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SPECIALTY SECTION

This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

RECEIVED 07 September 2022 ACCEPTED 21 October 2022 PUBLISHED 14 November 2022

CITATION

Ma J-C, Zhang J-X, Wang F, Yu J and Chen D (2022) The Effect of immunotherapy on oligometastatic non-small cell lung cancer patients by sites of metastasis. *Front. Immunol.* 13:1039157. doi: 10.3389/fimmu.2022.1039157

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The Effect of immunotherapy on oligometastatic non-small cell lung cancer patients by sites of metastasis

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Introduction: The efficacy of immunotherapy for treatment of patients with oligometastatic non-small cell lung cancer (NSCLC) at different metastatic sites remains controversial. We investigated the effect of different metastatic sites on immunotherapy for oligometastatic NSCLC following local treatment (LT).

Methods: We retrospectively analyzed patients with oligometastatic NSCLC from the latest 2018 registry on the SEER Stat software (8.3.9. Version) and a Chinese single-center cohort. The effects of immunotherapy on OS (overall survival) and CSS (cancer specific survival) were estimated for patients with different metastatic sites.

Results: A total of 483 patients in the SEER-18 database and 344 patients in the **single-center** cohort were included. Immunotherapy was significantly correlated with improved OS (SEER: Hazard ratio 0.754, 95% CI 0.609–0.932; P=0.044; China: Hazard ratio 0.697, 95% CI 0.542–0.896; P=0.005) and CSS (SEER: Hazard ratio 0.743, 95% CI 0.596–0.928; P=0.009; China: Hazard ratio 0.725, 95% CI 0.556–0.945; P=0.018). Subgroup analysis showed that OS was improved after immunotherapy in the BRM (SEER: Hazard ratio 0.565, 95% CI 0.385–0.829; P=0.004; China: Hazard ratio 0.524, 95% CI 0.312–0.920; P=0.024) and MOM (SEER: Hazard ratio 0.524, 95% CI 0.290–0.947; P=0.032; China: Hazard ratio 0.469, 95% CI 0.235–0.937; P=0.032) subgroups, but not in the BOM (SEER: P=0.334; China: P=0.441), LIM (SEER: P=0.301; China: P=0.357), or OTM (SEER: P=0.868; China: P=0.489) subgroups.

Conclusions: This study showed that immunotherapy conferred survival benefits on patients with oligometastatic NSCLC. Our subgroup analysis suggested that patients with oligometastatic NSCLC in the brain or multiple organs may particularly benefit from aggressive front-line therapies.

KEYWORDS

non-small cell lung cancer, immunotherapy, oligometastases, overall survival, metastatic sites

Introduction

Non-small cell lung cancer accounts for 85% of lung cancer and is the leading cause of cancer-related mortality (1). Nonsmall cell lung cancer is the primary cause of cancer-related death in the world mainly because patients with lung cancer often develop advanced metastases (2). Approximately 25-50% of patients with NSCLC exhibit an oligometastatic status (3). The concept of "oligometastasis" builds on two models of cancer progression: the Halsted model of continuous progression and a systemic model that hypothesizes that disease is a manifestation of extensive systemic clinical involvement (4). Patients with oligometastatic NSCLC may achieve long-term disease control and may even be cured. In retrospective studies, survival in patients with oligometastatic NSCLC had better overall survival (OS) than patients with a large number of metastases (3, 5). Therefore, it is important to investigate selection of treatment for these patients with limited metastatic NSCLC.

A number of previous studies (6–8) on oligometastatic NSCLC have shown that use of local treatment (LT) at all metastatic sites resulted in longer OS and progression-free survival (PFS) than those following palliative treatment. Immunotherapy has become the standard treatment for patients with metastatic NSCLC (9). The KEYNOTE-189 (10) and KEYNOTE-407 (11) studies have shown that pembrolizumab in combination with specific chemotherapy improved OS and PFS in patients with untreated metastatic NSCLC, regardless of PD-L1 expression. Therefore, use of LT combined with immunotherapy for treatment of oligometastatic NSCLC is an area of active investigation.

Joshua M et al (12) reported in a phase II clinical study that pembrolizumab improved PFS in patients with oligometastatic NSCLC after LT. Although this study showed that pembrolizumab could improve the prognosis of patients with oligometastatic NSCLC, this study did not consider the effect of factors such as the location and the number of organs affected by oligometastases on prognosis, and there are no phase III clinical prospective trials focused on oligometastatic NSCLC. Several previous studies have confirmed that the prognosis of patients with oligometastatic NSCLC was closely related to the site and number of metastatic organs (3, 13, 14). Ashworth AB et al (14) reported that prognosis in patients with oligometastatic NSCLC was associated with brain metastasis but did not address the relationship between prognosis and other metastatic sites.

No study has elucidated the effects of immunotherapy in patients with oligometastatic NSCLC at different metastatic sites. Therefore, our goal was to investigate the effect of different metastatic sites on immunotherapy for oligometastatic NSCLC following LT.

Methods

Patient cohort

Patient data were collected from the incidence-SEER 18 registries from the National Cancer Institute SEER Stat software (Version 8.3.9), with additional treatment fields added. According to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) and the AJCC 7th TNM staging of NSCLC, we screened patients who were first primarily diagnosed with malignant tumors of the lung and bronchus with M1b stage in 2010 and 2015. We selected patients with oligometastatic NSCLC based on the time of approval of immunotherapy as the primary treatment (2015), with patients diagnosed in 2010 as a comparison. The inclusion criteria were as follows: 1) patients with metastatic non-small cell lung cancer treated with cancerdirected treatment; 2) no younger than 20 years old. The exclusion criteria were: 1) more than one primary tumor; 2) incomplete data on metastases of the bone, liver, and brain at diagnosis; 3) incomplete treatment and follow-up information; 4) 0 days of survival. The following variables were selected: ID number, age, sex, year of diagnosis, race (white, black, or other), marital status, site recode ICD-0-3, affected side, tissue grade, histology, T stage (AJCC 7th), N stage (AJCC 7th), metastases of the bone, liver, and brain at diagnosis, radiation (radiation or other), chemotherapy (yes or no), surgery information, survival months, COD to site rec KM, vital status record. Patients were divided into five subgroups: BOM (bone metastasis), BRM (brain metastasis), LIM (liver metastasis), MOM (multiple organ metastasis), and OTM (other metastasis). The detailed inclusion and exclusion criteria are summarized in Figure 1.

An independent cohort of patients with oligometastatic NSCLC from 2016 to 2019 from Shandong Cancer Hospital in China was used for external validation. These patients met the same inclusion and exclusion criteria as those from the SEER Database.

Statistical analysis

The Pearson chi-squared test was used to compare demographics, pathology, and site of metastasis in patients with or without immunotherapy. We chose 36 months as the cutoff value. Overall survival and CSS were analyzed using the Kaplan-Meier (KM) method *via* the log-rank test. Univariate and multivariate analyses was performed using the Cox proportional hazards risk model. Variables that were significantly associated with survival in the univariate analysis were included in the multivariate Cox analysis. All tests were two-sided tests, and P <0.05 was considered statistically significant. SPSS 26 (IBM,

Armonk, USA) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for analysis.

Results

Patient characteristics

A total of 483 patients in the SEER cohort and 344 patients in the single-center cohort who met the eligibility criteria were included in this study. The baseline characteristics of each cohort are listed in Tables 1 and 2. In the SEER cohort, at a median followup of 24.8 months (range, 1-107 months), 370 patients died, among whom 339 died of lung cancer. And in the single-center cohort, 245 deaths, including 219 cases dying from NSCLC with a median follow-up of 20.3 months (range, 3-53 months).

In the SEER cohort, 54.2% were aged <65. The majority of patients were men (56.9%). The distribution of the metastasis sites was 21.3%, 33.1%, 9.3%, 12.2%, and 24.0% for BOM, BRM, LIM, MOM, and OTM, respectively (Table 1). Moreover, this cohort enrolled 222 (46.0%) patients who received immunotherapy, 275 (57.0%) male patients, and 285 (59.0%) patients with adenocarcinoma histology. The different metastasis site subgroups were evenly distributed between the no immunotherapy and immunotherapy groups (Table 2). None of the factors, including age, sex, origin, histology, T stage, N stage, radiation status,



chemotherapy, bone metastasis, brain metastasis, and liver metastasis differed significantly between the two groups (Table 2).

In the validation cohort, the metastasis sites included BOM (23.0%), BRM (23.8%), LIM (8.7%), MOM (19.5%), and OTM (25.0%) (Table 2). In this cohort, no factors, including metastasis-site subgroups, age, sex, origin, histology, T stage, or N stage correlated with immunotherapy.

TABLE 1 Baseline characteristics of all patients in the SEER and the single-center cohorts.

Characteristics	SEER Cohort N=483(%)	Single-Center Cohort N=344(%)	Р	
Age				
<65	262 (54.2%)	120 (34.9%)	< 0.001	
_65	221 (45.8%)	224 (65.1%)		
Sex				
Male	275 (56.9%)	198 (57.6%)	0.859	
Female	208 (43.1%)	146 (42.4%)		
Origin				
Left	205 (42.4%)	136 (39.5%)	0.402	
Right	278 (57.6%)	208 (60.5%)		
Histology				
Squamous cell carcinoma	146 (30.2%)	119 (34.6%)	0.185	
Others	337 (69.8%)	225 (65.4%)		
T stage				
T1	119 (24.6%)	44 (12.8%)	< 0.001	
T2	85 (17.6%)	113 (32.8%)		
Т3	168 (34.8%)	143 (41.6%)		
T4	108 (22.4%)	38 (11.0%)		
Unknown	3 (0.6%)	6 (1.7%)		
N stage				
N0	200 (41.4%)	161 (46.8%)	0.201	
N1	64 (13.3%)	41 (11.9%)		
N2	147 (30.4%)	91 (26.5%)		
N3	56 (11.6%)	46 (13.4%)		
Unknown	16 (3.3%)	5 (1.5%)		
Radiation status				
No	217 (44.9%)	159 (46.2%)	0.713	
Yes	266 (55.1%)	185 (53.8%)		
Immunotherapy				
No	261 (54.0%)	163 (47.4%)	0.059	
Yes	222 (46.0%)	181 (52.6%)		
Bone metastasis				
No	323 (66.9%)	218 (63.4%)	0.297	
Yes	160 (33.1%)	126 (36.6%)		
Brain metastasis				
No	283 (58.6%)	216 (62.8%)	0.224	
Yes	200 (41.4%)	128 (37.2%)		
Liver metastasis				
No	400 (82.8%)	268 (77.9%)	0.094	

(Continued)

TABLE 1 Continued

Characteristics	SEER Cohort N=483(%)	Single-Center Cohort N=344(%)	Р	
Yes	83 (17.2%)	76 (22.1%)		
Metastasis site				
BOM	103 (21.3%)	79 (23.0%)	0.274	
BRM	160 (33.1%)	82 (23.8%)		
LIM	45 (9.3%)	30 (8.7%)		
MOM	59 (12.2%)	67 (19.5%)		
OTM	116 (24.0%)	86 (25.0%)		

BOM, bone metastases only; BRM, brain metastases only; LIM, liver metastases only; MOM, multiple organ metastases; OTM, other metastases. *P value is significant

Immunotherapy and survival outcomes

Kaplan-Meier probability plots showed improved OS and CSS after immunotherapy in both cohorts (Figure 2). We performed univariate and multivariate cox proportional hazards analyses to determine whether any clinical or pathological features were associated with OS and CSS (Table 3). In the univariate analysis, we found that immunotherapy was associated with better OS (SEER: Hazard ratio 0.797, 95% CI 0.649-0.980; P=0.027; China: Hazard ratio 0.693, 95% CI 0.539-0.890; P=0.004) and CSS (SEER: Hazard ratio 0.796, 95% CI 0.642-0.987; P=0.043; China: Hazard ratio 0.715, 95% CI 0.548-0.932; P=0.013). Moreover, we showed that sex, site, T stage, N stage, chemotherapy, and liver metastasis were significantly associated with clinical outcome in the univariate analysis. These factors were adjusted to evaluate the effect of immunotherapy. In the multivariate analysis, we found that immunotherapy was significantly correlated with improved OS (SEER: Hazard ratio 0.754, 95% CI 0.609-0.932; P=0.044; China: Hazard ratio 0.697, 95% CI 0.542-0.896; P=0.005) and CSS (SEER: Hazard ratio 0.743, 95% CI 0.596-0.928; P=0.009; China: Hazard ratio 0.725, 95% CI 0.556-0.945; P=0.018) (Table 3). Male patients had significantly worse OS (SEER: Hazard ratio 1.311, 95% CI 1.057-1.626; P=0.014; China: Hazard ratio 1.599, 95% CI 1.225-2.088; P=0.001) and CSS (SEER: Hazard ratio 1.282, 95% CI 1.020-1.610; P=0.033; China: Hazard ratio 1.502, 95% CI 1.143-1.976; P=0.004) than female patients in the multivariate analyses. Patients with lesions located in the main bronchus had a worse prognosis than those with lesions located at other sites. Patients with higher T and N stage showed better prognosis. Liver metastasis was associated with poor prognosis for the SEER cohort but not for the single-center cohort.

