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Effects of primary tumor resection on the survival of patients with stage IV extrathoracic metastatic non-small cell lung cancer: A population-based study

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ABSTRACT

Background: Selected non-small cell lung cancer (NSCLC) patients with extrathoracic metastases might benefit from surgical intervention; however, the evidence is limited. We investigated the benefit of surgery in these patients regarding the extent of the metastatic disease.

Methods: Patients with extrathoracic metastatic NSCLC were identified in the US National Cancer Institute Surveillance, Epidemiology, and End Results database (2010–2015). Survival was compared before and after matching. Multivariate Cox regression models were built to identify factors associated with survival and to adjust for covariates in subgroup analysis.

Results: Of the 39,655 patients, 1206 underwent primary tumor resection, and 630 patients were identified 1:1 in surgical and nonsurgical groups after matching. In the entire cohort, patients who underwent surgery had significant prolonged overall survival (OS) in both unmatched (median survival time, [MST]: 14 vs. 6 months, $p < 0.001$) and matched (MST: 11 vs. 7 months, $p < 0.001$) cohorts. In the highly selected surgery-recommended cohort, surgical group still had a significantly longer OS (MST: 14 vs. 6 months, $p < 0.001$). Multivariate regression showed that surgery was independently associated with improved OS and lung cancer-specific mortality (LCSM) (OS: hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.56-0.64, $p < 0.001$; LCSM: subhazard ratio [SHR]: 0.61, 95% CI: 0.57-0.66, $p < 0.001$). Subgroup analysis showed that surgery was an independent favorable predictor to survival in all cohorts except patients with N3 disease, and patients with single-organ metastasis were associated with the most prominent survival benefit from surgery.

Conclusions: Primary tumor resection was associated with improved survival in extrathoracic metastatic NSCLC patients, particularly for those with single-organ metastasis.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Based on the updated Surveillance, Epidemiology, and End Results (SEER) data, up to 55% of all patients with newly diagnosed lung cancer have advanced disease with extrathoracic metastases. Systemic therapy is the main therapeutic strategy for patients with stage IV lung cancer [1]. Yet, the 5-year overall survival (OS) rate for patients with distant metastatic disease still remains extremely low (2%). Local consolidative therapy based multidisciplinary management, other than palliative treatment for relieving localized symptoms, has been attempted to improve the long-term outcome for selected patients with distant metastases. A phase 2 study applied radical treatment to patients with pathologically proven stage IV NSCLC with less than five synchronous metastases and achieved prolonged progression-free survival (PFS) [2]. Another phase 2 study compared local consolidative therapy (surgery or radiation) with maintenance therapy for NSCLC patients with three or fewer metastases after initial systemic therapy and also demonstrated a significantly improved PFS [3]. These studies suggested that aggressive local therapy may provide survival benefit for patients with stage IV NSCLC.

As a main approach of local therapy, surgical resection of the primary tumor has been applied for selected patients with extrathoracic metastatic disease. A series of small, retrospective studies demonstrated that some patients might benefit from surgical intervention for both primary chest and metastatic tumors, especially when the brain or

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adrenal gland was the only involved site [4–12]. Moreover, the NCCN guidelines have also recommended that aggressive local therapy should be considered as a choice for selected patients with limited metastases [13]. However, owing to the absence of high-level evidence, the precise judgement of clinicians for treatment decision and approach choice was still impracticable. As such, a population-based study may be helpful for physicians to identify the potential patients who might benefit from surgical intervention in the real world, thus helping with the decision making in clinical practice.

In this study, we sought to investigate the benefit of primary tumor resection in NSCLC patients with extrathoracic metastases and tried to identify the patients' characteristics that were associated with survival gain from surgery based on the updated SEER data, including information on extrathoracic metastatic sites at the time of initial lung cancer diagnosis.

2. Patients and methods

2.1. Study population

We used the National Cancer Institute SEER*Stat software version 8.3.5 (seer.cancer.gov/seerstat) to select patients from the Incidence-SEER 18 Regs Research Database based on the November 2017 submission, which covers approximately 28.0% of the U.S. population. Cases that were diagnosed as malignant tumors of the lung and bronchus according to the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3) between 2010 and 2015 were included in the eligibility screening process. Of these cases, we used the following patient inclusion criteria: 1) pathologically confirmed NSCLC (only the major histologic subtypes comprising adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma were included); 2) stage IV M1b disease according to the 7th edition of the American Joint Committee on Cancer (AJCC) TNM classification or M1NOS (not otherwise specified) disease with confirmed extrathoracic metastasis at the time of diagnosis; and 3) diagnosed as the first primary malignancy in patient's lifetime. Patients were excluded: 1) if their information on distant metastatic involvement, survival month or surgical status was unavailable; 2) if the patients were younger than 18 years; or 3) if the patients had T0 local disease.

Baseline sociodemographic information (age, sex, race, insurance coverage, and marital status), tumor characteristics (location, histologic subtype, grade, T/N descriptor, and metastatic site), and treatment details (metastasectomy, surgery type of primary tumor resection, and reason for no surgery of primary site) were collected from the database. In this study, histologic subtype was classified according to the ICD-O-3 histology codes (adenocarcinoma: 8140, 8230, 8250 to 8255, 8260, 8310, 8333, 8470, 8480 to 8481, 8490, 8550; squamous cell carcinoma: 8052, 8070 to 8073, 8083 to 8084; larger cell carcinoma: 8012 to 8014, 8082, 8123; adenosquamous carcinoma: 8560). Surgery type was classified according to SEER surgery code (local tumor destruction: 12 to 13, 15; sublobar resection: 20 to 25; lobe or bilobectomy: 30, 33, 45 to 48; pneumonectomy: 55 to 56, 65 to 66, 70). Overall survival (OS) and lung cancer-specific mortality (LCSM) were the primary and secondary outcomes of interest. OS was defined as the time interval from the diagnosis of metastatic NSCLC to all-cause death, while LCSM was defined as the time interval between the diagnosis of metastatic NSCLC and death attributed to lung cancer.

