Original Article

Optimal therapeutic strategy for non-small cell lung cancer with thoracic extrathoracic metastasis: a study based on SEER database

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Background: Non-small cell lung cancer (NSCLC) patients with extrathoracic metastasis (EM) are a highly heterogeneous cohort. Some of these patients could benefit from primary tumor surgery. This study aimed to identify potential NSCLC patients with EM suitable for primary tumor resection and to determine the optimal therapeutic strategy.

Methods: NSCLC patients with EM were extracted from the Surveillance, Epidemiology and End Results database between 2010 and 2015. They were stratified into subgroups with single and multi-EMs. Cox regression analysis was adopted to identify prognostic factors for overall survival (OS). The Kaplan-Meier method was used to compare the OS among patients who received different treatment modalities.

Results: The univariate Cox regression analysis demonstrated that advanced age, male sex, race (black), married status, squamous cell carcinoma, higher histological grade, advanced T or N stage, contralateral lung metastasis, multi-EMs, tumor size >2 cm, and lack of treatment were associated with poorer OS in patients with NSCLC (P<0.05). Multivariate Cox regression analysis revealed that the number of EM and treatment modalities were independent prognostic factors affecting OS (P<0.001). For patients with single EM, those who did not receive treatment and those who underwent single-agent chemotherapy, single-agent surgery, surgery combined with chemotherapy, surgery combined with radiotherapy, or surgery combined with chemoradiotherapy had median OS times of 3.0, 11.0, 12.0, 26.0, 11.0, and 25.0 months, respectively. Compared to monotherapy, combination therapy showed significant benefits for patients with single EM in NSCLC. Furthermore, patients with single EM who underwent lobectomy, bilobectomy, or pneumonectomy had significantly longer survival than those who underwent sublobar resection, even when the primary tumor size was ≤2 cm (P=0.04).

Conclusions: Primary tumor surgery could benefit NSCLC patients with single EM; lobectomy was at least warranted to improve survival even for primary tumors with size ≤2 cm.

Keywords: Lobectomy; sublobar resection; advanced non-small cell lung cancer (advanced NSCLC); single extrathoracic metastasis (single EM); multiple extrathoracic metastases

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Introduction

Lung cancer is the leading cause of cancer-related mortality, with non-small cell lung cancer (NSCLC) accounting for approximately 80–90% of all cases (1). Nearly 55% of NSCLC patients have extrathoracic metastasis (EM) at initial diagnosis, which is more common in young patients (2). Despite the evolution of systemic treatment for advanced NSCLC, survival remains dismal. Surgical resection is the cornerstone of cancer treatment, but the use of pneumonectomy for metastatic NSCLC has decreased over the decades (3). Radiation therapy is a non-invasive treatment method that has been used for local treatment of lung cancer since the early 20th century (4). Local ablative therapy can benefit patients with limited metastases, especially those with low-volume metastases (5,6).

The definition of oligometastasis remains nonuniform, where the total number of eligible metastases ranges from one to eight (7). Besides, the number of organs involved and the maximum number of metastases per organ are unclear. This ambiguous definition impedes precisely selecting patients with metastatic NSCLC who could benefit from aggressive treatments such as pneumonectomy. According to a consensus published by the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group, oligometastasis is defined as a maximum of five metastases and involvement of three organs (8). Although prospective clinical trials have confirmed that local consolidative therapy to all disease sites can prolong the survival of NSCLC patients with limited metastases, studies have barely included patients who receive surgical resection for primary sites (9,10). Patients with metastatic NSCLC may have a better chance of survival if they undergo primary tumor resection. In recent years, significant advancements in diagnostic imaging technologies have substantially increased the detection rate of tumors. Coupled with the emergence of targeted therapies such as anti-epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), the survival rates of patients with metastatic diseases have improved. More and more patients are experiencing metastasis in only a few locations, leading to an overall improvement in long-term prognosis (11). However, to avoid overtreatment, it is necessary to further select appropriate candidates (12-14). The choice of treatment method requires careful consideration of various factors, including the patient's overall health, tumor staging, and available treatment options (15,16).

A multicenter phase II randomized study has shown that local consolidative therapy, either radical radiotherapy or surgical treatment aimed at controlling all known sites of disease, improves overall survival (OS) in patients with oligometastatic NSCLC who have not progressed after first-line systemic therapy (4). Despite the availability of various anticancer strategies for treating NSCLC such as surgery, chemotherapy, and radiation therapy being available, there is still an urgent need for effective approaches to control NSCLC, especially in advanced or NSCLC with EM patients (17). Furthermore, the scope of pneumonectomy remains to be determined, apart from identifying metastatic NSCLC patients who are suitable for surgical resection. The survival rates for early-stage NSCLC, segmentectomy, or sublobar resection are similar to lobectomy (18,19). Whether this finding applies to the pneumonectomy in advanced NSCLC needs reassessment because advanced tumors are more likely to have occult micrometastases, necessitating a larger resection margin (20,21). Therefore, in this study, we aim to determine if patients with NSCLC and EM can benefit from primary tumor resection and to identify the optimal treatment modalities within this cohort, which holds significant implications for the survival benefits of NSCLC patients with EM. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-516/rc).

Highlight box

Key findings

- Primary tumor surgery can benefit non-small cell lung cancer (NSCLC) patients with single extrathoracic metastasis (EM); lobectomy is at least warranted to improve survival even for primary tumors with size ≤2 cm.

What is known and what is new?

- Surgical resection of the primary tumor has the potential to benefit patients with NSCLC and EM.
- Only NSCLC patients with single EM can benefit from primary tumor surgery; lobectomy is at least warranted to improve survival in NSCLC patients with single EM.