Subgroup analysis and validation

In the subgroup analysis, Kaplan-Meier probability plots displayed differences in OS and CSS improvement after

<table-container>No immunotherary N=261 (%)Immunotherary N=261 (%)PNo immunotherary N=163 (%)Immunotherary N=163 (%)PAgeeffeffeffeff15 (41%)106 (62.%)115 (41%)106 (67.%)115 (41%)106 (67.%)115 (41%)106 (12.%)116 (22.%)117 (61.%)118 (21.%)118 (21.%)119 (41.%)111 (42.%)110 (52.%)111 (41.%)111 (41.%)111 (41.%)111 (41.%)111 (41.%)111 (41.%</table-container>	Variable	SEE	R Cohort	Single-Center Cohort			
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Squamous cell carcinoma 89 (34.1%) 57 (25.7%) 0.056 60 (36.8%) 59 (32.6%) 0.412 Others 17 (55.9%) 167 (43.9%) 0.056 60 (36.8%) 122 (67.4%) 0.412 T stage 52 (31.9%) 61 (33.7%) 0.10 T2 45 (17.2%) 40 (18.0%) 52 (31.9%) 61 (33.7%) 0.10 T4 69 (36.4%) 73 (32.9%) 61 (36.8%) 73 (31.9%) 61 (33.7%) 0.10 T4 49 (18.8%) 59 (26.4%) 14 (46.5%) 24 (13.3%) 24 (13.3%) 24 (13.3%) 0.43 Vbknown 3 (14.0%) 80 (38.7%) 0.483 82 (50.3%) 79 (43.6%) 0.666 N1 14 (43.7%) 86 (38.7%) 0.483 82 (50.3%) 79 (43.6%) 0.666 N2 81 (31.0%) 66 (39.7%) 0.483 82 (50.3%) 79 (43.6%) 0.666 N2 81 (31.0%) 66 (39.7%) 0.481 82 (64.9%) 92 (62.6%) 92 (62.6%) Utknown 17 (44.8%)	Histology						
Others 172 (65.9%) 165 (74.3%) 103 (63.2%) 122 (67.4%) T star T<	Squamous cell carcinoma	89 (34.1%)	57 (25.7%)	0.056	60 (36.8%)	59 (32.6%)	0.412
T sige 1 6.9 (26.49) 5.0 (2.5%) 0.086 2.8 (7.2%) 1.6 (5.8.7) 0.10 12 4.5 (7.2%) 4.0 (18.0%) 5.2 (3.19%) 6.1 (3.3.7%) 1.0 (13.7%) 13 9.5 (5.6.4%) 7.3 (2.9.%) 6.5 (3.9.9%) 7.4 (4.13.7%) 7.4 (4.13.7%) 7.4 (4.13.7%) 7.4 (4.13.7%) 7.4 (4.2.5%) 2.1 (1.3.7%) 7.4 (4.2.5%) 2.1 (1.3.7%) 7.6 (3.1.7%)	Others	172 (65.9%)	165 (74.3%)		103 (63.2%)	122 (67.4%)	
T169 (26.4%)50 (22.5%)0.08628 (17.2%)16 (8.8%)0.110T245 (17.2%)40 (18.0%)52 (31.9%)61 (33.7%)78T395 (36.4%)73 (32.9%)14 (8.6%)78 (43.1%)T449 (18.8%)59 (26.6%)14 (8.6%)24 (13.3%)Unknown3 (11.0%)0 (0.0%)4 (25.5%)2 (1.1%)NameNameNameNameNameN0114 (43.7%)86 (38.7%)0.48382 (50.3%)79 (43.6%)N248 (10.6%)66 (29.7%)48 (26.4%)48 (26.5%)N281 (30.6%)66 (29.7%)48 (26.4%)28 (15.5%)N325 (6.6%)31 (14.0%)18 (11.0%)28 (15.5%)Unknown7 (2.7%)9 (41.%)2 (12.%)3 (17.%)Valiation statusNameNameNameNameNo117 (44.8%)100 (45.0%)0.69269 (42.3%)90 (49.7%)No128 (59.7%)141 (63.5%)0.148108 (66.3%)110 (60.8%)0.292Yes70 (30.3%)130 (58.6%)0.989109 (66.9%)107 (59.1%)0.169Yes130 (41.4%)92 (41.4%)54 (33.1%)74 (40.9%)24 (23.2%)0.601Yes130 (41.6%)130 (58.6%)0.989109 (66.9%)107 (59.1%)0.169Yes130 (41.4%)92 (41.4%)54 (33.1%)74 (40.9%)0.61Yes130 (41.6%)130 (68.3%)0.52444 (2.5%)42 (23.2%)0.601 <t< td=""><td>T stage</td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	T stage						
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T395 (36.4%)73 (32.9%)65 (39.9%)78 (43.1%)T449 (18.8%)59 (26.6%)14 (8.6%)24 (13.3%)Unknown30 (10%)00(0%)4 (2.5%)24 (13.3%)NT4(43.7%)86 (38.7%)0.48382 (50.3%)79 (43.6%)0.666N134 (13.0%)30 (13.5%)18 (11.0%)23 (12.7%)0.666N281 (31.0%)66 (29.7%)43 (26.4%)48 (26.5%)48 (26.5%)N281 (31.0%)66 (29.7%)43 (26.4%)48 (26.5%)100 (45.0%)0.962Nakow25 (9.6%)31 (14.0%)18 (11.0%)28 (15.5%)28 (15.5%)Nakow25 (9.6%)100 (45.0%)0.96269 (42.3%)90 (49.7%)0.206Yes147 (44.8%)100 (45.0%)0.96269 (42.3%)90 (49.7%)0.206Yes144 (55.2%)122 (55.0%)94 (57.7%)91 (50.3%)0.206Yes120 (30.3%)13 (36.5%)0.949100 (66.3%)110 (60.8%)0.292Yes130 (36.6%)0.148108 (66.3%)110 (60.8%)0.292Yes108 (41.4%)92 (41.4%)54 (33.1%)74 (40.9%)0.169Yes108 (41.4%)92 (41.4%)54 (33.1%)74 (40.9%)0.169Yes108 (41.4%)92 (41.4%)13 (8.0%)110 (60.8%)0.66Yes108 (41.4%)92 (41.4%)13 (20.9%)130 (75.6%)0.169Yes108 (41.4%)13 (8.3%)0.52440 (20.5%)41 (22.	T2	45 (17.2%)	40 (18.0%)		52 (31.9%)	61 (33.7%)	
T449 (18.8%)59 (26.6%)14 (8.6%)24 (13.3%)Uknown3 (1.1%)0 (0.0%)4 (2.5%)2 (1.1%)N stage V V V V V N014 (43.7%)86 (38.7%)0.48382 (50.3%)79 (43.6%)0.666N134 (13.0%)66 (29.7%)43 (26.4%)48 (26.5%) V N281 (10.9%)62 (29.7%)43 (26.4%)48 (26.5%) V N325 (9.6%)31 (14.0%)0.96269 (42.3%)90 (49.7%)0.206Taktation V V V V V V V V No117 (44.8%)100 (45.0%)0.96269 (42.3%)90 (49.7%)0.206Yes127 (43.8%)100 (45.0%)0.96269 (42.3%)90 (49.7%)0.206Yes128 (69.7%)121 (63.5%)0.148108 (66.3%)110 (60.8%)0.292Yes79 (30.3%)81 (36.5%)0.989109 (66.9%)110 (60.8%)0.292Yes133 (58.6%)130 (58.6%)0.989109 (66.9%)107 (51.%)0.169Yes38 (14.6%)32 (13.4%)0.52434 (20.9%)34 (23.2%)0.601Yes38 (14.6%)37 (16.7%)0.52434 (20.9%)39 (21.5%)0.601Yes38 (14.6%)37 (16.7%)0.52434 (20.9%)39 (21.5%)0.601Yes38 (14.6%)35 (23.3%)0.52434 (20.9%)39 (21.5%)0.61Yes36 (25.9%)35 (Т3	95 (36.4%)	73 (32.9%)		65 (39.9%)	78 (43.1%)	
Unknown $3 (1.1\%)$ $0 (0.0\%)$ $4 (2.5\%)$ $2 (1.1\%)$ N stageN0 $114 (43.7\%)$ $86 (38.7\%)$ 0.483 $82 (50.5\%)$ $79 (43.6\%)$ 0.666 N1 $34 (13.0\%)$ $30 (13.5\%)$ $18 (11.0\%)$ $23 (12.7\%)$ 0.666 N2 $34 (13.0\%)$ $66 (29.7\%)$ $43 (26.4\%)$ $48 (26.5\%)$ $13 (10.0\%)$ $25 (9.5\%)$ $11 (10.0\%)$ $22 (12.3\%)$ $3 (1.7\%)$ N3 $25 (9.6\%)$ $31 (14.0\%)$ $12 (12.3\%)$ $3 (1.7\%)$ $21 (2.3\%)$ $3 (1.7\%)$ $2.02.5\%$ Toknown $7 (2.7\%)$ $9 (41.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $125 (9.2\%)$ $120 (25.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $125 (9.2\%)$ $120 (55.0\%)$ 0.962 $69 (42.3\%)$ $91 (49.7\%)$ 0.202 Yes $125 (9.2\%)$ $141 (65.5\%)$ 0.148 $108 (66.3\%)$ $11 (0.60.8\%)$ 0.292 Yes $79 (30.3\%)$ $81 (36.5\%)$ 0.989 $109 (66.9\%)$ $17 (92.9\%)$ 0.169 Yes $135 (1.6\%)$ $129 (2.9\%)$ $13 (2.2\%)$ 0.61 Yes $32 (1.6\%)$ $37 (16.7\%)$ $129 (2.9\%)$	T4	49 (18.8%)	59 (26.6%)		14 (8.6%)	24 (13.3%)	
N stageN0 $114 (43.7\%)$ $86 (38.7\%)$ 0.483 $82 (50.3\%)$ $79 (43.6\%)$ 0.666 N1 $34 (13.0\%)$ $30 (13.5\%)$ $18 (11.0\%)$ $23 (12.7\%)$ N2 $81 (31.0\%)$ $66 (29.7\%)$ $43 (26.4\%)$ $48 (26.5\%)$ N3 $25 (9.6\%)$ $31 (14.0\%)$ $18 (11.0\%)$ $28 (15.5\%)$ Unknown $25 (9.6\%)$ $31 (14.0\%)$ $21 (12.9\%)$ $31 (1.7\%)$ Rolation $28 (15.5\%)$ $22 (12.9\%)$ $31 (1.7\%)$ $21 (12.9\%)$ Rolation $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $144 (55.2\%)$ $122 (55.0\%)$ $94 (57.7\%)$ $91 (50.3\%)$ 0.206 Yes $144 (55.2\%)$ $122 (55.0\%)$ $94 (57.7\%)$ $91 (50.3\%)$ 0.206 Yes $79 (30.3\%)$ $81 (36.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $79 (30.3\%)$ $81 (36.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $79 (30.3\%)$ $81 (36.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $310 (58.6\%)$ 0.149 $109 (66.3\%)$ $10 (0.9\%)$ 0.992 Yes $132 (69.7\%)$ $131 (0.58.6\%)$ 0.989 $109 (66.9\%)$ $10 (0.97\%)$ 0.992 Yes $138 (14.0\%)$ $120 (58.0\%)$ 0.989 $109 (66.9\%)$ $10 (50.9\%)$ 0.992 Yes $138 (14.0\%)$ $120 (58.0\%)$ 0.524 $34 (20.9\%)$ $42 (23.2\%)$ 0.601 <tr< td=""><td>Unknown</td><td>3 (1.1%)</td><td>0 (0.0%)</td><td></td><td>4 (2.5%)</td><td>2 (1.1%)</td><td></td></tr<>	Unknown	3 (1.1%)	0 (0.0%)		4 (2.5%)	2 (1.1%)	
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NI $34 (13.0\%)$ $30 (13.5\%)$ $18 (11.0\%)$ $23 (12.7\%)$ N2 $81 (31.0\%)$ $66 (29.7\%)$ $43 (26.4\%)$ $48 (26.5\%)$ N3 $25 (9.6\%)$ $31 (14.0\%)$ $18 (11.0\%)$ $28 (15.5\%)$ Unknown $7 (2.7\%)$ $9 (4.1\%)$ $2 (1.2\%)$ $3 (1.7\%)$ Ratiation status No $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $110 (52.9\%)$ $120 (52.5\%)$ $94 (57.7\%)$ $91 (50.3\%)$ 0.292 Some metastasisNo $182 (69.7\%)$ $141 (63.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $79 (30.3\%)$ $81 (36.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $182 (69.7\%)$ $141 (63.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $182 (69.7\%)$ $141 (63.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $108 (14.4\%)$ $92 (14.4\%)$ $54 (33.1\%)$ $74 (40.9\%)$ $110 (59.1\%)$ 0.169 Yes $38 (14.6\%)$ $37 (16.7\%)$ $129 (79.1\%)$ $139 (75.8\%)$ $10 (23.2\%)$ 0.611 Yes $38 (14.6\%)$ $37 (16.7\%)$ $129 (79.1\%)$ $139 (75.8\%)$ $10 (23.2\%)$ 0.611 Yes $38 (14.6\%)$ $55 (21.6\%)$ 0.225 $40 (24.5\%)$ <	N0	114 (43.7%)	86 (38.7%)	0.483	82 (50.3%)	79 (43.6%)	0.666