2.2. Statistical analysis

To compare the baseline characteristics between surgical and nonsurgical groups, we analyzed the categorical variables by the Pearson's χ^2 test and the nonnormally distributed continuous variables by Mann-Whitney U test. The Kaplan-Meier method was used to determine OS, and the log-rank test was applied to compare the survival curves. Propensity score matching (PSM) was performed to reduce potential selection bias from patient selection. A logistic regression model was built to calculate the propensity scores of the following covariates: age, sex, race, insurance coverage, marital status, tumor location, histologic subtype, grade, T/N descriptor, metastatic site, and metastasectomy. Patients treated with surgery were matched with patients without surgery by a 1:1 greedy algorithm without replacement.

A multivariate Cox proportional hazard model was constructed to identify factors associated with OS. Likewise, a multivariate competing risks regression model was established to recognize factors associated with LCSM. Analysis of the cumulative incidence of lung cancer-specific death considered noncancer-specific death as competing risk. Fine and Gray's competing risk regression was conducted to estimate the subhazard ratio (SHR). In addition, multivariate Cox proportional hazard and competing risks regression models were applied to adjust for covariates in the subgroup analysis. Multivariate regression included all variables with $p < 0.10$ in the univariate analysis.

All of the statistical analyses were performed using Stata/SE 14.0 for Windows (StataCorp, College Station, TX). A two-sided p-value of < 0.05 was considered statistically significant in this study.

3. Results

Patient selection process is presented in Fig. 1. A total of 39,655 patients with extrathoracic metastatic NSCLC were identified in this study. In total, 1206 patients (3.0%) underwent surgical resection of primary tumors. The baseline characteristics are reported in Table 1. Compared with patients in the nonsurgical group, patients who underwent primary tumor resection were more likely to be young, white, and married, with tumors located at lobes, non-squamous histologic subtype, well/moderate differentiation, early T/N descriptor, single-organ extrathoracic metastasis, without contralateral lung metastasis, and with metastasectomy (all $p < 0.05$).

Of the 39,655 patients, 8416 (21.2%), 12,254 (30.9%), and 2850 (7.2%) had brain, bone, and liver metastases, respectively, and 9340 (23.6%) had multiorgan metastases involving 2–3 organs of the brain, bone, and liver, while 6795 (17.1%) had extrathoracic metastatic sites other than these three above-mentioned organs (see Figure, Supplemental Data 1 A, which demonstrates metastatic site by sector). When considering the surgery rate, patients with brain metastasis had the highest primary tumor resection rate (5.5%), followed by liver (2.4%) and bone (2.1%) metastasis, while patients with multiorgan metastasis had the lowest surgical resection rate (1.2%). Moreover, in the surgical group, 537 (44.5%), 474 (39.3%), 73 (6.1%), and 46 (3.8%) patients underwent lobe or bilobectomy, sublobar resection, local tumor destruction, and pneumonectomy, respectively, while 76 (6.3%) patients underwent surgery not otherwise specified (see Figure, Supplemental Data 1B, which demonstrates surgical type by sector).

Most patients in this study cohort were not recommended for the surgery because surgical intervention was contraindicated for stage IV disease. However, 1888 (4.8%) patients were recommended for the primary tumor resection, comprising 1206 patients who underwent surgery and 682 patients who did not undergo surgery but were originally recommended for surgery by their physician, likely due to low risk factors (e.g., comorbid conditions). Among the latter surgery-recommended nonsurgical cohort, 38 (5.6%) patients died prior to the surgery, 128 (18.8%) patients refused the surgery, and 516 (75.6%) patients did not undergo the surgery for unknown reasons.

In the entire cohort, Kaplan-Meier analysis was conducted to compare the OS between the surgical and nonsurgical groups. Before PSM, patients who underwent primary tumor resection had significantly longer OS than patients without surgery (median survival time [MST]: 14 vs. 6 months, log-rank $p < 0.001$, Fig. 2A). After PSM, 630 patients in total were matched 1:1 in two groups, and all covariates were well balanced (see Figure, Supplemental Data 2, which demonstrates standardized bias of covariates before and after matching). Consistent with

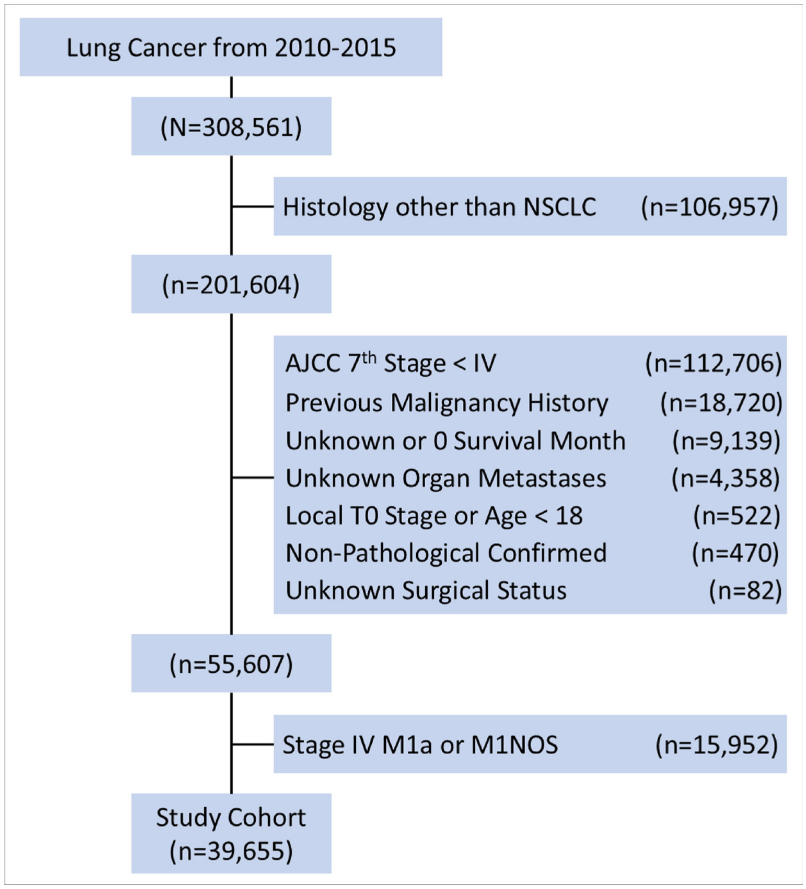

Fig. 1. Flow diagram of the study.

the results from the non-PSM cohort, the PSM cohort also showed that the surgical group had a significantly longer OS (MST: 11 vs. 7 months, log-rank $p < 0.001$, Fig. 2B).