What is the implication, and what should change now?

- Patients with NSCLC who have single EM should undergo primary tumor surgery, which should be at least a lobectomy if physically possible.

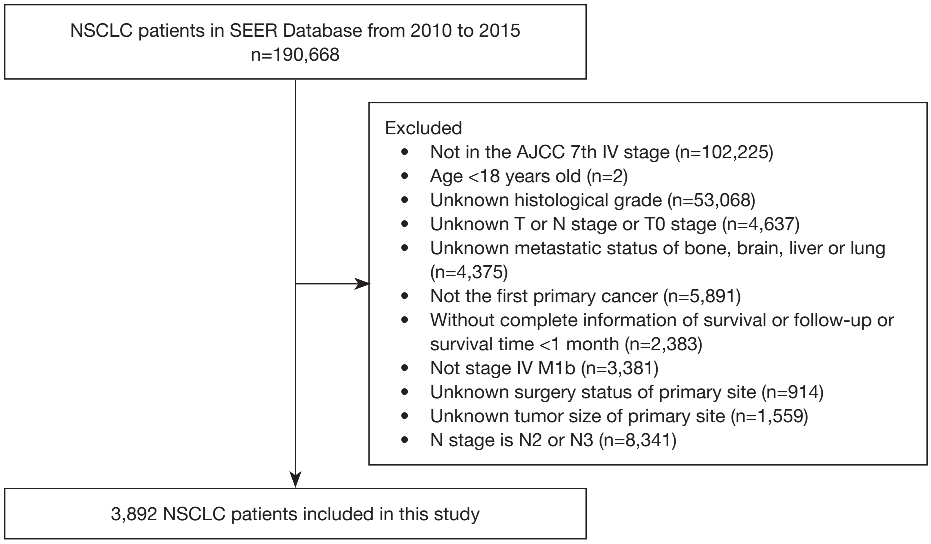

Figure 1 The flowchart of NSCLC patients enrolled in this study. NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

Methods

Case selection and subgroup classification

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients with NSCLC were identified in the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015, which covers approximately 28% of the US population (22). The main exclusion criteria were as follows: (I) with disease other than IV stage; (II) with unknown T or T0 stage; (III) with N2 and N3 lymph nodes; (IV) with unknown metastatic status of bone, brain, liver, or lung; (V) not in American Joint Committee on Cancer (AJCC) 7th stage IV M1b; (VI) with unknown surgery status of the primary site; or (VII) with unknown tumor size of the primary site. The details of the screening processes are presented in *Figure 1*.

We extracted demographic and clinicopathological data from eligible patients, including age, sex, race, marital status, histologic type and grade, T and N stages, metastatic sites, treatment modalities, and the tumor size of the primary site. Patients were divided into subgroups according to the number of EMs (single-EM *vs.* multi-EMs), which has been identified as the prognostic factor for metastatic NSCLC patients (23). The types of lung surgery included local tumor destruction, sublobar resection, lobectomy, bilobectomy, and pneumonectomy. The above operation modes were further classified into two categories based on the extent of surgery. The SEER data had been de-identified and publicly available for research purposes, so the study was exempt from approval by local research ethics committees.

Statistical analysis

The Chi-square test was adopted to compare patients' demographic and clinicopathological characteristics with single and multi-EMs. Univariate and multivariate Cox regression analyses were performed to identify significant prognostic factors for OS. Kaplan-Meier method with log-rank test was used to compare OS among patients with different treatment modalities stratified by the number of EMs. The statistical analyses and survival curve plotting were performed with IBM SPSS, version 26.0, and the R software, version 3.5.0. The significant difference was set at a two-sided P value less than 0.05.

Results

Baseline characteristics

This study included 3,892 eligible NSCLC patients with NSCLC EM lesions. Among them, 3,316 patients had single EM, and 576 patients had multi-EMs. There were no significant differences between the two groups in terms of sex, age, and race (P=0.167, P=0.204, P=0.337). Multi-EMs were more common in adenocarcinoma than in squamous cell carcinoma (P<0.001). There was no statistically significant association between the number of EM lesions and histological grade (P=0.885). As expected, patients with multi-EMs had higher T and N stages than those with single EM (P=0.011 and P=0.017). Moreover, patients with multi-EMs were more likely to develop bone metastases, brain metastases, liver metastases, and contralateral lung metastases (P<0.001). Regarding treatment modalities, patients with single EM were more likely to receive primary site surgical treatment (P<0.001). In comparison, patients with multi-EMs were more likely to receive radiation therapy (P=0.009). Please refer to *Table 1* for more information. The baseline characteristics of different treatment strategies, including chemotherapy, surgery, surgery + chemotherapy, surgery + radiotherapy, and surgery + chemoradiotherapy, are detailed in Table S1.

Univariate and multivariate analyses

The results of univariate and multivariate analyses are shown in *Table 2*. Univariate analysis revealed that age, male sex, race (black), married status, squamous cell carcinoma, higher histological grade, advanced T or N stage, contralateral lung metastasis, multi-EMs, tumor size >2 cm, and lack of treatment were all associated with lower survival rates (P<0.05). Multivariate Cox regression analysis demonstrated that the number of EM and treatment modalities (surgery and chemotherapy) were independent prognostic factors influencing OS (P<0.001).