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Unknown $7 (2.7\%)$ $9 (4.1\%)$ $2 (1.2\%)$ $3 (1.7\%)$ Radiation statusNo $117 (44.8\%)$ $100 (45.0\%)$ 0.962 $69 (42.3\%)$ $90 (49.7\%)$ 0.206 Yes $144 (55.2\%)$ $122 (55.0\%)$ $94 (57.7\%)$ $91 (50.3\%)$ 0.202 Bone metastasisNo $182 (69.7\%)$ $141 (63.5\%)$ 0.148 $108 (66.3\%)$ $110 (60.8\%)$ 0.292 Yes $79 (30.3\%)$ $81 (36.5\%)$ $55 (33.7\%)$ $71 (39.2\%)$ 0.292 Yes $79 (30.3\%)$ $81 (36.5\%)$ $55 (33.7\%)$ $71 (39.2\%)$ 0.169 Brain metastasis V V $71 (39.2\%)$ 0.169 Yes $153 (58.6\%)$ $130 (58.6\%)$ 0.989 $109 (66.9\%)$ $107 (59.1\%)$ 0.169 Yes $153 (58.6\%)$ $130 (58.6\%)$ 0.989 $109 (66.9\%)$ $107 (59.1\%)$ 0.169 Yes $0.223 (85.4\%)$ $130 (58.6\%)$ 0.989 $109 (66.9\%)$ $107 (59.1\%)$ 0.169 Yes $0.238 (14.0\%)$ $25 (1.5\%)$ 0.524 $34 (20.9\%)$ $24 (23.2\%)$ 0.601 Yes $23 (85.4\%)$ $185 (83.3\%)$ 0.524 $34 (20.9\%)$ $24 (23.2\%)$ 0.601 Yes $23 (85.4\%)$ $55 (21.6\%)$ 0.225 $40 (24.5\%)$ $39 (21.5\%)$ 0.654 Mota $29 (35.2\%)$ $68 (30.6\%)$ $41 (25.2\%)$ $41 (22.7\%)$ $110 (20.9\%)$ Image: Home statistististististis $13 (8.1\%)$ $13 (8.0\%)$ $13 (8.0\%)$ $17 (9.4\%)$ Image: Home s	N3	25 (9.6%)	31 (14.0%)		18 (11.0%)	28 (15.5%)	
Radiation status No 117 (44.8%) 100 (45.0%) 0.962 69 (42.3%) 90 (49.7%) 0.206 Yes 144 (55.2%) 122 (55.0%) 94 (57.7%) 91 (50.3%) 0 Bom entastasis No 182 (69.7%) 141 (63.5%) 0.148 108 (66.3%) 110 (60.8%) 0.292 Yes 79 (30.3%) 81 (36.5%) 55 (33.7%) 71 (39.2%) 0 Bom entastasis No 153 (58.6%) 130 (58.6%) 0.989 109 (66.9%) 107 (59.1%) 0.169 Yes 108 (41.4%) 92 (41.4%) 54 (33.1%) 74 (40.9%) 0.169 Yes 108 (41.4%) 92 (41.4%) 54 (33.1%) 74 (40.9%) 0.169 Yes 108 (41.6%) 13 (58.6%) 0.524 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 129 (79.1%) 139 (76.8%) 0.601 Yes 38 (14.6%) 55 (21.6%) 0.225 40 (24.5%) 39 (21.5%) 0.563	Unknown	7 (2.7%)	9 (4.1%)		2 (1.2%)	3 (1.7%)	
No 117 (44.8%) 100 (45.0%) 0.962 69 (42.3%) 90 (49.7%) 0.206 Yes 144 (55.2%) 122 (55.0%) 94 (57.7%) 91 (50.3%) Bone metastasis 9 </td <td>Radiation status</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Radiation status						
Yes 144 (55.2%) 122 (55.0%) 94 (57.7%) 91 (50.3%) Bone metastasis No 182 (69.7%) 141 (63.5%) 0.148 108 (66.3%) 110 (60.8%) 0.292 Yes 79 (30.3%) 81 (36.5%) 0.148 108 (66.3%) 110 (60.8%) 0.292 Yes 79 (30.3%) 81 (36.5%) 0.148 108 (66.3%) 110 (60.8%) 0.292 Brain metastasis T T T T T T No 153 (58.6%) 130 (58.6%) 0.989 109 (66.9%) 107 (59.1%) 0.169 Yes 168 (41.4%) 92 (41.4%) 54 (33.1%) 74 (40.9%) 107 (59.1%) 0.169 Yes 38 (14.6%) 37 (16.7%) 0.524 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 0.225 40 (24.5%) 39 (21.5%) 0.563 BOM 55 (21.1%) 55 (21.6%) 0.225 40 (24.5%) 39 (21.5%) 0.563 BRM 92 (35.2%) 68 (30.6%)	No	117 (44.8%)	100 (45.0%)	0.962	69 (42.3%)	90 (49.7%)	0.206
Bone metastasis No 182 (69.7%) 141 (63.5%) 0.148 108 (66.3%) 110 (60.8%) 0.292 Yes 79 (30.3%) 81 (36.5%) 55 (33.7%) 71 (39.2%) Brain metastasis 55 (33.7%) 71 (39.2%) No 153 (58.6%) 130 (58.6%) 0.989 109 (66.9%) 107 (59.1%) 0.169 Yes 108 (41.4%) 92 (41.4%) 54 (33.1%) 74 (40.9%) 0.169 Ver metastasis 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 0.524 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 0.524 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 0.525 40 (24.5%) 39 (21.5%) 0.563 BOM 55 (21.1%) 55 (21.6%) 0.225 40 (24.5%) 39 (21.5%) 0.563 BRM 92 (35.2%) 68 (30.6%) 13 (8.0%) 17 (9.4%) 17 (9.4%)	Yes	144 (55.2%)	122 (55.0%)		94 (57.7%)	91 (50.3%)	
No 182 (69.7%) 141 (63.5%) 0.148 108 (66.3%) 110 (60.8%) 0.292 Yes 79 (30.3%) 81 (36.5%) 55 (33.7%) 71 (39.2%) Brain metastasis	Bone metastasis						
Yes 79 (30.3%) 81 (36.5%) 55 (33.7%) 71 (39.2%) Brain metastasis	No	182 (69.7%)	141 (63.5%)	0.148	108 (66.3%)	110 (60.8%)	0.292
Brain metastasis No 153 (58.6%) 130 (58.6%) 0.989 109 (66.9%) 107 (59.1%) 0.169 Yes 108 (41.4%) 92 (41.4%) 54 (33.1%) 74 (40.9%) 107 (59.1%) 0.169 Liver metastasis No 223 (85.4%) 185 (83.3%) 0.524 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 129 (79.1%) 139 (76.8%) 0.601 Metastasis site No 55 (21.1%) 55 (21.6%) 0.225 40 (24.5%) 39 (21.5%) 0.563 BRM 92 (35.2%) 68 (30.6%) 41 (25.2%) 41 (22.7%) 1000000000000000000000000000000000000	Yes	79 (30.3%)	81 (36.5%)		55 (33.7%)	71 (39.2%)	
No 153 (58.6%) 130 (58.6%) 0.989 109 (66.9%) 107 (59.1%) 0.169 Yes 108 (41.4%) 92 (41.4%) 54 (33.1%) 74 (40.9%) 100 Liver metastasis 54 (33.1%) 74 (40.9%) 100<	Brain metastasis						
Yes108 (41.4%)92 (41.4%)54 (33.1%)74 (40.9%)Liver metastasisNo223 (85.4%)185 (83.3%)0.52434 (20.9%)42 (23.2%)0.601Yes38 (14.6%)37 (16.7%)129 (79.1%)139 (76.8%)Metastasis siteBOM55 (21.1%)55 (21.6%)0.22540 (24.5%)39 (21.5%)0.563BRM92 (35.2%)68 (30.6%)41 (25.2%)41 (22.7%)LIM27 (10.3%)18 (8.1%)13 (8.0%)17 (9.4%)MOM24 (9.6%)35 (15.8%)26 (16.0%)43 (23.8%)	No	153 (58.6%)	130 (58.6%)	0.989	109 (66.9%)	107 (59.1%)	0.169
Liver metastasis No 223 (85.4%) 185 (83.3%) 0.524 34 (20.9%) 42 (23.2%) 0.601 Yes 38 (14.6%) 37 (16.7%) 129 (79.1%) 139 (76.8%) 0.601 Metastasis site E	Yes	108 (41.4%)	92 (41.4%)		54 (33.1%)	74 (40.9%)	
No223 (85.4%)185 (83.3%)0.52434 (20.9%)42 (23.2%)0.601Yes38 (14.6%)37 (16.7%)129 (79.1%)139 (76.8%)Metastasis siteBOM55 (21.1%)55 (21.6%)0.22540 (24.5%)39 (21.5%)0.563BRM92 (35.2%)68 (30.6%)41 (25.2%)41 (22.7%)LIM27 (10.3%)18 (8.1%)13 (8.0%)17 (9.4%)MOM24 (9.6%)35 (15.8%)26 (16.0%)41 (22.7%)OTM63 (23.8%)53 (23.9%)43 (26.4%)43 (23.8%)	Liver metastasis						
Yes38 (14.6%)37 (16.7%)129 (79.1%)139 (76.8%)Metastasis siteBOM55 (21.1%)55 (21.6%)0.22540 (24.5%)39 (21.5%)0.563BRM92 (35.2%)68 (30.6%)41 (25.2%)41 (22.7%)LIM27 (10.3%)18 (8.1%)13 (8.0%)17 (9.4%)MOM24 (9.6%)35 (15.8%)26 (16.0%)41 (22.7%)OTM63 (23.8%)53 (23.9%)43 (26.4%)43 (23.8%)	No	223 (85.4%)	185 (83.3%)	0.524	34 (20.9%)	42 (23.2%)	0.601
Metassis site S5 (21.1%) S5 (21.6%) 0.225 40 (24.5%) 39 (21.5%) 0.563 BRM 92 (35.2%) 68 (30.6%) 41 (25.2%) 41 (22.7%) LIM 27 (10.3%) 18 (8.1%) 13 (8.0%) 17 (9.4%) MOM 24 (9.6%) 35 (15.8%) 26 (16.0%) 41 (22.7%) OTM 63 (23.8%) 53 (23.9%) 43 (26.4%) 43 (23.8%)	Yes	38 (14.6%)	37 (16.7%)		129 (79.1%)	139 (76.8%)	
BOM 55 (21.1%) 55 (21.6%) 0.225 40 (24.5%) 39 (21.5%) 0.563 BRM 92 (35.2%) 68 (30.6%) 41 (25.2%) 41 (22.7%) LIM 27 (10.3%) 18 (8.1%) 13 (8.0%) 17 (9.4%) MOM 24 (9.6%) 35 (15.8%) 26 (16.0%) 41 (22.7%) OTM 63 (23.8%) 53 (23.9%) 43 (26.4%) 43 (23.8%)	Metastasis site						
BRM92 (35.2%)68 (30.6%)41 (25.2%)41 (22.7%)LIM27 (10.3%)18 (8.1%)13 (8.0%)17 (9.4%)MOM24 (9.6%)35 (15.8%)26 (16.0%)41 (22.7%)OTM63 (23.8%)53 (23.9%)43 (26.4%)43 (23.8%)	BOM	55 (21.1%)	55 (21.6%)	0.225	40 (24.5%)	39 (21.5%)	0.563
LIM27 (10.3%)18 (8.1%)13 (8.0%)17 (9.4%)MOM24 (9.6%)35 (15.8%)26 (16.0%)41 (22.7%)OTM63 (23.8%)53 (23.9%)43 (26.4%)43 (23.8%)	BRM	92 (35.2%)	68 (30.6%)		41 (25.2%)	41 (22.7%)	
MOM24 (9.6%)35 (15.8%)26 (16.0%)41 (22.7%)OTM63 (23.8%)53 (23.9%)43 (26.4%)43 (23.8%)	LIM	27 (10.3%)	18 (8.1%)		13 (8.0%)	17 (9.4%)	
OTM 63 (23.8%) 53 (23.9%) 43 (26.4%) 43 (23.8%)	MOM	24 (9.6%)	35 (15.8%)		26 (16.0%)	41 (22.7%)	
	OTM	63 (23.8%)	53 (23.9%)		43 (26.4%)	43 (23.8%)	