In the surgery-recommended nonsurgical cohort (682 patients), patients who died before the surgery had significantly worse survival than patients who refused the surgery or did not undergo surgery for unknown reasons (log-rank $p < 0.001$, Fig. 2C). To diminish the immortal time bias, we excluded these 38 patients who died prior to the recommended surgery and compared the OS of the remaining 644 nonsurgical patients who were recommended for surgery with the 1206 surgical patients. In this highly selected surgery-recommended cohort (1850 patients), the surgical group still had a significantly longer OS (MST: 14 vs. 6 months, log-rank $p < 0.001$, Fig. 2D).

The survival outcomes of patients with different metastatic sites were also assessed. In the single-organ metastatic cohort, a small but significant decrease in OS was associated with patients with brain, bone, and liver metastases respectively. All patients with the three above-mentioned single-organ metastases had significantly longer OS than patients with multiorgan metastases (all log-rank $p < 0.001$, Fig. 3A). Moreover, in the surgical group, patients who underwent lobe or bilobectomy had the best survival, while patients with local tumor destruction had the poorest survival. Patients who underwent sublobar resection showed similar OS as those who underwent pneumonectomy (log-rank $p = 0.152$, Fig. 3B).

Multivariable models that adjusted demographic, tumor, and therapeutic characteristics were constructed to evaluate the associations between baseline variables and survival outcomes. Primary tumor resection was independently associated with both improved OS (hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.56-0.64, $p < 0.001$) and LCSM (SHR: 0.61, 95% CI: 0.57-0.66, $p < 0.001$) for the entire cohort. Similarly, surgery was again independently associated with longer OS (HR: 0.62, 95% CI: 0.55-0.70, $p < 0.001$) and lower LCSM (SHR: 0.64, 95% CI: 0.57-0.73, $p < 0.001$) in the highly selected surgery-recommended cohort. In addition, other characteristics, such as young age, female, Asian/Pacific Islander, insurance coverage, married status, tumor located at lobe, adenocarcinoma, well-differentiated tumor, early T/N descriptor, single-organ extrathoracic metastasis, no contralateral lung metastasis, and with metastasectomy were also independent favorable predictors for OS and LCSM (Table 2).

To explore which kind of patient might benefit from the surgery, subgroup analyses were performed with multivariate regression adjusting for the covariates. The effectiveness of primary tumor resection was evaluated in different subgroups stratified by sex, race, histologic subtype, T/N descriptor, contralateral lung metastasis, and the extrathoracic metastatic site. Surgery was a significant independent favorable predictor to survival in all subgroups except N3 disease. Survival benefit was the most prominent in each of the following subgroups: female, Asian/Pacific Islander, non-squamous histology, early T/N descriptor, no contralateral lung metastasis, and single-organ metastasis. In the single-organ metastatic cohort, patients with brain metastasis were associated with the most outstanding survival benefit, whereas those with bone metastasis were associated with the least survival gain (Fig. 4).

4. Discussion

To our knowledge, this is the largest report focusing on the surgical intervention of stage IV NSCLC patients with extrathoracic metastases. We found that primary tumor resection was associated with significantly longer OS. Although our study is retrospective, the survival advantage of surgery was observed in both the non-PSM cohort and the large PSM cohort. Our results showed that despite the aggressive

Table 1
Baseline Characteristics by Surgery before and after Propensity Score Matching.