Association of treatment modality and number of EMs with survival

The survival curves for NSCLC patients are shown in *Figures 2,3*. As indicated in the graphs, patients with single EM had significantly longer median survival compared to those with multi-EMs (8.0 *vs.* 4.0 months, P<0.0001) (*Figure 2A*). Regarding treatment modalities, the median OS times for patients who received no treatment, chemotherapy, surgery, and surgery + chemotherapy were 3.0, 10.0, 11.5, and 26.0 months, respectively (*Figure 2B*). Due to the greater benefit observed in patients with single EM, we conducted an analysis specifically for patients with single EM. The median OS times for patients who received no treatment, chemotherapy alone, surgery alone, and surgery combined with chemotherapy were 3.0, 11.0, 12.0, and 26.0 months, respectively (*Figure 2C*). Similar to the surgery + chemotherapy grouping mentioned above, the survival outcomes for all patients and those with single EM for surgery + radiotherapy, and surgery + chemoradiotherapy are shown in *Figure 3*. The median survival times for surgery + chemotherapy, surgery + radiotherapy, and surgery + chemoradiotherapy in patients with multi-EMs are shown in Figure S1. The patient population is smaller, resulting in poorer survival curve outcomes. Kaplan-Meier curve analysis (log-rank test) of different treatment modalities indicates a significant benefit of combined treatment for NSCLC patients with single EM compared to monotherapy. However, there was no significant extension in OS for patients with multi-EMs compared to monotherapy (Table S2).

Impacts of operation modes on survival

Although surgery at the primary site can improve the survival rates of NSCLC patients with single EM, the optimal surgical approach must be evaluated. We categorized surgical types into two groups: local tumor destruction/sublobar resection and lobectomy/bilobectomy/pneumonectomy. Survival rates were further compared among different surgical approaches based on the primary tumor size. For patients with tumors >2 cm, those who underwent local tumor destruction/sublobar resection had significantly lower survival rates than those who underwent lobectomy/bilobectomy/pneumonectomy (P<0.0001) (*Figure 4A*). This finding was similar among patients with tumors ≤2 cm (P=0.04) (*Figure 4B*).

Discussion

This study evaluated the survival benefits of different treatment modalities for NSCLC patients with EM, especially the impacts of primary tumor surgery. We found that only patients with single EM could benefit from surgery for primary sites, with no significant survival benefits for patients with multi-EMs. Furthermore, we compared the prognostic impact of different operation modes on single EM patients with different primary tumor sizes. Unlike early-stage NSCLC, sublobar resection was insufficient in metastatic NSCLC, even for primary tumors with sizes ≤2 cm. This study systematically identified potentially metastatic NSCLC patients with invasive pulmonary lesions who were suitable for surgical intervention and evaluated the optimal treatment strategy for these patients. Our findings contribute to the rational expansion of indications for total pneumonectomy in advanced NSCLC patients

Table 1 Baseline characteristics

Characteristics	The whole cohort, n (%)	Single extrathoracic metastasis, n (%)	Multiple extrathoracic metastasis, n (%)	P value
Sample size	3,892	3,316	576	–
Age (years)				0.204
≤60	1,070 (27.5)	907 (27.4)	163 (28.3)	
61–75	1,898 (48.8)	1,605 (48.4)	293 (50.9)	
>75	924 (23.7)	804 (24.2)	120 (20.8)	
Sex				0.167
Male	2,167 (55.7)	1,862 (56.2)	305 (53.0)	
Female	1,725 (44.3)	1,454 (43.8)	271 (47.0)	
Race				0.337
White	3,095 (79.5)	2,641 (79.6)	454 (78.8)	
Black	457 (11.7)	394 (11.9)	63 (10.9)	
Other	340 (8.7)	281 (8.5)	59 (10.2)	
Marital status				0.008
Unmarried	1,849 (47.5)	1,605 (48.4)	244 (42.4)	
Married	2,043 (52.5)	1,711 (51.6)	332 (57.6)	
Histologic type				<0.001
Adenocarcinoma	2,398 (61.6)	2,009 (60.6)	389 (67.5)	
Squamous cell carcinoma	916 (23.5)	823 (24.8)	93 (16.1)	
Others	578 (14.9)	484 (14.6)	94 (16.3)	
Histologic grade				0.885
Well, I	200 (5.1)	170 (5.1)	30 (5.2)	
Moderate, II	1,138 (29.2)	970 (29.3)	168 (29.2)	
Poor, III	2,470 (63.5)	2,107 (63.5)	363 (63.0)	
Undifferentiated, IV	84 (2.2)	69 (2.1)	15 (2.6)	
T stage				0.011
T1	579 (14.9)	509 (15.3)	70 (12.2)	
T2	1,362 (35.0)	1,176 (35.5)	186 (32.3)	
T3	1,012 (26.0)	858 (25.9)	154 (26.7)	
T4	939 (24.1)	773 (23.3)	166 (28.8)	
N stage				0.017
N0	2,735 (70.3)	2,355 (71.0)	380 (66.0)	
N1	1,157 (29.7)	961 (29.0)	196 (34.0)	
Bone metastasis				<0.001
No	2,217 (57.0)	2,159 (65.1)	58 (10.1)	
Yes	1,675 (43.0)	1,157 (34.9)	518 (89.9)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	The whole cohort, n (%)	Single extrathoracic metastasis, n (%)	Multiple extrathoracic metastasis, n (%)	P value
Brain metastasis				<0.001
No	2,301 (59.1)	2,107 (63.5)	194 (33.7)	
Yes	1,591 (40.9)	1,209 (36.5)	382 (66.3)	
Liver metastasis				<0.001
No	3,292 (84.6)	3,030 (91.4)	262 (45.5)	
Yes	600 (15.4)	286 (8.6)	314 (54.5)	
Contralateral lung metastasis				<0.001
No	3,194 (82.1)	2,782 (83.9)	412 (71.5)	
Yes	698 (17.9)	534 (16.1)	164 (28.5)	
Tumor size of primary site				0.059
≤2 cm	385 (9.9)	341 (10.3)	44 (7.6)	
>2 cm	3,507 (90.1)	2,975 (89.7)	532 (92.4)	
Surgery for primary site				<0.001
No	3,470 (89.2)	2,909 (87.7)	561 (97.4)	
Yes	422 (10.8)	407 (12.3)	15 (2.6)	
Radiotherapy				0.009
No	1,594 (41.0)	1,387 (41.8)	207 (35.9)	
Yes	2,298 (59.0)	1,929 (58.2)	369 (64.1)	
Chemotherapy				0.87
No	1,640 (42.1)	1,395 (42.1)	245 (42.5)	
Yes	2,252 (57.9)	1,921 (57.9)	331 (57.5)	