TABLE 2 Characteristics of all patients according to receipt of immunotherapy in each cohort.

BOM, bone metastases only; BRM, brain metastases only; LIM, liver metastases only; MOM, multiple organ metastases; OTM, other metastases. *p value is significant

immunotherapy in both cohorts and among the five metastatic subgroups in both cohorts (Figure S1). As shown in Figure 3, immunotherapy had similar effects on the different metastatic subgroups. No improvement in OS was found in the BOM (SEER: Hazard ratio 1.171, 95% CI 0.732-1.874; P=0.510; China: Hazard ratio 1.136, 95% CI 0.637-2.025; P=0.666), LIM (SEER: Hazard ratio 0.737, 95% CI 0.361-1.503; P=0.401; China: Hazard ratio 0.779, 95% CI 0.312-1.946; P=0.594), or OTM (SEER: Hazard ratio 0.923, 95% CI 0.606-1.408; P=0.712; China: Hazard ratio 0.730, 95% CI 0.444-1.200; P=0.214) subgroups. However, immunotherapy significantly increased OS in the BRM (SEER: Hazard ratio 0.565, 95% CI 0.385-0.829; P=0.004; China: Hazard ratio 0.536, 95% CI 0.312-0.920; P=0.024) and MOM (SEER: Hazard ratio 0.546, 95% CI 0.308-0.968; P=0.038; China: Hazard ratio 0.467, 95% CI 0.238-0.914; P=0.026) subgroups. Immunotherapy significantly improved CSS in the BRM (SEER: Hazard ratio 0.551, 95% CI 0.370-0.820; P=0.003; China: Hazard ratio 0.540, 95% CI 0.307-0.950; P=0.033) and MOM (SEER: Hazard ratio 0.524, 95% CI 0.290-0.947; P=0.032; China: Hazard ratio 0.469, 95% CI 0.235-0.937; P=0.032) subgroups, but not in the BOM (SEER: P=0.334; China: P=0.441), LIM (SEER: P=0.301; China:

P=0.357), or OTM (SEER: P=0.868; China: P=0.489) subgroups (Figure 3).

We also merged the data from the two cohorts. Adjuvant immunotherapy improved OS (Hazard ratio 0.729, 95% CI 0.620– 0.856; P<0.001) and CSS (Hazard ratio 0.726, 95%CI 0.612–0.862; P<0.001) significantly in the merged cohort (Figure 3). We found different benefits from immunotherapy within each metastatic subgroup. This benefit was greatest in the BRM (OS: Hazard ratio 0.565, 95% CI 0.385–0.829; P=0.004; CSS: Hazard ratio 0.536, 95% CI 0.312–0.920; P=0.024) and MOM (OS: Hazard ratio 0.565, 95% CI 0.385–0.829; P=0.004; CSS: Hazard ratio 0.536, 95% CI 0.385–0.829; P=0.004; CSS: Hazard ratio 0.536, 95% CI 0.312– 0.920; P=0.024) subgroups. In the BOM, LIM, and OTM subgroups, immunotherapy did not result in significant differences in OS or CSS.

Discussion

We analyzed the prognostic significance of immunotherapy at different sites in patients with oligometastatic NSCLC from



Kaplan-Meier probability plots of Overall Survival and Cancer Specific Survival between the Immunotherapy group and the No immunotherapy group: SEER Database (A, C) and Single-Center cohort (B, D).