Variable	Unmatched Cohort, No. (%) of Patients				Matched Cohort, No. (%) of Patients			
	Total (39,655)	None (38,449)	Surgery (1206)	P	Total (630)	None (315)	Surgery (315)	P
Age, years, mean ± SD	65.7 ± 10.8	65.8 ± 10.8	62.6 ± 10.4	**< 0.001**	65.6 ± 9.3	65.6 ± 9.5	65.6 ± 9.1	0.804
Sex				0.671				0.470
Male	21775 (54.9)	21,120 (54.9)	655 (54.3)		351 (55.7)	180 (57.1)	171 (54.3)	
Female	17880 (45.1)	17,329 (45.1)	551 (45.7)		279 (44.3)	135 (42.9)	144 (45.7)	
Race				**0.011**				0.529
White	30530 (77.0)	29,554 (76.9)	976 (80.9)		548 (87.0)	280 (88.9)	268 (85.1)	
Black	5224 (13.2)	5089 (13.2)	135 (11.2)		48 (7.6)	21 (6.7)	27 (8.6)	
Asian/Pacific Islander	3616 (9.1)	3527 (9.2)	89 (7.4)		30 (4.8)	12 (3.8)	18 (5.7)	
Other	285 (0.7)	279 (0.7)	6 (0.5)		4 (0.6)	2 (0.6)	2 (0.6)	
Insurance				0.083				0.176
Insured	31331 (79.0)	30,350 (78.9)	981 (81.3)		558 (88.6)	286 (90.8)	272 (86.4)	
Uninsured/Medicaid	7782 (19.6)	7568 (19.7)	214 (17.7)		68 (10.8)	28 (8.9)	40 (12.7)	
Unknown	542 (1.4)	531 (1.4)	11 (0.9)		4 (0.6)	1 (0.3)	3 (1.0)	
Marital Status				**< 0.001**				0.857
Married	20717 (52.2)	20,006 (52.0)	711 (59.0)		412 (65.4)	208 (66.0)	204 (64.8)	
Unmarried	17221 (43.4)	16,773 (43.6)	448 (37.2)		202 (32.1)	100 (31.8)	102 (32.4)	
Unknown	1717 (4.3)	1670 (4.3)	47 (3.9)		16 (2.5)	7 (2.2)	9 (2.9)	
Location				**< 0.001**				0.409
Lobe	32534 (82.0)	31,482 (81.9)	1052 (87.2)		552 (87.6)	281 (89.2)	271 (86.0)	
Bronchus	1751 (4.4)	1695 (4.4)	56 (4.6)		28 (4.4)	11 (3.5)	17 (5.4)	
Unknown	5370 (13.5)	5272 (13.7)	98 (8.1)		50 (8.0)	23 (7.3)	27 (8.6)	
Histologic Subtype				**< 0.001**				0.811
Adenocarcinoma	29406 (74.2)	28,530 (74.2)	876 (72.6)		481 (76.4)	237 (75.2)	244 (77.5)	
Squamous Cell Carcinoma	8380 (21.1)	8146 (21.2)	234 (19.4)		121 (19.2)	65 (20.6)	56 (17.8)	
Large Cell Carcinoma	1156 (2.9)	1102 (2.9)	54 (4.5)		21 (3.3)	10 (3.2)	11 (3.5)	
Adenosquamous Carcinoma	713 (1.8)	671 (1.8)	42 (3.5)		7 (1.1)	3 (1.0)	4 (1.3)	
Grade				**< 0.001**				0.141
Well	803 (2.0)	751 (2.0)	52 (4.3)		10 (1.6)	7 (2.2)	3 (1.0)	
Moderate	4842 (12.2)	4491 (11.7)	351 (29.1)		120 (19.1)	57 (18.1)	63 (20.0)	
Poor/Undifferentiated	10611 (26.8)	10,059 (26.2)	552 (45.8)		264 (41.9)	122 (38.7)	142 (45.1)	
Unknown	23399 (59.0)	23,148 (60.2)	251 (20.8)		236 (37.5)	129 (41.0)	107 (34.0)	
AJCC 7th, T Stage				**< 0.001**				0.862
T1	4396 (11.1)	4190 (10.9)	206 (17.1)		82 (13.0)	45 (14.3)	37 (11.8)	
T2	9960 (25.1)	9575 (24.9)	385 (31.9)		192 (30.5)	98 (31.1)	94 (29.8)	
T3	9258 (23.4)	8972 (23.3)	286 (23.7)		152 (24.1)	74 (23.5)	78 (24.8)	
T4	11624 (29.3)	11,343 (29.5)	281 (23.3)		168 (26.7)	81 (25.7)	87 (27.6)	
Tx	4417 (11.1)	4369 (11.4)	48 (4.0)		36 (5.7)	17 (5.4)	19 (6.0)	
AJCC 7th, N Stage				**< 0.001**				0.819
N0	8273 (20.9)	7768 (20.2)	505 (41.9)		167 (26.5)	86 (27.3)	81 (25.7)	
N1	3155 (8.0)	2997 (7.8)	158 (13.1)		47 (7.5)	23 (7.3)	24 (7.6)	
N2	17481 (44.1)	17,092 (44.5)	389 (32.3)		298 (47.3)	146 (46.4)	152 (48.3)	
N3	8788 (22.2)	8664 (22.5)	124 (10.3)		100 (15.9)	53 (16.8)	47 (14.9)	
Nx	1958 (4.9)	1928 (5.0)	30 (2.5)		18 (2.9)	7 (2.2)	11 (3.5)	
Extrathoracic Metastasis				**< 0.001**				0.376
Single-organ	23520 (59.3)	22,731 (59.1)	789 (65.4)		456 (72.4)	227 (72.1)	229 (72.7)	
Multiorgan	9340 (23.6)	9225 (24.0)	115 (9.5)		78 (12.4)	44 (14.0)	34 (10.8)	
Other	6795 (17.1)	6493 (16.9)	302 (25.0)		96 (15.2)	44 (14.0)	52 (16.5)	
Contralateral Lung Metastasis				**< 0.001**				0.668
No	28948 (73.0)	27,944 (72.7)	1004 (83.3)		503 (79.8)	255 (81.0)	248 (78.7)	
Yes	10064 (25.4)	9875 (25.7)	189 (15.7)		119 (18.9)	57 (18.1)	62 (19.7)	
Unknown	643 (1.6)	630 (1.6)	13 (1.1)		8 (1.3)	3 (1.0)	5 (1.6)	
Metastasectomy				**< 0.001**				0.611
No	35779 (90.2)	34,897 (90.8)	882 (73.1)		593 (94.1)	298 (94.6)	295 (93.7)	
Yes	3876 (9.8)	3552 (9.2)	324 (26.9)		37 (5.9)	17 (5.4)	20 (6.4)	

Note: Categoric variables were compared by using the Pearson X2 test, and continuous variables were compared by using the Mann-Whitney U test. Statistically significant P values are indicated by boldface.

nature, using primary tumor resection as a local tumor control strategy for lung cancer patients with distant metastatic disease seemed to result in prolonged survival. In addition, among different surgical procedures, lobectomy showed the greatest survival gain. Moreover, this study explored the relationship between the extent of extrathoracic metastases and the survival benefit of surgery, which to our knowledge was the first SEER-based study focusing on this specific issue. The result indicated that the subgroup of single extrathoracic metastatic site combined with other characteristics, such as early T stage, early N stage, was associated with more prominent survival gain. These findings drew a more detailed outline for clinicians to select stage IV extrathoracic metastatic NSCLC patients who would be more likely to be benefit from primary tumor resection.

Current practice guidelines have revised the recommendation of primary tumor resection to a considerable choice for patients with stage IV disease, especially for those with both limited extrathoracic metastatic disease and early-staged pulmonary tumors. However, the selection criteria for surgery are somewhat vague. In this study, we calculated the surgical recommendation and performance rates of patients with extrathoracic metastatic disease in the real world. Only 4.8% of the patients were recommended for surgery by their physician, and 3.0% eventually underwent primary tumor resection. Thus, although the guidelines have accepted surgery as a local control strategy for selected stage IV NSCLC patients, the actual surgical performance rate

