with LM. Although those with LM achieved slightly less PFS benefit (ratio of PFS-HRs, 1.19, 95% CI, 1.02 - 1.39), comparable OS benefit was observed (ratio of OS-HRs, 1.10;



At risk (month)		0	12	24	36	48
IO	Yes	15,553	8,510	5,202	3,135	856
	No	15,553	5,581	3,218	2,017	919

Figure 5. Propensity score-matched cases without liver metastasis. Matched cases among those without liver metastasis were compared for overall survival.

95% CI, 0.94 - 1.29). They also reported that presence of LM was a poor prognostic indicator for OS among those who are treated with ICI in real-word setting (HR, 1.21; 95% CI, 1.17 - 1.27). Similar analyses using pooled data from RCTs have been reported [14, 15]. Our findings further support their observations of immunotherapy benefit in patients with LM.

Limitation

We acknowledge limitations in our study. First, although NCDB prospectively collects data from CoC participating institutions, its use is still based on retrospective analyses. Data validity still remains a concern for any analysis. Second, information regarding immunotherapy is restricted to presence or absence of its use. No identification of immunotherapy agent is available. However, we generally assume ICI is the primary intervention in immunotherapy of NSCLC in recent years. Third, NCDB database may lack important prognostic factors that are commonly used in prospective clinical trials. Those include patient's performance status, regimens/doses/cycles of systemic therapy, response to therapy, and detail about second/third-line treatments. Nevertheless, this study reports the largest collection of NSCLC cases for any analysis. Both primary and the secondary analyses including PSM demonstrated a similar survival benefit of immunotherapy between LM-positive and negative groups in univariate and multivariate analyses.

In conclusion, our findings suggest that although presence of LM is a poor prognostic indicator in OS, it is not necessarily associated with lack of benefit from immunotherapy. Further investigation may help us determine its validity.

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Financial Disclosure

None to declare.

Conflict of Interest

Takefumi Komiya received advisory fees from G1 Therapeutics and Regenerone, and institutional research funding from Gilead. The other authors declared no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Takefumi Komiya. The first draft of the manuscript was written by Takefumi Komiya and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are available via NCDB upon request.

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