Characteristic Invariate and sector Invariate and s		SEER Cohort				Single-Center Cohort				
RR (95% CI)PRR (95% CI)PRR (95% CI)PRR (95% CI)PSetSigner SetSigner S	Characteristics	Univariate analysis (OS)		Multivariate analysis (OS)		Univariate analysis (OS)			Multivariate analysis (OS)	
Sec Fermine 1.353 (1.098-1.666) 0.004* 1.311 (1.057-1.626) 0.014* 1.603 (1.237-2.077) c0.001* 1.599 (1.225-2.088) 0.001* Male 1 0.002* 0.013* 0.016* 1.599 (1.225-2.088) 0.001* Tatage 0.002* 0.013* 0.850 (0.620-1.202) 0.359 0.968 (0.640-1.465) 0.878 0.911 (0.599-1.323) 0.881 T3 1.120 (0.854-1.690) 0.141 1.241 (0.331-6.32) 0.140 1.041 (0.697-1.553) 0.844 0.989 (0.655-1.490) 0.827 T4 1.608 (1.199-2.158) 0.002 1.475 (1.080-2.015) 0.015 1.501 (0.372-0.491) 0.076 Natage 0.001* <0.001* * 0.014* 0.014* Natage 0.001* <0.001* * 0.014* 0.014* Natage 0.001* 2.502 (0.872-0.401) 0.010 1.332 (0.872-0.401) 0.16 Natage 0.001* 1.592 (0.222-0.815) 0.301 1.333 (0.872-0.401) 0.16 Natage 0.001* 2.022 (0.812-		HR (95% CI)	Р	HR (95% CI)	Р	HR (95% CI)	Р	HR (95% CI)	Р	
Ferminal Mater1,533 (1,099-1.08)0,0011,111 (1,057.168)0,1011,0010,0	Sex									
National structureNational Struct	Female	1.353 (1.098-1.666)	0.004*	1.311 (1.057-1.626)	0.014*	1.603 (1.237-2.077)	< 0.001*	1.599 (1.225-2.088)	0.001*	
T sige0,020,13'0,13'0,13'0,13'TReferenceKarcanceKarc	Male									
International Network Network Network Network Ta 0.870 (0.03-1.03) 0.470 0.400 0.410 0.471 0.400 0.400 0.410 0.471 0.400 0.400 Ta 0.400 (1.03-0.130) 0.400 0.410 0.471 0.400 0.400 0.400 0.400 Variant 0.400 (0.02-0.20) 0.10 0.470 (0.02-0.20) 0.400 0.400 0.400 Name Referee Referee Referee Referee Referee 0.400 Name 1.400/07-1.87) 0.400 0.400 0.200 0.200 0.400 0.400 0.400 0.400 Name 0.404(1.42.02) 0.400 0.400 0.400 0.400 0.400 0.400 0.400 0.400 Name 0.404(1.42.00) 0.400 0.400 0.400 0.400 0.400 0.400 0.400 Name 0.404(1.42.00) 0.400 0.400 0.400 0.400 0.400 0.400 0.400 Name 0.404(1.42.00) 0.400 0.400 0.400 0.400 0.400 0.400 0.400 Name 0.404(1.400-1.400 0.400 0.400 0.400 0.400 <td>T stage</td> <td></td> <td>0.002*</td> <td></td> <td>0.013*</td> <td></td> <td>0.016*</td> <td></td> <td>0.126</td>	T stage		0.002*		0.013*		0.016*		0.126	
T20.878 (0.832.1219)0.4870.487 (0.802.1202)0.3890.988 (0.400.1.405)0.8780.11 (0.991-135)0.881T31.200 (0.851.4149)0.1411.241 (0.933.1632)0.171.175 (1.11.235)0.161.010 (0.929.2450)0.57T41.693 (1.997.1557)0.0101.75 (1.11.235)0.1611.370 (0.13.241.101)0.588NagoReferenceReference1.220 (0.816.435.136)0.0111.370 (0.74.34.101)0.588Na1.347 (0.977.1857)0.0091.692 (1.12.363)0.011.221 (0.816.435.136)1.333 (0.887.200)0.683Na1.349 (0.977.1857)0.0091.692 (1.12.363)0.011.214 (2.12.406)0.0011.380 (0.74.21.435)0.011Unknown1.359 (0.711.2216)0.011.212 (0.816.435.136)0.021.380 (0.74.21.435)0.011Unknown1.250 (0.711.2216)0.0310.754 (0.690.932)0.0410.903 (0.593.9489)0.0400.907 (0.542.0896)0.015Unknown0.577 (0.649.038)0.3140.754 (0.690.932)0.0410.903 (0.539.989)0.0440.907 (0.542.0896)0.015YeHardistandsYeNational Association (1.199.948)0.0450.9040.907 (0.542.0896)0.015Na0.577 (0.649.038)0.61National Association (1.999.948)0.9040.970 (0.542.0896)0.901Na0.531 (0.610.91)National Association (1.999.948)National Association (1.999.948)National Association (1.999.948)0.004Na	T1	Reference		Reference		Reference		Reference		
T31.20 (0.854.1469)0.4141.24 (0.933.1632)0.401.24 (0.937.1535)0.8440.898 (0.656.1490)0.827T41.608 (1.199.218)0.000.371 (0.801.139.2380)0.100.570 (0.929.2425)0.076Vage0.0010.001 (0.247.259)0.010.006 (0.766.590)0.100.101 (0.270,74.74.101)0.58NageReferenceReferenceReferenceReference0.1010.331 (0.871.401)0.164Nag1.349(0.971.857)0.0091.570(120-2204)0.0011.714 (1.21.402)0.001.333(0.872.001)0.161Na0.944(1.42.772)0.001.671(1.02.2405)0.011.714 (1.21.405)0.021.734(0.26.21.010)0.161Na0.944(1.64.772)0.010.673 (0.537.483)0.1310.133(0.872.403)0.1610.161Na0.944(1.64.772)0.021.734 (0.699.492)0.0111.714 (1.21.405)0.181.932(0.721.463)0.161Na0.947(1.64.790)0.40.573 (0.537.483)0.140.933 (0.539.489)0.1631.942(1.24.59)0.161.942(1.24.59)0.161Na1.947(1.64.790)0.740.743 (0.54.91.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89)0.743 (0.571.51.89) <td>T2</td> <td>0.878 (0.632-1.219)</td> <td>0.437</td> <td>0.850 (0.602-1.202)</td> <td>0.359</td> <td>0.968 (0.640-1.465)</td> <td>0.878</td> <td>0.911 (0.599-1.385)</td> <td>0.838</td>	T2	0.878 (0.632-1.219)	0.437	0.850 (0.602-1.202)	0.359	0.968 (0.640-1.465)	0.878	0.911 (0.599-1.385)	0.838	
T4Loss (1.199-2.18)0.0011.475 (1.089-2.01)0.75 (1.13-2.83)0.0141.51 (0.292-2.42)0.076Nage0.0140.301 (0.307-3.457)0.0140.3010.301 (0.307-3.457)0.0140.301NageReferenceReferenceReferenceReferenceReference0.0140.3311.333 (0.872-20.01)0.164N11.347 (0.977-1857)0.0011.602 (1.21-236)0.0011.714 (2.10-136)0.0311.733 (0.887-20.01)0.164N21.944 (1.42-077-1857)0.0011.602 (1.21-236)0.0011.714 (2.10-136)0.0011.704 (2.10-136)0.0011.704 (2.10-136)0.0011.704 (2.10-136)0.0011.704 (2.10-136)0.0011.704 (2.10-136)0.0011.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0141.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.0151.704 (2.10-136)0.704 (2.10-136) </td <td>Т3</td> <td>1.120 (0.854-1.469)</td> <td>0.414</td> <td>1.234 (0.933-1.632)</td> <td>0.140</td> <td>1.041 (0.697-1.555)</td> <td>0.844</td> <td>0.989 (0.656-1.490)</td> <td>0.827</td>	Т3	1.120 (0.854-1.469)	0.414	1.234 (0.933-1.632)	0.140	1.041 (0.697-1.555)	0.844	0.989 (0.656-1.490)	0.827	
Idename1.69(0)0.90(1) <t< td=""><td>T4</td><td>1.608 (1.199-2.158)</td><td>0.002</td><td>1.475 (1.080-2.015)</td><td>0.015</td><td>1.775 (1.113-2.830)</td><td>0.016</td><td>1.501 (0.929-2.425)</td><td>0.076</td></t<>	T4	1.608 (1.199-2.158)	0.002	1.475 (1.080-2.015)	0.015	1.775 (1.113-2.830)	0.016	1.501 (0.929-2.425)	0.076	
NameOO	Unknown	1.693(0.535-5.361)	0.371	0.801(0.247-2.597)	0.711	2.006(0.706-5.698)	0.191	1.377(0.473-4.011)	0.558	
MReferenceReferenceReferenceReferenceReferenceN11,24(0,97,18,0)0,001,62(1,12,2,00)0,300,30(0,82,7,2,00)0,300,30(0,82,7,2,00)0,30N21,24(0,14,2,10)0,001,20(0,27,2,0,0)0,000,30(0,27,2,10,0)0,300,30(0,27,2,10,0)0,30N31,24(0,12,12,00)0,201,20(0,27,2,10,0)0,101,20(0,27,2,10,0)0,100,10N41,25(0,71,2,10)0,301,27(0,27,2,10,0)0,301,20(0,27,2,10,0)0,100,10N41,25(0,12,10,0)0,301,27(0,37,2,00)0,300,30(0,12,0,0)0,100,10N41,25(0,12,10,0)0,301,27(0,12,00)0,301,20(0,12,0,0)0,100,10N41,25(0,12,10,0)0,101,27(0,12,00)0,101,27(0,12,00)0,101,27(0,12,00)N41,25(0,12,10,0)1,21,20(0,12,0)0,101,27(0,12,00)0,101,27(0,12,00)1,27(0,12,00)N41,25(0,12,10,0)1,21,20(0,12,0)1,20(0,12,0)1,20(0,12,0)1,20(0,12,0)1,27(0,12,0)1,27(0,12,0)N41,27(0,12,10,0)1,27(0,12,10,0)1,27(0,12,10,0)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)N41,27(0,12,10)1,27(0,12,10)1,27(0,12,10,0)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)N41,27(0,12,10)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)1,27(0,12,10)	N stage		0.001*		< 0.001*	*	0.015*		0.014*	
N11.347(0.977.1.877)0.0691.692(1.217.2.363)0.0021.222(0.815.1.823)0.3311.333(0.887.2.04)0.166N21.389(1.084-1.77)0.0010.570(1.207.2.043)0.010.797(0.571.3.00)0.9001.32(0.727.4.1.85)0.01Valcow1.255(0.71-2.2010.0010.202(0.775.4.080)0.0121.840(7.48-0.501)0.021.800(2.0775.4.080)0.012Valcow1.257(0.71-2.2010.0140.572(0.574.2.080)0.0140.318(0.870.0190)0.0040.907(0.52-0.890)0.05*Var0.797(0.649-0.908)0.31*0.754(0.609-0.923)0.04*0.633(0.539-0.890)0.04*0.697(0.52-0.890)0.05*YesVariat analysisM104yariat analysisM104yariat analysisM104yariat analysisM104yariat analysisM104yariat analysisYesVariatNational AndoreNational AndoreNational AndoreNational AndoreNational AndoreFenderNational AndoreNational AndoreNational AndoreNational AndoreNational AndoreYesNational AndoreNational AndoreNational AndoreNational AndoreNational AndoreTamumoticNational AndoreNational AndoreNational AndoreNational AndoreNational AndoreYesNational AndoreNational AndoreNational AndoreNational AndoreNational AndoreYesNational AndoreNational AndoreNational AndoreNational AndoreNational AndoreYesNational AndoreNational Andore <td< td=""><td>N0</td><td>Reference</td><td></td><td>Reference</td><td></td><td>Reference</td><td></td><td>Reference</td><td></td></td<>	N0	Reference		Reference		Reference		Reference		
N21389(1.084-1.79)0.0091.570(1.207-2.043)0.010.979(0.705-1.360)0.9001.320(0.72-1.451)0.01N31.944(1.412-2.67)0.012.062(1.471-2.80)0.011.74(1.212-1.240)0.0201.780(1.267-2.01)0.01Immond2.052(0.71-2.20)0.040.752(0.270-2.20)0.040.931(0.752-1.680)0.0120.012ImmondererVV0.970(0.489-0.90)0.0130.754 (0.009-0.92)0.0440.93 (0.539-0.80)0.040.970 (0.542-0.80)0.057YasMutvariate analysisMutvariate analysisVVMutvariate analysisMutvariate analysisNo0.970 (0.542-0.80)0.057YasMutvariate analysisNo0.9140.931 (0.537-0.80)0.040.970 (0.542-0.80)0.057YasMutvariate analysisNoMutvariate analysisNoNoNoNoNoYasMutvariate analysisNoNoNoNoNoNoNoYasNoNoNoNoNoNoNoNoNoYasNoNoNoNoNoNoNoNoNoNoYasNoNoNoNoNoNoNoNoNoNoYasNoNoNoNoNoNoNoNoNoNoNoYasNoNoNoNoNoNoNoNoNoNoNoYasNo	N1	1.347(0.977-1.857)	0.069	1.692(1.211-2.363)	0.002	1.222(0.815-1.832)	0.331	1.333(0.887-2.004)	0.166	
N3194(1,412-267)0,0012.062(1,471-2.80)0.011.71(1,212-1.40)0.021.78(1,262-5.01)0.01Unknown1.255(0,711-2.10)0.4341.72(0,874-2.80)0.1311.814(0,748-4.50)0.1611.902(0,754-6.68)0.161ImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemNo0.75(0,609-0932)0.4410.630,039-03900.4040.630,039-03900.4040.697 (0.52-0.89)0.405NoImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemNa0.75(0,609-0.92)0.4140.6470.630,039-0.9300.4040.630,039-0.9300.4050.697 (0.52-0.89)0.697TorImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemTorImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemTorImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemTorImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemTorImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemImmuthemTorImmuthemImmuthemImmuthemImmuthemImmuthem </td <td>N2</td> <td>1.389(1.084-1.779)</td> <td>0.009</td> <td>1.570(1.207-2.043)</td> <td>0.001</td> <td>0.979(0.705-1.360)</td> <td>0.900</td> <td>1.032(0.742-1.435)</td> <td>0.853</td>	N2	1.389(1.084-1.779)	0.009	1.570(1.207-2.043)	0.001	0.979(0.705-1.360)	0.900	1.032(0.742-1.435)	0.853	
Unknown12550/11-2200.441572(0.874-2.8300.111834(0.748-4.501)0.181902(0.754-6.68)0.01ImmunchnemNa0.707 (0.649-0.980)0.01*0.754 (0.609-0.922)0.04*0.603 (0.530-0.890)0.00*0.607 (0.542-0.896)0.005*YesImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemYesImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemImmunchnemHardson1.633 (1.094.1087)0.00*1.628 (1.020-1.010)0.03*1.519 (1.156-1.98)0.00*ImmunchnemImmunchnemFernale1.633 (1.094.1087)0.00*1.628 (1.020-1.610)0.03*1.519 (1.156-1.98)0.03*1.502 (1.143-1.97)0.00*Tatac0.00*0.00*0.00*0.00*1.628 (1.020-1.610)0.03*1.519 (1.156-1.98)0.040.502 (1.143-1.97)0.00*Tatac0.01*0.02*0.03*0.03*0.508 (1.567-0.18)0.040.6020.603*0.6040.603*0.6040.604*0.604*Tatac0.02*0.02*0.03*0.03*0.508 (0.570-1.58)0.600.202 (0.562.61.29)0.600.604*Tatac0.02*0.02*0.02*0.02*0.02*0.60*0.60*0.60*0.60*0.60*Tatac0.02*0.02*0.02*0.02*0.02*0.04* <th< td=""><td>N3</td><td>1.944(1.412-2.676)</td><td>< 0.001</td><td>2.062(1.471-2.890)</td><td>< 0.001</td><td>1.714(1.221-2.406)</td><td>0.002</td><td>1.780(1.266-2.501)</td><td>0.001</td></th<>	N3	1.944(1.412-2.676)	< 0.001	2.062(1.471-2.890)	< 0.001	1.714(1.221-2.406)	0.002	1.780(1.266-2.501)	0.001	