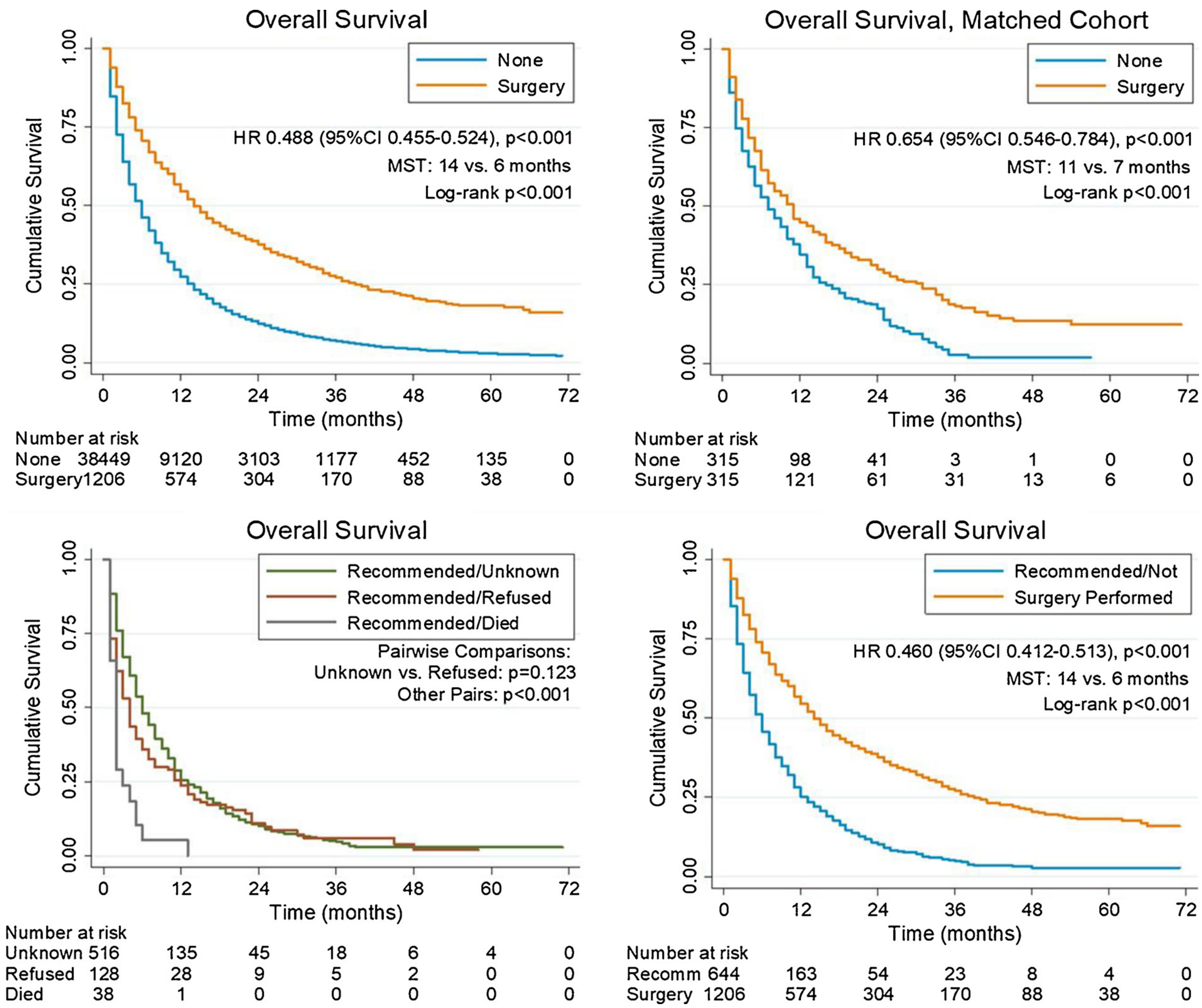

Fig. 2. OS stratified by surgery in the entire cohort before (A) and after (B) matching. OS stratified by reason for no surgery in the surgery-recommended nonsurgical cohort (C). OS stratified by surgery in the highly selected surgery-recommended cohort (D).

still remained low. Additionally, surprisingly, in contrast to the guidelines' recommendation, up to 58.2% of the patients who were recommended for surgery in the real world had primary tumors that were more advanced than T1-3, N0-1. These findings suggested that whether surgical intervention was performed in clinical practice likely mainly depended on an individual surgeon's judgement or the patient's consent, rather than the guidelines.

Though the reason why surgery was recommended for certain

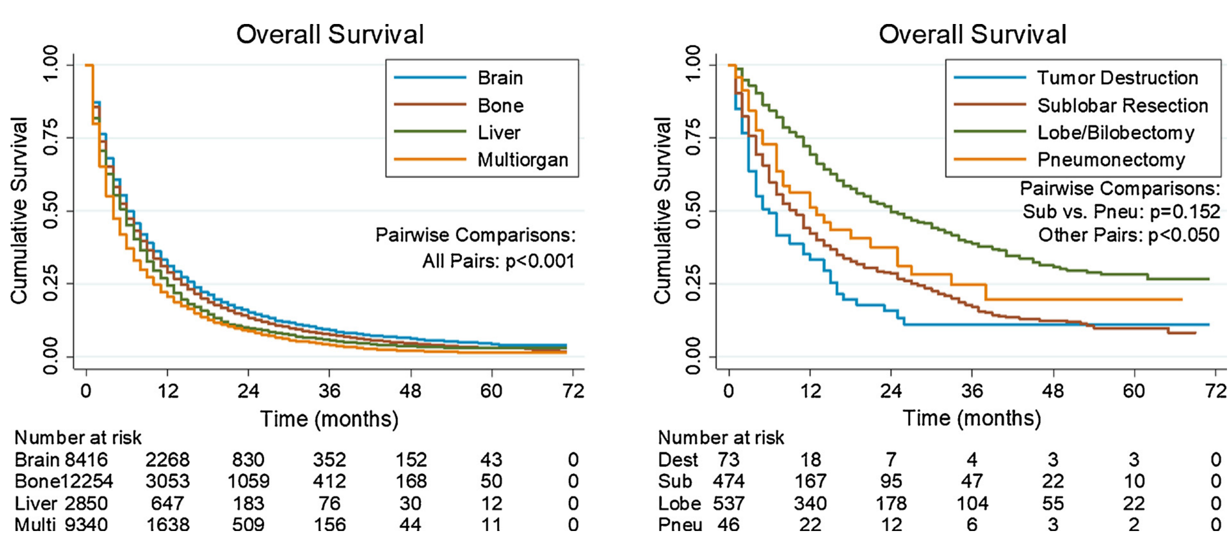

Fig. 3. OS stratified by metastatic site (A) and OS stratified by surgical type (B).

Table 2
Multivariate Cox Proportional Hazard Regression and Multivariate Competing Risks Regression.