Table 2 Univariate and multivariate Cox regression analyses

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
≤60	Ref		Ref	
61–75	1.211 (1.12–1.31)	<0.001	1.144 (1.056–1.239)	0.001
>75	1.651 (1.507–1.808)	<0.001	1.302 (1.183–1.432)	<0.001
Sex				
Male	Ref		Ref	
Female	0.839 (0.786–0.896)	<0.001	0.832 (0.778–0.89)	<0.001
Race				
White	Ref		Ref	
Black	1.105 (0.999–1.221)	0.052	0.951 (0.858–1.053)	0.335
Other	0.761 (0.675–0.857)	<0.001	0.775 (0.687–0.875)	<0.001

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Marital status				
Married	Ref		Ref	
Unmarried	0.815 (0.764–0.87)	<0.001	0.882 (0.824–0.943)	<0.001
Histologic type				
Adenocarcinoma	Ref		Ref	
Squamous cell carcinoma	1.335 (1.235–1.444)	<0.001	1.139 (1.05–1.236)	0.002
Others	1.247 (1.135–1.371)	<0.001	1.116 (1.012–1.231)	0.029
Grade				
Well, I	Ref		Ref	
Moderate, II	1.09 (0.931–1.276)	0.285	1.229 (1.046–1.445)	0.012
Poor, III	1.406 (1.208–1.635)	<0.001	1.525 (1.307–1.779)	<0.001
Undifferentiated, IV	1.654 (1.274–2.147)	<0.001	1.71 (1.312–2.229)	<0.001
T stage				
T1	Ref		Ref	
T2	1.321 (1.193–1.464)	<0.001	1.262 (1.129–1.411)	<0.001
T3	1.478 (1.328–1.645)	<0.001	1.422 (1.266–1.598)	<0.001
T4	1.511 (1.356–1.685)	<0.001	1.394 (1.238–1.57)	<0.001
N stage				
N0	Ref		Ref	
N1	1.117 (1.041–1.199)	0.002	1.111 (1.034–1.195)	0.004
Contralateral lung metastasis				
No	Ref		Ref	
Yes	1.205 (1.108–1.311)	<0.001	1.047 (0.957–1.145)	0.318
Extrathoracic metastasis				
Single site	Ref		Ref	
Multiple site	1.447 (1.322–1.584)	<0.001	1.449 (1.321–1.589)	<0.001
Tumor size				
≤2 cm	Ref		Ref	
>2 cm	1.391 (1.244–1.556)	<0.001	1.042 (0.921–1.179)	0.516
Surgery				
No	Ref		Ref	
Yes	0.43 (0.383–0.483)	<0.001	0.45 (0.4–0.508)	<0.001
Radiotherapy				
No	Ref		Ref	
Yes	0.897 (0.84–0.958)	0.001	0.954 (0.891–1.021)	0.172
Chemotherapy				
No	Ref		Ref	
Yes	0.494 (0.462–0.528)	<0.001	0.474 (0.442–0.508)	<0.001

HR, hazard ratio; CI, confidence interval.

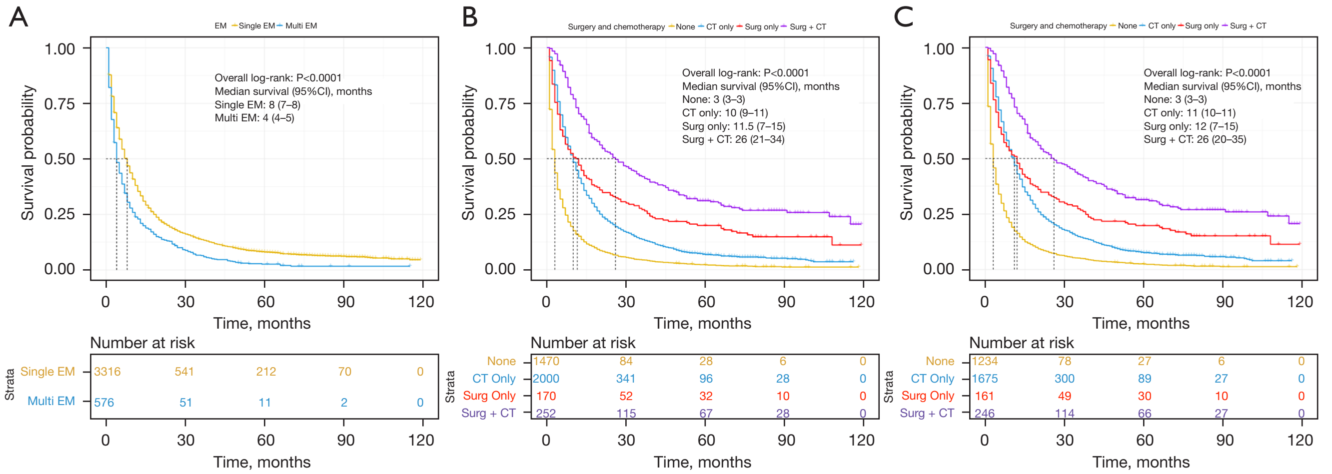

Figure 2 Kaplan-Meier survival analysis curves for non-small cell lung cancer patients. (A) Survival analysis for all patients based on the number of EM. (B) Survival analysis for all patients based on surgery combined with chemotherapy. (C) Survival analysis for patients with single EM based on surgery combined with chemotherapy. EM, extrathoracic metastasis; CI, confidence interval; Multi-EM, multiple EM; None, no surgery or chemotherapy or radiotherapy was performed; CT only, chemotherapy only; Surg only, only to have surgery; Surg + CT, surgery combined with chemotherapy.

while avoiding overtreatment.