Image: series of the series o	Unknown	1.255(0.711-2.216)	0.434	1.572(0.874-2.830)	0.131	1.834(0.748-4.501)	0.185	1.902(0.775-4.668)	0.161	
No0.797 (0.649-0.80)0.01*0.754 (0.609-0.922)0.04*0.693 (0.539-0.80)0.04*0.697 (0.542-0.86)0.005*Yes HROFARE ANDEXISE ON DEVINATIONAL ANDEXISE ON DEVINATIONAL ANDEXISE ON DEVINATIONAL ANDEXISE ON DEVINATIONAL ANDEXISEMultivariate analysiseMendesina ParticipandaMinitarite analysiseMultivariate analysiseMultivariate analysiseMultivariate analysiseSetTermaleJa63 (1.094-1.697)0.0041.282 (1.020-1.610)0.0301.519 (1.156-1.988)0.0031.502 (1.143-1.976)0.004SetTermaleReferenceReferenceTermaleT faceReferenceReferenceReferenceT 1ReferenceReferenceReferenceReferenceT 20.923 (0.655-1.301)0.6400.838 (0.618-1.240)0.603Cale Sectore SectoreT 4ReferenceReferenceReferenceReferenceT 4ReferenceReferenceReferenceReferenceReferenceT 4ReferenceReferenceReferenceReferenceReferenceT 4ReferenceReferenceReferenceReferenceReferenceReferenceRe	Immunotherapy									
Yea Mutariate analysis U Mutariate analy	No	0.797 (0.649-0.980)	0.031*	0.754 (0.609-0.932)	0.044*	0.693 (0.539-0.890)	0.004*	0.697 (0.542-0.896)	0.005*	
Industate analysicMultivariate analysicIndustriate analysicMultivariate analysicMultivariate analysicR (95% CI)PR (95% CI)PR (95% CI)PR (95% CI)PSetsetsetsetsetsetsetsetT alog0.0040.0041.282 (1.020-1.61)0.0341.519 (1.156-1.98)0.0041.502 (1.143-1.97)0.004MalesetsetsetsetsetsetsetsetT alog0.0050.0050.0050.0050.004Set0.0040.0040.004T alogsetReferenceReferenceReferenceReference1.0050.0040.0040.0040.0040.0040.0040.0050.0010.0050.0010.011 <t< td=""><td>Yes</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Yes									
HR (95% CI)PHR (95% CI)PHR (95% CI)PHR (95% CI)PHR (95% CI)PSetFenale1,363 (1.094.1.697)0.00*1,282 (1.020-1.610)0.03*1,519 (1.156-1.988)0.03*1,502 (1.143-1.976)0.004*Male0.00*0.03*0.03*1,519 (1.156-1.988)0.03*1,502 (1.143-1.976)0.004*T stage0.05*0.03*0.03*0.024*0.024*0.070*T stage0.23 (0.555-1.301)0.6470.884 (0.618-1.264)0.5000.888 (0.570-1.385)0.610.825 (0.526-1.294)0.403T 31.154 (0.867-1.537)0.321.228 (0.917-1.645)0.1681.080 (0.750-1.654)0.230.933 (0.644-1.531)0.974T 41.638 (1.201-2.235)0.021.414 (1.019-1.962)0.381.747 (1.068-2.857)0.021.438 (0.867-2.384)0.169T 40.636 (0.884-4.581)0.6240.281 (0.384-4.524)0.5011.445 (0.482-4.594)0.5010.576N 4 seg0.01*0.2011.414 (1.019-1.962)0.2011.450 (0.427-4.594)0.5010.5760.932 (0.526-3.41)0.992N 4 seg0.361 (0.584-5.236)0.0211.445 (0.382-2.584)0.0121.456 (0.482-4.594)0.5010.5760.576N 50.537 (1.38-1.989)0.0211.547 (1.329-2.297)0.0111.307 (0.212-1.119)0.161.456 (0.484-2.491)0.6010.601N 50.537 (1.347-2.493)0.619 (1.576-3.581)0.0111.560 (1.11-2.304		Univariate analysi	ariate analysis (CSS) Multivariate analysis (CSS)		Univariate analysis (CSS) Multivariate a		Multivariate ar	nalysis (CSS)		
Sex Image 1.633 (1.094-1.697) 0.00* 1.282 (1.020-1.610) 0.03* 1.519 (1.156-1.988) 0.00* 1.502 (1.143-1.976) 0.00* Male Image 0.00* 0.00* 0.00* 0.00* 0.00* 0.00* 0.00* T stage 0.00* Reference Reference Reference Reference Reference 0.00* 0.303 (0.404-1.538) 0.01 0.825(0.526-1.904) 0.403 T 1 Reference Reference Reference Reference Reference 0.00* 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.005		HR (95% CI)	Р	HR (95% CI)	Р	HR (95% CI)	Р	HR (95% CI)	Р	
Fenale 1,363 (1,094-1.67) 0.00* 1.282 (1,020-1.610) 0.03* 1,519 (1,156-1.998) 0.00* 1,502 (1,143-1.976) 0.004* Male 7 1 0.005* 0.005* 0.030* 0.024* 0.017* T stage 0.005* 0.005* 0.030* 0.024* 0.024* 0.017* T1 Reference Reference Reference 0.017* 0.047* 0.017* T3 0.923 (0.655-1.301) 0.647 0.884 (0.618-1.264) 0.500 0.888 (0.570-1.385) 0.601 0.825 (0.526-1.294) 0.403 T3 1.154 (0.867-1.537) 0.326 1.228 (0.917-1.645) 0.168 1.080 (0.705-1.654) 0.723 0.933 (0.644-1.531) 0.974 T4 1.638 (1.201-2.235) 0.021 1.414 (1.019-1.962) 0.038 1.416 (0.492-0.483) 0.991 0.9	Sex									
MaleT stage 0.05° 0.03° 0.24° 0.70° T stage $0.23(0.655-1.30)$ 0.67 0.667 0.676 0.676 T2 $0.23(0.655-1.30)$ 0.67 $0.84(0.618-1.264)$ 0.500 $0.88(0.570-1.385)$ 0.601 $0.825(0.526-1.294)$ 0.403 T3 $1.154(0.867-1.537)$ 0.326 $1.228(0.917-1.645)$ 0.618 0.703 0.723 $0.933(0.644-1.53)$ 0.974 T4 $0.636(0.88+1.53)$ 0.02 $1.414(1.019-1.962)$ 0.38 $1.747(1.068-2.857)$ 0.26 $0.992(0.295.341)$ 0.992 T stage $0.636(0.88+1.53)$ 0.61 $0.281(0.38-2.054)$ 0.21 $1.405(0.472-4.56)$ 0.576 $0.992(0.295.341)$ 0.992 N stage 0.01° 0.615° 0.01° 0.015° $0.992(0.295.341)$ 0.992 N stage 0.01° $0.851(1.329.208)$ 0.01 $1.495(0.942-1.97)$ 0.01° $0.992(0.295.341)$ <td>Female</td> <td>1.363 (1.094-1.697)</td> <td>0.006*</td> <td>1.282 (1.020-1.610)</td> <td>0.033</td> <td>1.519 (1.156-1.998)</td> <td>0.003*</td> <td>1.502 (1.143-1.976</td> <td>i) 0.004*</td>	Female	1.363 (1.094-1.697)	0.006*	1.282 (1.020-1.610)	0.033	1.519 (1.156-1.998)	0.003*	1.502 (1.143-1.976	i) 0.004*	
T stage 0.05^{+} 0.03^{+} 0.024^{+} Reference $Reference$ <	Male									
T1ReferenceReferenceReferenceReferenceT2 $0.923(0.655-1.301)$ 0.647 $0.884(0.618-1.264)$ 0.500 $0.888(0.570-1.385)$ 0.601 $0.825(0.526-1.294)$ 0.403 T3 $1.154(0.867-1.537)$ 0.326 $1.228(0.917-1.645)$ 0.168 $1.080(0.705-1.564)$ 0.723 $0.933(0.644-1.531)$ 0.974 T4 $1.638(1.201-2.235)$ 0.002 $1.414(1.019-1.962)$ 0.38 $1.747(1.068-2.857)$ 0.026 $1.438(0.867-2.386)$ 0.160 Tstage $0.036(0.888-4.581)$ 0.654 $0.281(0.382-2.054)$ 0.221 $1.405(0.427-4.626)$ 0.576 $0.992(0.295-3.341)$ 0.990 N stage 0.01^* 0.01^* 0.01^* 0.01^* 0.01^* 0.01^* 0.01^* NoReferenceReferenceReference 0.01^* 0.01^* 0.016^* 0.016^* N1 $1.466(1.049-2.049)$ 0.025 $1.825(1.289-2.583)$ 0.01 $1.397(0.921-2.119)$ 0.116 $1.496(0.984-2.274)$ 0.060 N2 $1.539(1.188-1.995)$ 0.001 $1.747(1.329-2.297)$ <0.01 $1.600(1.111-2.304)$ 0.012 $1.637(1.136-2.359)$ 0.008 N3 $1.905(1.347-2.693)$ 0.031 $1.981(1.376-2.851)$ <0.01 $1.600(1.111-2.304)$ 0.012 $1.637(1.136-2.359)$ 0.066 ImmutheremImmutheremImmutheremImmutheremImmutheremImmutheremImmutheremImmutheremNo $0.796(0.642-0.987)$ 0.043^* $0.743(0.596-0.928)$ <td< td=""><td>T stage</td><td></td><td>0.005*</td><td></td><td>0.030</td><td>+</td><td>0.024*</td><td></td><td>0.170*</td></td<>	T stage		0.005*		0.030	+	0.024*		0.170*	
T2 0.923(0.655-1.301) 0.647 0.884(0.618-1.264) 0.500 0.888(0.570-1.385) 0.601 0.825(0.526-1.294) 0.403 T3 1.154(0.867-1.537) 0.326 1.228(0.917-1.645) 0.168 1.080(0.705-1.654) 0.723 0.933(0.644-1.531) 0.974 T4 1.638(1.201-2.235) 0.002 1.414(1.019-1.962) 0.038 1.747(1.068-2.857) 0.026 1.438(0.867-2.386) 0.160 Unknown 0.636(0.088-4.581) 0.654 0.281(0.038-2.054) 0.221 1.405(0.427-4.626) 0.576 0.992(0.295-3.341) 0.990 N stage 0.001* 0.015* 0.014* N0 Reference Reference Reference 0.014* 0.014* 0.060 0.097(0.775-1.552) 0.061 0.001 0.997(0.775-1.552) 0.601 0.601 0.997(0.775-1.552) 0.601 0.608 0.008 0.008 0.008 0.007 0.329(0.945-5.738) 0.008 0.007 0.329(0.945-5.738) 0.008 0.008 0.014* 0.725 (0.556-0.945) 0.018* 0.018* N3 1.905(1.347-2.693) 0.043* 0.743 (0.5	T1	Reference		Reference		Reference		Reference		
T3 1.154(0.867-1.537) 0.326 1.228(0.917-1.645) 0.168 1.080(0.705-1.654) 0.723 0.933(0.644-1.531) 0.974 T4 1.638(1.201-2.235) 0.002 1.414(1.019-1.962) 0.038 1.747(1.068-2.857) 0.026 1.438(0.867-2.386) 0.160 Unknown 0.636(0.088-4.581) 0.654 0.281(0.038-2.054) 0.221 1.405(0.427-4.626) 0.576 0.992(0.295-3.341) 0.990 N stage 0.001* 0.015* 0.014* 0.014* N0 Reference Reference Reference 0.014* 0.001 0.001* 0.016* 0.092(0.295-3.341) 0.001 N0 Reference Reference 0.015* 0.014*<	T2	0.923(0.655-1.301)	0.647	0.884(0.618-1.264)	0.500	0.888(0.570-1.385)	0.601	0.825(0.526-1.294) 0.403	
T4 1.638(1.201-2.235) 0.002 1.414(1.019-1.962) 0.038 1.747(1.068-2.857) 0.026 1.438(0.867-2.386) 0.160 Unknown 0.636(0.088-4.581) 0.654 0.281(0.038-2.054) 0.221 1.405(0.427-4.626) 0.576 0.992(0.295-3.341) 0.990 N stage 0.001* 0.015* 0.015* 0.014* N0 Reference Reference Reference 0.016* 0.060 N1 1.466(1.049-2.049) 0.025 1.825(1.289-2.583) 0.001 1.397(0.921-2.119) 0.116 1.496(0.984-2.274) 0.060 N2 1.539(1.188-1.995) 0.001 1.747(1.329-2.297) <0.001	T3	1.154(0.867-1.537)	0.326	1.228(0.917-1.645)	0.168	1.080(0.705-1.654)	0.723	0.933(0.644-1.531) 0.974	
Unknown 0.636(0.088-4.581) 0.654 0.281(0.038-2.054) 0.221 1.405(0.427-4.626) 0.576 0.992(0.295-3.341) 0.990 N stage 0.001* 0.015* 0.015* 0.014* N0 Reference Reference Reference 0.016 1.496(0.984-2.274) 0.060 N2 1.539(1.188-1.995) 0.001 1.747(1.329-2.297) <0.001	T4	1.638(1.201-2.235)	0.002	1.414(1.019-1.962)	0.038	1.747(1.068-2.857)	0.026	1.438(0.867-2.386) 0.160	
N stage 0.01* <0.01* 0.015* 0.01* N0 Reference Reference Reference 0.014 N1 1.466(1.049-2.049) 0.025 1.825(1.289-2.583) 0.001 1.397(0.921-2.119) 0.116 1.496(0.984-2.274) 0.060 N2 1.539(1.188-1.995) 0.001 1.747(1.329-2.297) <0.001	Unknown	0.636(0.088-4.581)	0.654	0.281(0.038-2.054)	0.221	1.405(0.427-4.626)	0.576	0.992(0.295-3.341) 0.990	
N0 Reference Reference N1 1.466(1.049-2.049) 0.025 1.825(1.289-2.583) 0.001 1.397(0.921-2.119) 0.116 1.496(0.984-2.274) 0.060 N2 1.539(1.188-1.995) 0.001 1.747(1.329-2.297) <0.001	N stage		0.001*		< 0.001	*	0.015*		0.014*	
N1 1.466(1.049-2.049) 0.025 1.825(1.289-2.583) 0.001 1.397(0.921-2.119) 0.116 1.496(0.984-2.274) 0.060 N2 1.539(1.188-1.995) 0.001 1.747(1.329-2.297) <0.001	N0	Reference		Reference		Reference				
N2 1.539(1.188-1.995) 0.001 1.747(1.329-2.297) <0.001 1.046(0.740-1.477) 0.800 1.097(0.775-1.552) 0.601 N3 1.905(1.347-2.693) <0.001	N1	1.466(1.049-2.049)	0.025	1.825(1.289-2.583)	0.001	1.397(0.921-2.119)	0.116	1.496(0.984-2.274) 0.060	
N3 1.905(1.347-2.693) <0.001 1.981(1.376-2.851) <0.001 1.600(1.111-2.304) 0.012 1.637(1.136-2.359) 0.008 Unknown 1.342(0.741-2.429) 0.332 1.649(0.894-3.043) 0.110 2.254(0.916-5.550) 0.077 2.329(0.945-5.738) 0.066 Immunotherapy V No 0.796 (0.642-0.987) 0.043* 0.743 (0.596-0.928) 0.009* 0.715 (0.548-0.932) 0.013* 0.725 (0.556-0.945) 0.018* Yes	N2	1.539(1.188-1.995)	0.001	1.747(1.329-2.297)	< 0.00	1.046(0.740-1.477)	0.800	1.097(0.775-1.552) 0.601	
Unknown 1.342(0.741-2.429) 0.332 1.649(0.894-3.043) 0.110 2.254(0.916-5.550) 0.077 2.329(0.945-5.738) 0.066 Immunotherapy No 0.796 (0.642-0.987) 0.043* 0.743 (0.596-0.928) 0.009* 0.715 (0.548-0.932) 0.013* 0.725 (0.556-0.945) 0.018* Yes Colspan="4">Colspan="4">Colspan="4">Colspan="4">Colspan="4">Colspan="4">Colspan="4">Colspan="4">Colspan="4"Colspan="4">Colspan="4"Colspan="4	N3	1.905(1.347-2.693)	< 0.001	1.981(1.376-2.851)	<0.00	1.600(1.111-2.304)	0.012	1.637(1.136-2.359) 0.008	
Immunotherapy No 0.796 (0.642-0.987) 0.043* 0.743 (0.596-0.928) 0.009* 0.715 (0.548-0.932) 0.013* 0.725 (0.556-0.945) 0.018* Yes	Unknown	1.342(0.741-2.429)	0.332	1.649(0.894-3.043)	0.110	2.254(0.916-5.550)	0.077	2.329(0.945-5.738) 0.066	
No 0.796 (0.642-0.987) 0.043* 0.743 (0.596-0.928) 0.009* 0.715 (0.548-0.932) 0.013* 0.725 (0.556-0.945) 0.018* Yes	Immunotherapy									
Yes	No	0.796 (0.642-0.987)	0.043*	0.743 (0.596-0.928	3) 0.009	0.715 (0.548-0.932)	0.013*	0.725 (0.556-0.945	0.018*	
	Yes									