Variable	The Entire Cohort (N = 39,655/N' = 39,219)										Surgery-Recommended Cohort (n = 1850/n' = 1833)									
	Overall Survival					Lung Cancer Specific Mortality					Overall Survival					Lung Cancer Specific Mortality				
	HR	95% CI			P	SHR	95% CI			P	HR	95% CI			P	SHR	95% CI			P
Age, per 1 year increased	1.018	1.017	to	1.019	< **0.001**	1.014	1.013	to	1.015	< **0.001**	1.022	1.016	to	1.028	< **0.001**	1.014	1.008	to	1.020	< **0.001**
Sex																				
Male	Reference					Reference					Reference					Reference				
Female	0.830	0.811	to	0.849	< **0.001**	0.861	0.842	to	0.880	< **0.001**	0.756	0.676	to	0.846	< **0.001**	0.786	0.702	to	0.880	< **0.001**
Race																				
White	Reference					Reference					Reference					Reference				
Black	1.011	0.979	to	1.045	0.497	0.988	0.956	to	1.022	0.492	0.966	0.827	to	1.128	0.659	0.913	0.771	to	1.081	0.291
Asian/Pacific Islander	0.683	0.656	to	0.712	< **0.001**	0.728	0.700	to	0.757	< **0.001**	0.553	0.426	to	0.718	< **0.001**	0.589	0.456	to	0.760	< **0.001**
Other	0.895	0.782	to	1.025	0.108	0.931	0.810	to	1.070	0.312	0.477	0.176	to	1.299	0.148	0.555	0.180	to	1.714	0.306
Insurance																				
Insured	Reference					Reference					Reference					Reference				
Uninsured/Medicaid	1.205	1.171	to	1.241	< **0.001**	1.138	1.105	to	1.172	< **0.001**	1.206	1.038	to	1.402	**0.014**	1.207	1.039	to	1.402	**0.014**
Unknown	1.114	1.014	to	1.224	**0.024**	1.097	0.998	to	1.206	0.055	1.020	0.734	to	1.417	0.908	1.124	0.813	to	1.554	0.481
Marital Status																				
Married	Reference					Reference					Reference					Reference				
Unmarried	1.168	1.141	to	1.195	< **0.001**	1.129	1.104	to	1.156	< **0.001**	1.132	1.007	to	1.274	**0.038**	1.089	0.966	to	1.227	0.163
Unknown	1.087	1.029	to	1.148	**0.003**	1.037	0.981	to	1.097	0.196	1.176	0.913	to	1.514	0.209	1.075	0.819	to	1.412	0.602
Location																				
Lobe	Reference					Reference					Reference					Reference				
Bronchus	1.154	1.095	to	1.217	< **0.001**	1.121	1.062	to	1.183	< **0.001**	1.035	0.807	to	1.328	0.785	1.129	0.884	to	1.442	0.330
Unknown	1.144	1.106	to	1.182	< **0.001**	1.124	1.087	to	1.163	< **0.001**	1.074	0.896	to	1.288	0.438	1.081	0.889	to	1.314	0.435
Histologic Subtype																				
Adenocarcinoma	Reference					Reference					Reference					Reference				
Squamous Cell Carcinoma	1.264	1.230	to	1.299	< **0.001**	1.208	1.175	to	1.242	< **0.001**	1.204	1.052	to	1.378	**0.007**	1.172	1.014	to	1.355	**0.032**
Large Cell Carcinoma	1.290	1.211	to	1.374	< **0.001**	1.295	1.219	to	1.377	< **0.001**	1.306	0.990	to	1.722	0.059	1.317	0.999	to	1.735	0.051
Adenosquamous Carcinoma	1.151	1.061	to	1.247	**0.001**	1.062	0.978	to	1.153	0.153	1.050	0.756	to	1.458	0.773	0.958	0.678	to	1.353	0.808
Grade																				
Well	Reference					Reference					Reference					Reference				
Moderate	1.120	1.029	to	1.219	**0.009**	1.123	1.036	to	1.216	**0.005**	1.411	1.013	to	1.966	**0.042**	1.401	1.006	to	1.951	**0.046**
Poor/Undifferentiated	1.355	1.249	to	1.470	< **0.001**	1.316	1.218	to	1.422	< **0.001**	1.822	1.318	to	2.517	< **0.001**	1.677	1.211	to	2.323	**0.002**
Unknown	1.267	1.169	to	1.373	< **0.001**	1.237	1.147	to	1.335	< **0.001**	1.676	1.208	to	2.324	**0.002**	1.699	1.222	to	2.364	**0.002**
AJCC 7th, T Stage																				
T1	Reference					Reference					Reference					Reference				
T2	1.137	1.092	to	1.184	< **0.001**	1.151	1.108	to	1.197	< **0.001**	1.072	0.898	to	1.281	0.441	1.134	0.954	to	1.346	0.153
T3	1.245	1.194	to	1.298	< **0.001**	1.223	1.175	to	1.274	< **0.001**	1.244	1.030	to	1.504	**0.024**	1.214	1.001	to	1.473	**0.049**
T4	1.227	1.178	to	1.279	< **0.001**	1.237	1.189	to	1.287	< **0.001**	1.328	1.099	to	1.604	**0.003**	1.307	1.077	to	1.587	**0.007**
Tx	1.247	1.187	to	1.309	< **0.001**	1.221	1.163	to	1.282	< **0.001**	1.196	0.923	to	1.549	0.176	1.034	0.779	to	1.374	0.817
AJCC 7th, N Stage																				
N0	Reference					Reference					Reference					Reference				
N1	1.052	1.005	to	1.101	**0.031**	1.030	0.984	to	1.077	0.205	1.397	1.159	to	1.684	< **0.001**	1.278	1.059	to	1.543	**0.011**
N2	1.150	1.117	to	1.185	< **0.001**	1.130	1.098	to	1.163	< **0.001**	1.510	1.319	to	1.729	< **0.001**	1.398	1.221	to	1.600	< **0.001**
N3	1.131	1.092	to	1.171	< **0.001**	1.113	1.076	to	1.151	< **0.001**	1.554	1.293	to	1.868	< **0.001**	1.413	1.165	to	1.713	< **0.001**
Nx	1.167	1.104	to	1.234	< **0.001**	1.124	1.060	to	1.191	< **0.001**	1.595	1.198	to	2.122	**0.001**	1.312	0.966	to	1.781	0.082
Extrathoracic Metastasis																				
Single-organ	Reference					Reference					Reference					Reference				
Multiorgan	1.329	1.294	to	1.365	< **0.001**	1.310	1.275	to	1.345	< **0.001**	1.527	1.295	to	1.802	< **0.001**	1.629	1.378	to	1.925	< **0.001**
Other	0.784	0.760	to	0.808	< **0.001**	0.795	0.772	to	0.819	< **0.001**	0.770	0.673	to	0.880	< **0.001**	0.815	0.707	to	0.939	**0.005**
Contralateral Lung Metastasis																				
No	Reference					Reference					Reference					Reference				
Yes	1.028	1.001		1.056	**0.040**	1.032	1.005		1.060	**0.020**	1.100	0.943	to	1.283	0.227	1.188	1.013	to	1.392	**0.034**