Consistent with previous studies, surgical resection can prolong the survival of patients with metastatic NSCLC (24,25). Yang *et al.* reported that the median OS was 18 months in patients with M1 NSCLC treated with surgery (24). Surgery could prolong the survival time of NSCLC patients with EM by eight months (25). These studies, however, did not specify whether primary or metastatic sites were treated with resection. Moreover, they did not stratify these heterogenous patients according to the number of metastatic lesions and sites, which are vital predictors for the survival of advanced NSCLC patients (26). Although surgical resection was beneficial for NSCLC patients with oligometastasis, the definition of oligometastasis varies, making the selection of optimal candidates for surgery difficult (7). It has been reported that only 4.8% of extrathoracic metastatic NSCLC patients are recommended for primary tumor resection, with only 3.0% undergoing surgery, indicating an urgent need to precisely identify the metastatic patients suitable for primary tumor resection and optimize current clinical guidelines (26). According to our results, NSCLC patients with single EM could benefit from primary tumor surgery, while those with multi-EMs could not. Although the SEER database only gathered information on bone, brain, liver, and lung metastases, these account for approximately 80% of NSCLC metastases (27). In addition, it has been reported that both the number of metastatic lesions and sites affect survival, but the former has a more significant impact (26). Our results further confirmed that the number of metastatic sites was a powerful predictor for the prognosis and the indication for primary site surgery. It can be inferred that patients with fewer metastases may benefit more from primary tumor surgery.

The median survival times of patients with single EM or multi-EMs who received primary tumor surgery were 16.0 and 7.0 months, respectively. These survival data were comparable to the prognosis reported by Sun *et al.*, and they also found that single-organ metastasis was a significant indicator for primary tumor surgery (26). However, they did not evaluate the impacts of different surgical modes on metastatic NSCLC patients with different primary tumor sizes. Lobectomy has been the standard treatment for early-stage NSCLC. It has been reported that sublobar resection can achieve comparable survival to lobectomy in peripheral stage IA NSCLC ≤2 cm (18). Whether this finding is suitable for primary tumor resection in metastatic NSCLC has been barely studied. Lymph node metastasis is more common in advanced NSCLC than in early-stage NSCLC. Even in stage I NSCLC, the incidence of lymph node metastasis can reach 5–15%, and after adequate dissection, the positive rate may exceed 20% (28-30). Besides, primary sites of advanced tumors have a higher possibility for occult micrometastasis than early-stage ones, necessitating a wider excision range (20,21). Kneuertz *et al.* found that lobectomy