TABLE 3 Univariate and multivariate analyses of OS and CSS for different characteristics of oligometastatic NSCLC in each cohort.

*p value is significant.

the SEER and the single-center cohorts. To our knowledge, this was the largest sample size, and the first analysis to assess the role of immunotherapy in treating oligometastatic NSCLC according to different metastatic sites. Immunotherapy is US Food and Drug Administration approved for use alone or in combination with chemotherapy for patients with NSCLC, and has been evaluated after locally ablative therapy for oligometastatic disease (12). However, phase III clinical studies are still lacking in the field of immunotherapy treatment of oligometastatic NSCLC. Whether immunotherapy can confer a survival benefit in patients with oligometastatic NSCLC remains controversial, particular in those with different metastatic sites.

1			metastati	ic sites analysis of overall survival	
Subgrou	ps	Immunotherapy (events/patients)	Noimmunotherapy (events/patients)	Hazard Ratio Q95%C) P Value
BOM					
SEER Dat	tabase	40/48	38/55	1.171 (0.732-1.874)	0.510
Single-Ce	nter Cohort	31/39	26/40	1.136(0.637-2.025)	0.666
All		71/87	64/95	1.241(0.873-1.762)	0.229
BRM					
SEER Dat	tabase	41/68	77/92	0.565(0.385-0.829)	0.004
Single-Ce	nter Cohort	22/41	34/41	0 536(0 312-0 920)	0.024
All		63/109	111/133	0.546(0.400-0.746)	<0.001
LIM					
SEER Dat	tabase	14/18	24/27	0.737(0.361-1.503)	0.401
Single-Ce	nter Cohort	10/17	12/15	0.779(0.312-1.946)	0.594
All		24/35	36/42	0.756(0.444-1.287)	0.303
MOM					
SEER Dat	tabase	25/35	23/24	0 546(0 308-0 968)	0.038
Single-Ce	nter Cohort	24/41	19/22	0.467(0.238-0.914)	0.026
All		49/76	42/46	0.469(0.303-0.726)	0.001
OTM					
SEER Dat	tabase	38/53	50/63	0.923(0.606-1.408)	0.712
Single-Ce	nter Cohort	29/43	38/45	0.730(0.444-1.200)	0.214
All		67/96	88/108	0 858(0 620-1.186)	0.353
All					
SEER Dat	tabase	158/222	212/261	0.754(0.609-0.932)	0.044
Single-Ce	nter Cohort	116/181	129/163	0.697(0.542-0.896)	0.005
All		274/403	341/424	0.729(0.620-0.856)	<0.001

в

metastatic sites analysis of cancer-specific survival

Subgroups	Immunotherapy	Noimmunotherapy		Hazard Ratio C95%CI)	P Value
	(events/patients)	(events/patients)			
BOM					
SEER Database	37/48	35/55	⊢ ⊢ ⊢	1.279(0.776-2.106)	0.334
Single-Center Cohort	28/39	21/40		1.285(0.679-2.433)	0.441
All	65/87	56/95	× *	1.366(0.939-1.988)	0.103
BRM					
SEER Database	38/68	70/92	1B1	0.551 (0.370-0.820)	0.003
Single-Center Cohort	20/41	31/41	IBI	0.540(0.307-0.950)	0.033
All	58/109	101/133	1	0.549(0.397-0.760)	<0.001
LIM					
SEER Database	12/18	22/27	F	0.667(0.309-1.438)	0.301
Single-Center Cohort	8/17	12/15	· · · · · · · · · · · · · · · · · · ·	0.581 (0.183-1.845)	0.357
All	20/35	34/42	H	0.591 (0.339-1.030)	0.064
MOM					
SEER Database	23/35	22/24	II	0.524(0.290-0.947)	0.032
Single-Center Cohort	21/41	18/22	IBI	0.469(0.235-0.937)	0.032
All	44/76	40/46	11	0.492(0.320-0.758)	0.001
OTM					
SEER Database	35/53	45/63		0.963(0.615-1.506)	0.868
Single-Center Cohort	27/43	33/45	⊢ <u> </u>	0.831(0.492-1.403)	0.489
All	62/96	78/108	⊢	0.903(0.642-1.270)	0.558
All					
SEER Database	145/222	194/261	I	0.743(0.596-0.928)	0.009
Single-Center Cohort	104/181	115/163	II	0.725(0.556-0.945)	0.018
All	249/403	309/424		0.726(0.612-0.862)	<0.001
		0	0.2 0.4 0.6 0.8 1 1.5 2 The estimates		

FIGURE 3

Forest plots displaying the relationship between immunotherapy and overall survival (A) and cancer-specific survival (B) within different subgroups in each cohort. BOM, bone metastases only; BRM, brain metastases only; CSS, cancer-specific survival; LIM, liver metastases only; MOM, multiple organ metastases; OS, overall survival; OTM, other metastases.

Our study showed that immunotherapy improved OS and CSS in patients with oligometastatic NSCLC. These findings agreed with previous findings of improved survival following treatment of metastatic NSCLC with PD-1 inhibitors (15, 16). Recent clinical trials focused on use of immunotherapy to treat various solid tumors have shown a clear association between immunotherapy and increased OS and improved prognosis (17, 18). We also observed reduced OS in patients in the LIM and MOM subgroups. This was consistent with the findings of previous studies showing that patients with NSCLC that had metastasized to multiple organs or the liver had worse OS relative to those with other metastases (19–22). These results showed the value of immunotherapy for treatment of oligometastatic NSCLC patients with liver and multiple organ metastases.

We found that being male was significantly associated with poorer prognosis, which agreed with the results of a study by Radkiewicz C et al, who reported that men with NSCLC had consistently poorer lung cancer-specific survival across stages (23). Moreover, our results showed that patient prognosis was related to tumor location, and patients with tumors located in the main bronchus had worse outcomes than those who had tumors in other locations, which agreed with the results of a study by Li C et al (24). A recent study showed that chemotherapy combined with immunotherapy had superior efficacy for improving anticancer activity (25). Radiotherapy is not an independent prognostic factor for improvement of OS and CSS, due to the remarkable effects of recently developed targeted therapies.

The definition of oligometastatic NSCLC differed across many previous studies, with the maximum number of metastases ranging from 3 to 6 (26). Recently, a number of studies have shown that LT improved the prognosis of patients with oligometastatic NSCLC (27, 28). However, several studies have also shown that immunotherapy was effective for treatment of patients with oligometastatic NSCLC, especially for those at high risk of distant metastases (29, 30). In the most recent NCCN guidelines, immunotherapy is a recognized front-line treatment approach for metastatic NSCLC (31). Therefore, we studied the efficacy of immunotherapy for treatment of oligometastatic NSCLC based on different metastatic sites.