(*continued on next page*)

Table 2 (*continued*)

Variable	The Entire Cohort (N = 39,655/N' = 39,219)								Surgery-Recommended Cohort (n = 1850/n' = 1833)							
	Overall Survival				Lung Cancer Specific Mortality				Overall Survival				Lung Cancer Specific Mortality			
	HR	95% CI		P	SHR	95% CI		P	HR	95% CI		P	SHR	95% CI		P
Unknown	1.094	1.007	1.189	**0.034**	1.061	0.974	1.154	0.174	1.490	0.927 to	2.396	0.100	1.089	0.587 to	2.021	0.787
Metastasectomy																
No	Reference				Reference				Reference				Reference			
Yes	0.832	0.800 to	0.864	**< 0.001**	0.851	0.821 to	0.883	**< 0.001**	0.858	0.740 to	0.994	**0.041**	0.856	0.738 to	0.993	**0.040**
Primary Tumor Resection																
No	Reference				Reference				Reference				Reference			
Yes	0.597	0.555 to	0.642	**< 0.001**	0.614	0.573 to	0.657	**< 0.001**	0.620	0.546 to	0.704	**< 0.001**	0.642	0.565 to	0.731	**< 0.001**

Note: N(n) indicate patient number enrolled in the Cox Regression; N'(n') indicate patient number enrolled in the Competing Risks Regression. Statistically significant P values are indicated by boldface. Abbreviation: AJCC, American Joint Committee on Cancer; HR, hazard ratio; SHR, subhazard ratio.

patients in SEER database was untraceable, we held a rational speculation that clinicians followed their consistent criteria to choose patients who were suitable for surgery. These selected patients likely had good performance status and might have a good response after induction therapy. In the absence of these important preoperative data (e.g., performance status and concurrent systematic treatment), analyzing the survival outcome of the pure surgery-recommended cohort could further reduce confounding variables and thus provide more convincing evidence demonstrating the role of the surgery. We compared the survival of patients who underwent surgery (code 0) with patients who were recommended for surgery but did not receive it (code 5–7). Patients who died prior to the recommended surgery (code 5) were excluded, since when compared with this cohort, patients who underwent surgery would be guaranteed to have a more favorable survival not resulting from the effect of surgery but rather from the inclusion of extra waiting time for resection (immortal time bias). The survival of patients who underwent primary tumor resection was significantly better than those who were just recommended for it. This result confirmed that surgical removal of the primary tumor provided better survival in patients with extrathoracic metastases. Multivariate regressions adjusting for baseline covariates were also established to evaluate if surgery was still a significant favorable predictor for survival in this highly selected surgery-recommended cohort, and the result was the same.

The extent of distant metastatic disease has been considered as a key factor when determining whether primary tumor resection should be performed. In clinical practice, the extent of extrathoracic metastatic disease has usually been estimated by counting the number of metastatic organs or the number of metastatic lesions. Escuín reported that both the number of metastatic lesions and the number of metastatic sites were prognostic factors for survival in patients with extrathoracic metastases, while Eberhardt et al. reported that it was the number of metastatic lesions that played the important role in predicting patients' survival. However, the prognostic value of the number of metastatic sites or lesions has not been verified in extrathoracic metastatic NSCLC patients who were treated with surgery. Limited data from retrospective series have suggested that oligometastatic NSCLC patients could achieve prolonged survival after definitive treatment of the primary tumor [14,15]. Unfortunately, the specific inclusion criteria of oligometastatic patients varied from study to study, which failed to reach a consensus in the selection of patients who could benefit from surgery. The SEER database collected distant organ involvement information, including brain, bone, and liver, at the time of lung cancer diagnosis, accounting for approximately 80% of all distant metastases [16]. Although the number of metastatic lesions was not accessible, analyzing the now available data may provide a better interpretation of the impact of metastatic organ distribution on survival after surgery. According to our result from the SEER database, we believe that the number of metastatic organs was one of the potential determinants implying the survival gain after surgery. Fewer distant organ metastases might be an indication of surgery for extrathoracic metastatic NSCLC patients.

Regarding the extrathoracic metastatic status, we evaluated the prognostic effect of metastatic site in patients who underwent primary tumor resection. For patients with solitary brain, liver, or bone metastasis, no significant survival difference was observed after surgery among patients with different metastatic organs. For all of the patients who received surgical resection of the primary tumor, regardless of the presence of a single-organ metastasis or multiorgan metastases involving 2 to 3 organs of the brain, liver, or bone, a prolonged survival was observed compared with those treated without surgery. To elaborate the relationship between the number of metastatic organs and the survival benefit from surgery, we further stratified the patients by the specific number of metastatic organs. The result demonstrated that surgical intervention was associated with the most prominent survival gain in patients with single-organ metastasis, while no association