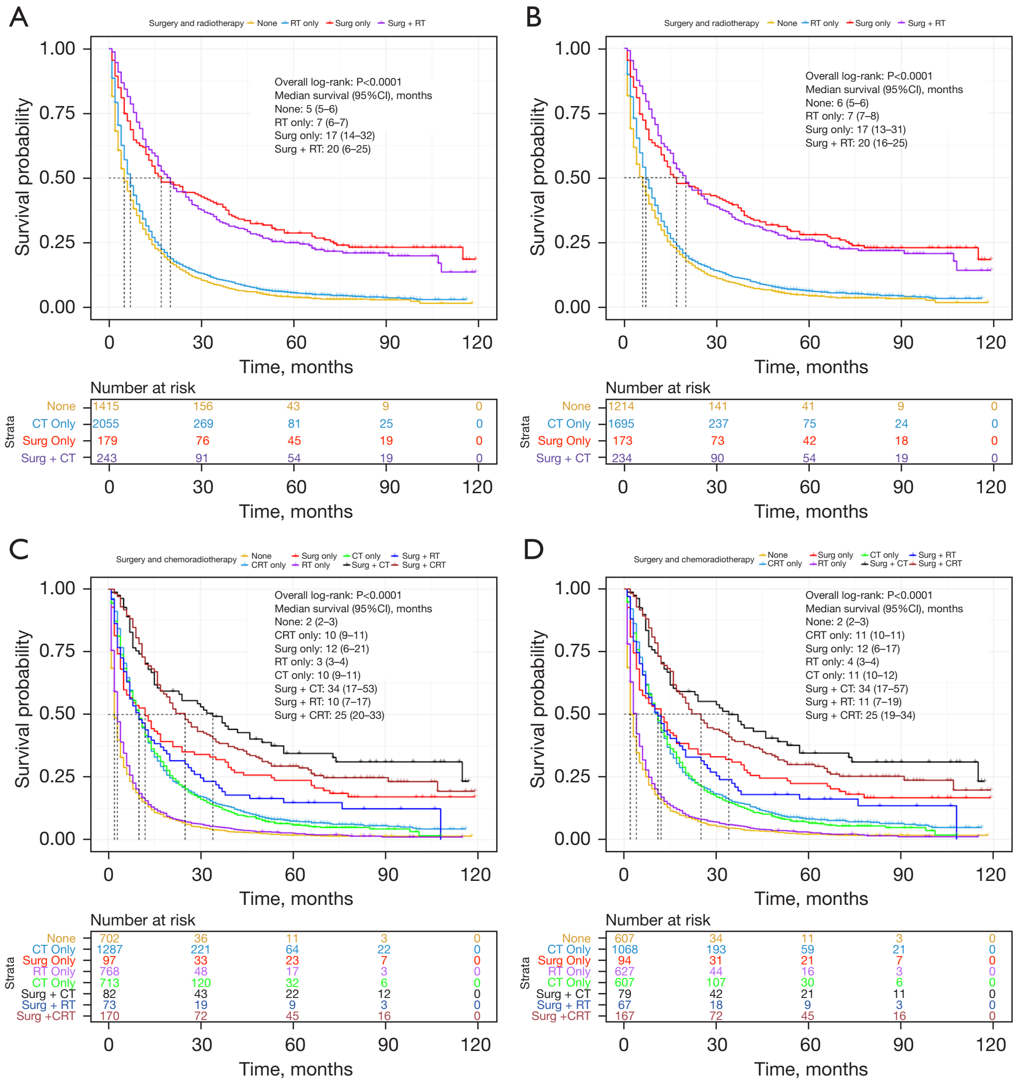

Figure 3 Kaplan-Meier survival analysis curves for non-small cell lung cancer patients. (A) Survival analysis for all patients based on surgery combined with radiotherapy. (B) Survival analysis for patients with single EM based on surgery combined with radiotherapy. (C) Survival analysis for all patients based on surgery combined with chemoradiotherapy. (D) Survival analysis for patients with EM based on surgery combined with chemoradiotherapy. EM, extrathoracic metastasis; CI, confidence interval; None, no surgery or chemotherapy or radiotherapy was performed; RT only, radiotherapy only; Surg only, only to have surgery; Surg + RT, surgery combined with radiotherapy; CT only, chemotherapy only; CRT only, chemotherapy combined with radiotherapy only; Surg + CRT, surgery combined with radiotherapy and chemotherapy; Surg + CT, surgery combined with chemotherapy.

may provide more survival benefits to stage IA NSCLC patients with occult lymph node metastasis than wedge resection (31). However, Ding *et al.* conducted a propensity matching analysis using data from the SEER database on patients who underwent cuneiform resection or lobectomy for small-sized (≤2 cm) NSCLC, and found that cuneiform resection combined with full lymphadenectomy had similar survival outcomes as lobectomy (32). While mediastinal lymph node involvement is a prognostic factor in metastatic NSCLC, lymph node metastasis is not considered a site of metastasis (8). Therefore, further hierarchical analysis of N0–N3 could be conducted in the future to better understand the impact of lymph node involvement on the survival outcomes of patients with NSCLC. Similarly, we

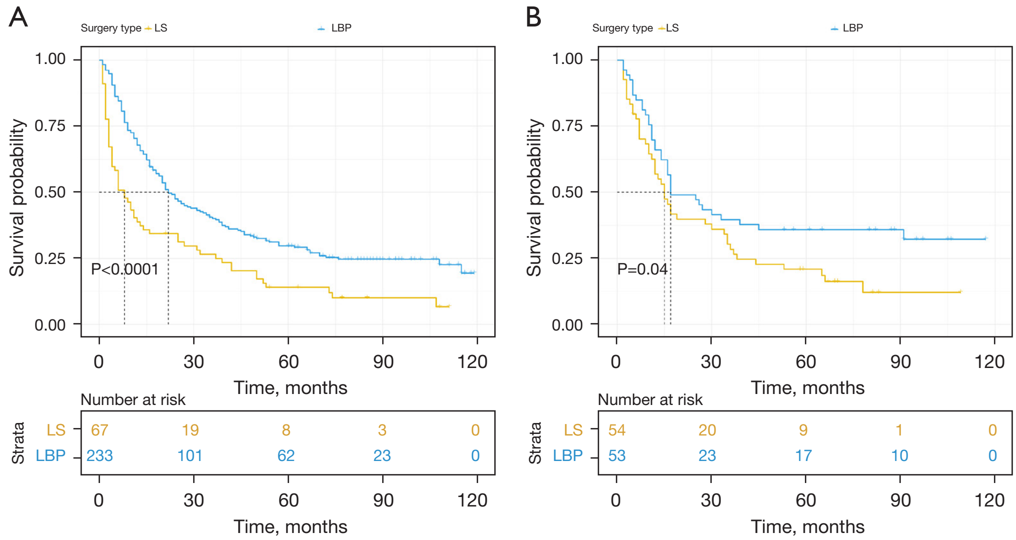

Figure 4 Survival curves for different surgical approaches in patients with single extrathoracic metastasis. (A) Patients with primary tumor size >2 cm. (B) Patients with primary tumor size ≤2 cm. LS, local tumor destruction/sublobar resection; LBP, lobectomy/bilobectomy/pneumonectomy.

discovered that lobectomy was at least warranted to improve the survival of metastatic NSCLC patients, even in those with primary tumor size ≤2 cm.

Our findings have a number of clinical implications. Primary tumor surgery plus systemic chemotherapy may be preferred for NSCLC patients with single EM, since this combined therapy could reduce mortality by 49% compared with chemotherapy alone. Since metastases occur more frequently in young NSCLC patients, these patients usually have better performance status and can tolerate surgical resection. Furthermore, sufficient excision range, such as at least lobectomy, should be noticed. Conversely, primary tumor surgery provided limited survival benefits for NSCLC patients with multi-EMs, indicating that overtreatment should be avoided. Although the combined treatment had the lowest hazard ratio (HR) in patients with multi-EMs referring to no treatment, this could be due to selection bias.