Previous studies focused on metastatic NSCLC have demonstrated that different sites of metastasis can predict clinical outcomes (20, 21, 32).Patients with NSCLC with bone metastasis have the best prognosis (32), which we further confirmed in the present study. We found that patients in the LOM and MOM subgroups had the worst OS and CSS compared to those in other subgroups, which was consistent with the results of a study by Yang J et al, which identified that the mortality risk was highest with MOM and liver metastases (20). We also found that immunotherapy improved OS and CSS in the BRM and MOM subgroups. A recent study found that local control and overall survival were both improved in patients with NSCLC who received concurrent immune checkpoint inhibitor treatment with radiosurgery (33), which was consistent with our results. Another study (34) that brain irradiation induces the strongest immune activation effects and patient outcome compared with those achieved through irradiation of other organs, which may be consistent with our results. However, patients in the LOM subgroup did not benefit from immunotherapy, which may have been associated with poorer response of liver metastasis to immunotherapy. A study reported that liver metastases diminish immunotherapy efficacy systemically in patients and preclinical models, resulting in a systemic immune desert through siphoning of activated CD8+ T cells from the systemic circulation (35). Our results showed that patients in the MOM subgroup benefited most from immunotherapy, which was consistent with the results of a study by Ma SC et al (36), who reported that increased number of metastatic sites (≥ 2) we associated with pronounced OS benefits from atezolizumab versus docetaxel. This may indicate that these patients represent a subgroup that may benefit from aggressive treatment.

Our study had several limitations. First, the SEER database does not provide a detailed description of the specific immunotherapy used. Second, limited information is provided by the SEER database, and there may be some degree of error in the coding of individual patients. Transfer of patients in a particular group (bone, brain, liver) were restricted to this organ, although patients may have had metastases at other sites not explicitly documented in the SEER database (the most common unrecorded site may be the adrenal). Finally, this study was a retrospective study, and the efficacy of immunotherapy in oligometastatic NSCLS with different metastatic sites should be evaluated in prospective clinical trials.

Conclusion

Our study showed that immunotherapy improved OS and CSS in patients in the SEER and the single-center cohorts. Furthermore, we found that immunotherapy improved the prognosis of patients in the BRM and MOM subgroups, but not those in the BOM, OTM, or LIM subgroups. The MOM subgroup experienced the greatest benefit from immunotherapy in both cohorts. Therefore, metastatic sites may affect the efficacy of immunotherapy. These subgroups may benefit from aggressive treatment, and our results may have implications for clinical guidance. However, our findings need to be validated in future large-sample prospective clinical trials.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

J-CM, J-XZ, FW, DC and JY contributed to the study. DC and JY designed the project and approved the final manuscript. J-XZ and FW are responsible for modifying and editing this article. J-CM collected the clinical patients information and drafted the article. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by National Natural Science Foundation of China (82172676), Science Foundation of Shandong (ZR2021YQ52, ZR2020LZL016), Foundation of

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics. CA Cancer J Clin (2021) 71:7-33. doi: 10.3322/caac.21654

2. Reck M, Heigener DF, Mok T, Soria JC, Rabe KF. Management of non-smallcell lung cancer: recent developments. *Lancet* (2013) 382:709–19. doi: 10.1016/ S0140-6736(13)61502-0

3. Parikh RB, Cronin AM, Kozono DE, Oxnard GR, Mak RH, Jackman DM, et al. Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2014) 89:880–7. doi: 10.1016/j.ijrobp.2014.04.007

4. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol (1995) 13:8-10. doi: 10.1200/JCO.1995.13.1.8

5. Torok JA, Gu L, Tandberg DJ, Wang X, Harpole DHJr., Kelsey CR, et al. Patterns of distant metastases after surgical management of non-small-cell lung cancer. *Clin Lung Cancer* (2017) 18:e57–70. doi: 10.1016/j.cllc.2016.06.011

6. Gomez DR, Tang C, Zhang J, Blumenschein GRJr., Hernandez M, Lee JJ, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-Small-Cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol* (2019) 37:1558–65. doi: 10.1200/JCO.19.00201

Bethune Charitable Foundation (2021434953), and the Young Elite Scientist Sponsorship Program by CAST (YESS20210137).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fimmu.2022.1039157/full#supplementary-material

SUPPLEMENTARY FIGURE 1

Kaplan-Meier probability plots of Overall Survival and Cancer Specific Survival between the Immunotherapy group and the No immunotherapy group within different metastatic site subgroups: BOM group (SEER: a and b; Single-Center: k and l), BRM group (SEER: c and d; Single-Center: m and n), LIM group (SEER: e and f; Single-Center: o and p), MOM group (SEER: g and h; Single-Center: q and r), and OTM group (SEER: i and j; Single-Center: s and t). *Abbreviations*: MOM, multiple organ metastases; OTM, other metastases.

7. Gomez DR, Blumenschein GRJr., Lee JJ, Hernandez M, Ye R, Camidge DR, 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* (2016) 17:1672–82. doi: 10.1016/S1470-2045(16)30532-0

8. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, 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) 393:2051-8. doi: 10.1016/S0140-6736(18)32487-5

9. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* (2019) 393:1819–30. doi: 10.1016/S0140-6736(18)32409-7

10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-Small-Cell lung cancer. *N Engl J Med* (2018) 378:2078–92. doi: 10.1056/NEJMoa1801005 11. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non-Small-Cell lung cancer. N Engl J Med (2018) 379:2040–51. doi: 10.1056/NEJMoa1810865

12. Bauml JM, Mick R, Ciunci C, Aggarwal C, Davis C, Evans T, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung cancer: A phase 2 trial. *JAMA Oncol* (2019) 5:1283–90. doi: 10.1001/jamaoncol.2019.1449

13. Hong JC, Ayala-Peacock DN, Lee J, Blackstock AW, Okunieff P, Sung MW, et al. Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: A multi-institutional pooled analysis. *PLoS One* (2018) 13: e0195149. doi: 10.1371/journal.pone.0195149

14. Ashworth AB, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* (2014) 15:346–55. doi: 10.1016/j.cllc.2014.04.003

15. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol* (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5

16. Goldberg SB, Schalper KA, Gettinger SN, Mahajan A, Herbst RS, Chiang AC, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol* (2020) 21:655–63. doi: 10.1016/S1470-2045(20)30111-X

17. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* (2018) 359:1350-5. doi: 10.1126/science.aar4060

18. Duan J, Cui L, Zhao X, Bai H, Cai S, Wang G, et al. Use of immunotherapy with programmed cell death 1 vs programmed cell death ligand 1 inhibitors in patients with cancer: A systematic review and meta-analysis. *JAMA Oncol* (2020) 6:375–84. doi: 10.1001/jamaoncol.2019.5367

19. Hendriks LE, Derks JL, Postmus PE, Damhuis RA, Houben RM, Troost EG, et al. Single organ metastatic disease and local disease status, prognostic factors for overall survival in stage IV non-small cell lung cancer: Results from a population-based study. *Eur J Cancer* (2015) 51:2534–44. doi: 10.1016/j.ejca.2015.08.008

20. Yang J, Zhang Y, Sun X, Gusdon AM, Song N, Chen L, et al. The prognostic value of multiorgan metastases in patients with non-small cell lung cancer and its variants: a SEER-based study. *J Cancer Res Clin Oncol* (2018) 144:1835–42. doi: 10.1007/s00432-018-2702-9

21. Xu Z, Yang Q, Chen X, Zheng L, Zhang L, Yu Y, et al. Clinical associations and prognostic value of site-specific metastases in non-small cell lung cancer: A population-based study. *Oncol Lett* (2019) 17:5590–600. doi: 10.3892/ol.2019.10225

22. Campos-Balea B, De Castro Carpeno J, Massuti B, Vicente-Baz D, Perez Parente D, Ruiz-Gracia P, et al. Prognostic factors for survival in patients with metastatic lung adenocarcinoma: An analysis of the SEER database. *Thorac Cancer* (2020) 11:3357–64. doi: 10.1111/1759-7714.13681

23. Radkiewicz C, Dickman PW, Johansson ALV, Wagenius G, Edgren G, Lambe M. Sex and survival in non-small cell lung cancer: A nationwide cohort study. *PLoS One* (2019) 14:e0219206. doi: 10.1371/journal.pone.0219206

24. Li C, Liu J, Lin J, Li Z, Shang X, Wang H. Poor survival of non-small-cell lung cancer patients with main bronchus tumor: a large population-based study. *Future Oncol* (2019) 15:2819–27. doi: 10.2217/fon-2019-0098

25. Lazzari C, Karachaliou N, Bulotta A, Viganó M, Mirabile A, Brioschi E, et al. Combination of immunotherapy with chemotherapy and radiotherapy in lung cancer: is this the beginning of the end for cancer? *Ther Adv Med Oncol* (2018) 10:1758835918762094. doi: 10.1177/1758835918762094

26. Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report. *J Thorac Oncol* (2019) 14:2109–19. doi: 10.1016/j.jtho.2019.07.025

27. Bansal P, Rusthoven C, Boumber Y, Gan GN. The role of local ablative therapy in oligometastatic non-small-cell lung cancer: hype or hope. *Future Oncol* (2016) 12:2713–27. doi: 10.2217/fon-2016-0219

28. Tibdewal A, Agarwal JP, Srinivasan S, Mummudi N, Noronha V, Prabhash K, et al. Standard maintenance therapy versus local consolidative radiation therapy and standard maintenance therapy in 1-5 sites of oligometastatic non-small cell lung cancer: a study protocol of phase III randomised controlled trial. *BMJ Open* (2021) 11:e043628. doi: 10.1136/bmjopen-2020-043628

29. Schanne DH, Heitmann J, Guckenberger M, Andratschke NHJ. Evolution of treatment strategies for oligometastatic NSCLC patients - a systematic review of the literature. *Cancer Treat Rev* (2019) 80:101892. doi: 10.1016/j.ctrv.2019.101892

30. Gauvin C, Krishnan V, Kaci I, Tran-Thanh D, Bedard K, Albadine R, et al. Survival impact of aggressive treatment and PD-L1 expression in oligometastatic NSCLC. *Curr Oncol* (2021) 28:593–605. doi: 10.3390/curroncol28010059

31. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN guidelines insights: Non-small cell lung cancer, version 2.2021. J Natl Compr Canc Netw (2021) 19:254–66. doi: 10.6004/jnccn.2021.0013

32. Gu Y, Zhang J, Zhou Z, Liu D, Zhu H, Wen J, et al. Metastasis patterns and prognosis of octogenarians with NSCLC: A population-based study. *Aging Dis* (2020) 11:82–92. doi: 10.14336/AD.2019.0414

33. Abdulhaleem M, Johnston H, D'agostino RJr., Lanier C, Lecompte M, Cramer CK, et al. Local control outcomes for combination of stereotactic radiosurgery and immunotherapy for non-small cell lung cancer brain metastases. J Neurooncol (2022) 157(1):101-7. doi: 10.1007/s11060-022-03951-7

34. Wu M, Liu J, Wu S, Liu J, Wu H, Yu J, et al. Systemic immune activation and responses of irradiation to different metastatic sites combined with immunotherapy in advanced non-small cell lung cancer. *Front Immunol* (2021) 12:803247. doi: 10.3389/fimmu.2021.803247

35. Yu J, Green MD, Li S, Sun Y, Journey SN, Choi JE, et al. Liver metastasis restrains immunotherapy efficacy *via* macrophage-mediated T cell elimination. *Nat Med* (2021) 27:152–64. doi: 10.1038/s41591-020-1131-x

36. Ma SC, Tang XR, Long LL, Bai X, Zhou JG, Duan ZJ, et al. Integrative evaluation of primary and metastatic lesion spectrum to guide anti-PD-L1 therapy of non-small cell lung cancer: results from two randomized studies. *Oncoimmunology* (2021) 10:1909296. doi: 10.1080/2162402X.2021.1909296