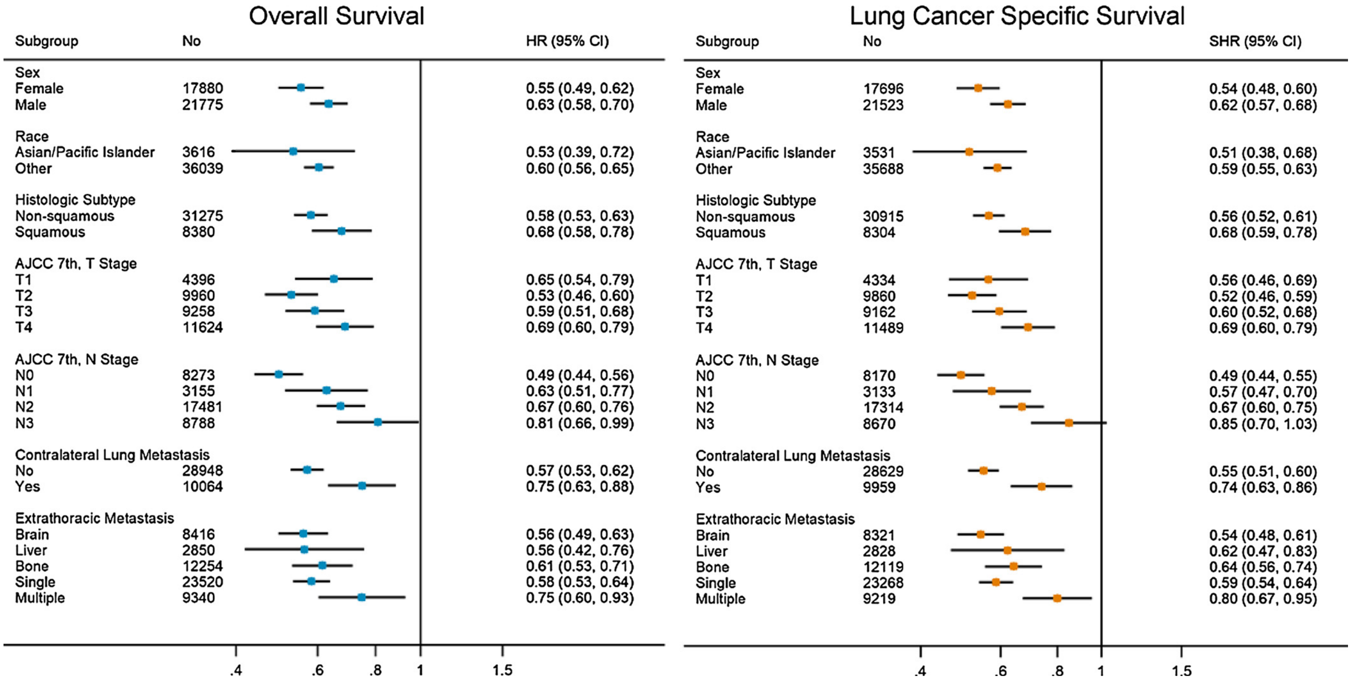

Fig. 4. Adjusted multivariate regression comparing surgery versus no surgery for OS (A) and LCSS (B) in different patient subgroups stratified by sex, race, histologic subtype, T/N descriptor, contralateral lung metastasis, and extrathoracic metastatic site.

between surgery and prolonged survival was observed in patients with three organ metastases (see Figure, Supplemental Data 3, which demonstrates subgroup analysis stratified by the number of metastatic organs). This finding implied that the number of metastatic organs might be more prognostic than the metastatic site itself when determining the survival benefit from surgery.

Moreover, in terms of the primary pulmonary tumor, our study showed that surgery might be associated with a more prominent survival benefit in patients with lower T and N stage. This result was similar to an NCDB study published by Yang and colleagues that identified the prognostic factors of stage IV NSCLC patients treated with primary tumor resection [17]. They found that surgery for cT1-2, N0-1, M1, and cT3, N0, or M1 disease (n = 1761) was associated with an outstanding 5-year survival of 25% [17]. This result roughly depicted the patients' characteristics that were associated with a promising survival outcome after surgery. However, in their study, nonsurgical cohorts were not included, and patients with M1a and M1b disease were not separately analyzed. Additionally, the extent of metastatic disease was unavailable in the NCDB database. Thus, by using the newly released SEER data, we could provide a more accurate analysis regarding the prognostic value of primary tumor resection in patients with extrathoracic metastatic disease.

From the surgical standpoint, the effect of primary tumor resection in patients with metastatic disease had been better assessed in other types of cancer. For colorectal cancer, a population-based study on patients with incurable stage IV disease demonstrated that palliative primary tumor resection is associated with better overall and cancer-specific survival than no resection [18]. Furthermore, new chemotherapy regimens and monoclonal antibody immunotherapies have significantly improved the response rate of advanced colon cancer; thus, the complete surgical removal of primary tumors and metastatic lesions is becoming increasingly feasible. Conversion therapy become acceptable for unresectable colon cancer and has been adopted as radical resection after induction therapy [19–21]. Removal of the primary tumor has also been verified by randomized trials in metastatic renal carcinoma, and compared with interferon treatment alone, nephrectomy followed by interferon therapy significantly improved OS [22,23]. Although the tumor biological features and therapeutic approaches are different between lung cancer and other cancers, substantial survival improvements, which have been observed in colorectal cancer, have also been achieved in patients with lung cancer due to the availability of new chemotherapy and targeted therapy agents. However, reports on salvage surgery or conversion surgery for lung cancer are extremely rare, which could be associated with the fact that few advanced lung cancer patients have symptomatic disease that requires palliative resection of the primary tumor. In view of the absence of high-level evidence, the SEER database provided real-world data that may carry weight in the way toward understanding the impact of primary tumor removal in advanced cancer. A prospective trial is indicated to validate these findings.

Nevertheless, this study has several limitations. First, selection bias was inevitable, although we performed PSM to balance the baseline characteristics in the surgical and nonsurgical groups. Potential confounding factors that were not captured in the SEER database, such as physical performance status and comorbidities index, could still cause selection bias in the analysis. Second, information on local therapies other than surgery (e.g., definitive radiation therapy) was unavailable. Comparison between radiation therapy and surgical resection of primary tumor may be very helpful for understanding the impact of local tumor control in the presence of extensive disease. Although the SEER database does include information regarding whether patients underwent radiation therapy in the first course of treatment, the specific radiation site was not provided in the database. Therefore, whether the radiation therapy was targeted to primary tumors or metastatic sites was unclear. Third, detailed information of multimodal management other than surgery was quite limited in the SEER database. We were unable to evaluate the effect of systemic therapies on survival. In addition, although the term "cancer-directed surgery" was defined in the SEER database, the goal of the surgery was not defined. Therefore, the intervention time of surgery in the multimodality management processing remained unexplored in this study. In addition, only the site of metastatic distribution was roughly collected in the SEER database; the number of metastatic lesions was not available. Therefore, it was impossible to define the oligometastatic status of the patients in this study. Findings in this study were incomparable with previous reports focusing on patients with oligometastatic disease. Finally, we should state that what we found in this study was the association but not the causal inference between surgical intervention and prolonged survival in patients with extrathoracic metastatic NSCLC. Thus, results should be interpreted with caution in the study. Rigorous clinical studies, such as randomized controlled trails, are required to prove the causal effect between surgery and survival in patients with stage IV NSCLC.

In conclusion, this real-world study found that compared with nonsurgical treatment, primary tumor resection was associated with improved survival in patients with extrathoracic metastatic NSCLC, particularly for those with single-organ metastasis. Patients underwent lobe or bilobectomy were associated with the best survival among the surgical cohort.

CONFLICTS OF INTEREST STATEMENT

All authors declare that they have no conflict of interest regarding this study.

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Appendix A. Supplementary data

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