Surgery has traditionally been the primary treatment option for patients with limited metastasis, with approximately 55% of patients undergoing surgical resection (33). However, these metastatic lesions are often unresectable for various reasons, or patients are deemed inoperable, requiring less invasive treatments such as radiation therapy (34). Stereotactic body radiation therapy (SBRT) has been proven beneficial for patients with both single and multi-EMs lesions (35). Despite the fact that early detection increases the likelihood of tumor removal, treatment, and successful outcomes, lung cancer remains lethal due to challenges like lack of appropriate screening platforms, metastasis, genetic heterogeneity, and minimal response to late-stage chemotherapy (36). For locally advanced and metastatic cancers, chemotherapy and radiation therapy (including neoadjuvant and/or adjuvant therapy) are recommended, but patients still experience limited OS and significant side effects under this approach (37).

There are several limitations to this study. First, although we stratified NSCLC patients based on the number of metastatic organs, whether these patients could be further divided according to the number of metastatic lesions needs further explored. Second, targeted therapy and immunotherapy have altered the treatment paradigm for metastatic NSCLC. It is unclear whether recognized driven mutations such as EGFR gene mutation, ALK/C-ros oncogene 1 (ROS1) rearrangement, and programmed death-ligand 1 (PD-L1) positivity affect the application of surgical resection. Third, the location of the primary tumor, such as peripheral or central type, has significant impacts on selecting the surgical patterns, so tumor location could be a potential bias in comparing the survival of patients receiving different operations. Fourth, this is a retrospective study, and its inherent selection bias resulted in the exclusion of a large number of patients. Fifth, the AJCC was updated to the 8th edition in 2016, which defined M1b as single EM. However, the patient population selected in this study ranged from 2010 to 2015, and the M1b stage patients were defined according to the 7th edition of the AJCC, which refers to patients with distant metastases outside the thorax but does not specify the number of metastases. As a result, some patients who were not suitable for surgery underwent surgery, resulting in biased data. Sixth, the number of lesions, and clinical factors such as cardiopulmonary function, smoking history, performance status, and comorbidities may also affect the choice of surgical methods, but this information is not available in the SEER database. At the same time, the reasons for patients choosing a particular surgical method are unknown, which may further bias our results. Despite these limitations, we believe that our findings may be helpful for future clinicians to select surgical methods more cautiously for patients with metastatic NSCLC and may contribute to future clinical research.

Conclusions

In summary, our study suggests that surgical resection of the primary tumor can benefit patients with single EM, but for patients with multi-EMs, the survival outcomes of chemotherapy combined with surgical treatment are equivalent to surgery alone. Lobectomy, bilobectomy, or pneumonectomy have higher survival rates than sublobar resection, even in patients with primary tumor size ≤2 cm.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-516/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-516/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Treatment strategies of grouping baseline characteristics

Characteristics	The whole cohort, n (%)	Single extrathoracic metastasis, n (%)	Multiple extrathoracic metastasis, n (%)	P value
Sample size	3,892	3,316	576	–
Surgery and chemotherapy				<0.001
None	1,470 (37.8)	1,234 (37.2)	236 (41.0)	
Chemotherapy only	2,000 (51.4)	1,675 (50.5)	325 (56.4)	
Surgery only	170 (4.4)	161 (4.9)	9 (1.6)	
Chemotherapy + surgery	252 (6.5)	246 (7.4)	6 (1.0)	
Surgery and radiotherapy				<0.001
None	1,415 (36.4)	1,214 (36.6)	201 (34.9)	
Radiotherapy only	2,055 (52.8)	1,695 (51.1)	360 (62.5)	
Surgery only	179 (4.6)	173 (5.2)	6 (1.0)	
Radiotherapy + surgery	243 (6.2)	234 (7.1)	9 (1.6)	
Surgery and chemoradiotherapy				<0.001
None	702 (18)	607 (18.3)	95 (16.5)	
Chemoradiotherapy only	1,287 (33.1)	1,068 (32.2)	219 (38.0)	
Surgery only	97 (2.5)	94 (2.8)	3 (0.5)	
Radiotherapy only	768 (19.7)	627 (18.9)	141 (24.5)	
Chemotherapy only	713 (18.3)	607 (18.3)	106 (18.4)	
Surgery + chemotherapy	82 (2.1)	79 (2.4)	3 (0.5)	
Surgery + radiotherapy	73 (1.9)	67 (2.0)	6 (1.0)	
Surgery + chemoradiotherapy	170 (4.4)	167 (5.0)	3 (0.5)	

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Table S2 Kaplan-Meier analysis was used to analyze the effects of surgery and chemotherapy, surgery and radiotherapy, surgery and chemoradiotherapy on non-small cell lung cancer patients

Variables	P value		
	Total	Single extrathoracic metastasis	Multiple extrathoracic metastasis
None *vs.* chemotherapy only	<0.0001	<0.0001	<0.0001
None *vs.* surgery only	<0.0001	<0.0001	0.013
None *vs.* surgery and chemotherapy	<0.0001	<0.0001	0..0022
Chemotherapy only *vs.* surgery only	0.00024	0.0015	0.26
Chemotherapy only *vs.* surgery and chemotherapy	<0.0001	<0.0001	0.082
Surgery only *vs.* surgery and chemotherapy	<0.0001	<0.0001	0.41
None *vs.* radiotherapy only	<0.0001	0.00012	0.18
None *vs.* surgery only	<0.0001	<0.0001	0.0066
None *vs.* surgery and radiotherapy	<0.0001	<0.0001	0.28
Radiotherapy only *vs.* surgery only	<0.0001	<0.0001	0.0090
Radiotherapy only *vs.* surgery and radiotherapy	<0.0001	<0.0001	0.45
Surgery only *vs.* surgery and radiotherapy	0.73	0.99	0.11
None *vs.* chemoradiotherapy only	<0.0001	<0.0001	<0.0001
None *vs.* surgery only	<0.0001	<0.0001	0.016
None *vs.* radiotherapy only	0.042	0.029	0.63
None *vs.* chemotherapy only	<0.0001	<0.0001	<0.0001
None *vs.* surgery and chemotherapy	<0.0001	<0.0001	0.030
None *vs.* surgery and radiotherapy	<0.0001	<0.0001	0.17
None *vs.* surgery and chemoradiotherapy	<0.0001	<0.0001	0.059
Chemoradiotherapy only *vs.* surgery only	0.0014	0.011	0.086
Chemoradiotherapy only *vs.* radiotherapy only	<0.0001	<0.0001	<0.0001
Chemoradiotherapy only *vs.* chemotherapy only	0.45	0.50	0.62
Chemoradiotherapy only *vs.* surgery and chemotherapy	<0.0001	<0.0001	0.17
Chemoradiotherapy only *vs.* surgery and radiotherapy	0.18	0.17	0.55
Chemoradiotherapy only *vs.* surgery and chemoradiotherapy	<0.0001	<0.0001	0.51
Surgery only *vs.* radiotherapy only	<0.0001	<0.0001	0.049
Surgery only *vs.* chemotherapy only	0.00029	0.0028	0.081
Surgery only *vs.* surgery and chemotherapy	0.0034	0.0028	0.95
Surgery only *vs.* surgery and radiotherapy	0.33	0.56	0.17
Surgery only *vs.* surgery and chemoradiotherapy	0.011	0.0061	0.47
Radiotherapy only *vs.* chemotherapy only	<0.0001	<0.0001	<0.0001
Radiotherapy only *vs.* surgery and chemotherapy	<0.0001	<0.0001	0.059
Radiotherapy only *vs.* surgery and radiotherapy	<0.0001	<0.0001	0.47

Table S2 *(continued)*

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Table S2 *(continued)*

Variables	P value		
	Total	Single extrathoracic metastasis	Multiple extrathoracic metastasis
Radiotherapy only *vs.* surgery and chemoradiotherapy	<0.0001	<0.0001	0.086
Chemotherapy only *vs.* surgery and chemotherapy	<0.0001	<0.0001	0.17
Chemotherapy only *vs.* surgery and radiotherapy	0.082	0.081	0.67
Chemotherapy only *vs.* surgery and chemoradiotherapy	<0.0001	<0.0001	0.47
Surgery and chemotherapy *vs.* surgery and radiotherapy	<0.0001	0.00028	0.28
Surgery and chemotherapy *vs.* surgery and chemoradiotherapy	0.33	0.37	0.67
Surgery and radiotherapy *vs.* surgery and chemoradiotherapy	0.00010	0.00054	0.46

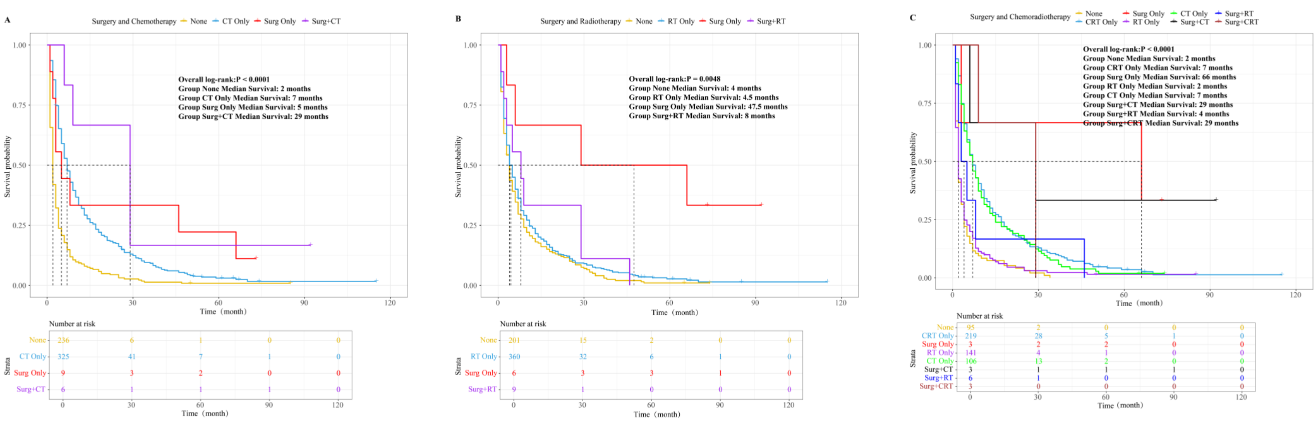

Figure S1 The survival curves of different treatment in patients with multiple extrathoracic metastasis. (A) Surgery combined with chemotherapy. (B) According to the surgery combined with radiotherapy. (C) Surgery combined with radiotherapy and chemotherapy. None, no surgery or chemotherapy or radiotherapy was performed; CT only, chemotherapy only; Surg only, only to have surgery; Surg + CT, surgery combined with chemotherapy; RT only, radiotherapy only; Surg + RT, surgery combined with radiotherapy; CRT only, chemotherapy combined with radiotherapy only; Surg + CRT, surgery combined with radiotherapy and chemotherapy.