Original Article

Prognostic value of surgical intervention in advanced lung adenocarcinoma: a population-based study

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Background: Surgical intervention is generally not considered as a treatment option in patients with advanced non-small cell lung cancer (NSCLC). Accumulating data suggest that surgery may have beneficial effects for these advanced patients. However, no evidence supports the significance of primary tumor resection (PTR) and metastatic tumor resection (MTR) in patients with stage IV lung adenocarcinoma (LUAD).

Methods: A total of 32,497 patients diagnosed with primary stage IV LUAD were selected through the Surveillance, Epidemiology, and End Results (SEER) database. Possible confounders were eliminated by propensity score matching (PSM). The overall survival (OS) and lung cancer-specific survival (LCSS) were estimated as the primary endpoints. Furthermore, the independent prognostic factors of patients with the surgical intervention were retrospectively analyzed.

Results: Patients underwent surgical intervention had better OS and LCSS than those who did not (P=0.001 for OS; P<0.001 for LCSS). Meanwhile, patients who underwent surgery combined with lymph node dissection had better survival outcomes (P<0.001 for OS and LCSS) in the K-M analysis. For different metastatic sites, PTR was beneficial to the survival of patients with isolated lung metastases (LUM) and multiple organ metastases (MOM) (LUM: P=0.041; MOM: P=0.003). As for metastatic surgery, no patients were found to benefit from resection of metastatic tumor [bone metastasis (BOM): P=0.696; brain metastasis (BRM): P=0.951; LUM: P=0.402; MOM: P=0.365].

Conclusions: Surgical intervention strategies can prolong survival to some extent, depending on different sites of metastasis and highly selected patients.

Keywords: Advanced lung adenocarcinoma (LUAD); metastasis; surgical intervention; prognosis

Introduction

As one of the most prevalent malignant tumors globally, lung cancer is the primary cause of cancer-related deaths, which seriously threatens human's health and life (1). Lung adenocarcinoma (LUAD) is the most common pathological subtype of lung cancer with only 5% relative survival rate of 5-year. About 57% patients have advanced stage and metastatic diseases (2). For early-stage lung cancer, the first treatment option is surgical resection. However, surgical intervention is generally not considered for stage IV patients. The recommended treatment strategy is systemic therapy (i.e., chemotherapy, radiation therapy, molecular

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targeted therapy, or immunotherapy) (3).

At present, it is still controversial whether to perform primary tumor resection (PTR) and/or metastatic tumor resection (MTR) for LUAD with distant metastasis. Previous studies (4-6) have shown that PTR treatment strategies combined with systemic therapy such as radiotherapy or chemotherapy are beneficial for stage IV non-small cell lung cancer (NSCLC) patients with single or several synchronous metastases. For distant metastasis, several clinical studies (5,7,8) have reported that MTR may show survival benefits for patients with limited metastatic sites. But few relevant studies are found with small sample size. Therefore, it is not yet confident that MTR can improve the survival rate of patients.

The general metastatic sites of LUAD are lung, bone, brain, adrenal gland, pleura, liver (9). Fewer studies are found concerning whether more significant survival benefits are provided by the surgical interventions (PTR and/or MTR) to patients with metastatic LUAD. To address this unresolved problem, we re-evaluated the significance of surgical intervention in stage IV LUAD patients registered within the Surveillance, Epidemiology, and End Results (SEER) database.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-997).

Methods

Patients and data collection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The population of this retrospective study was selected from the SEER database of the National Cancer Institute, a cancer registry program that collected tumor-related data and covered approximately 28% of the U.S. population (10). The SEER data were publicly available for studies of cancer-based epidemiology and survival analyses. We had been granted access to the data used in this study (SEER-Stat username: 25824-Nov2019).

A total of 148,587 patients diagnosed with LUAD from 2010 to 2015 were extracted through the SEER database (SEER-Stat 8.3.9). LUAD was defined on the basis of the third edition of the International Classification of Diseases for Oncology (ICD-O-3). The primary site was Lung and Bronchus, and the histological type code: 8140-8147, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, and 8572 (11).

We reclassified the TNM stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) TMN stage based on the information of "CS Tumor size" and "CS Extension". Exclusion criteria include: <18 years of age, unknown TNM stage, non-stage IV, surgical treatments for distant metastases other than MTR, diagnosed with more than one primary tumor, received radiotherapy.

In the end, 32,497 cases were included in this study. According to the surgical strategies, we divided eligible patients into four groups: primary tumor resection only (PTR), metastatic tumor resection only (MTR), both primary and metastatic tumor resection (PMTR). Metastatic sites were divided into (I) lung metastases only (LUM) without bone, brain, or liver metastases; (II) bone metastases only (BOM) without lung, brain, or liver metastases; (III) brain metastases only (BRM) without lung, bone, or liver metastases; (IV) liver metastases only (LIM) without lung, bone, or brain metastases; (V) multiple organ metastases (MOM): two or more metastatic organs among lung, liver, brain, and bone; (VI) other metastases (OTM): no metastases to lung, bone, brain, and liver.

Statistical analysis

The chi-square test for categorical variables compared patient characteristics. Overall survival (OS) and lung cancer-specific survival (LCSS) were the primary endpoints. OS was defined as the time from the date of diagnosis to death from any cause. LCSS was the time from the date of diagnosis to specific death due to lung cancer.

A 1:1 propensity score matching (PSM) was used to reduce unbalanced baseline characteristics between the surgery and no-surgery groups. The match was conducted using the nearest-neighbor algorithm with a caliper width of 0.02. Propensity scores were calculated using logistic regression with the following covariates: age, race, sex, location, T stage, N stage, lymph node dissection, chemotherapy, metastatic site. Similarly, we also performed 1:4 PSM for patients with surgical intervention (PTR or MTR) in different metastatic sites. P>0.05 was regarded as an acceptable balance.

OS and LCSS were estimated by the Kaplan-Meier method and compared with the log-rank test. The multivariate Cox proportional hazards regression analysis was used to determine the independent prognostic factors of surgical intervention patients. The hazard ratio (HR) was calculated with a 95% confidence interval (CI). Statistical analysis was performed with SPSS version 23.0 (IBM,

Armonk, NY, USA). R (version 4.1.0) was utilized to carry out the PSM. P<0.05 was considered statistically significant.

Results

Characteristics of patients

Table 1 shows the demographic and clinicopathological characteristics of the enrolled patients. In total, 32,497 LUAD patients with distant metastases were identified. The average age at diagnosis was 67.1±11.4 years old. The most common single metastatic site was bone (17.86%), followed by the lung (14.16%), brain (10.89%), and liver (3.58%). Nevertheless, MOM had a higher proportion, accounting

for 30.86%. A total of 1,363 LUAD patients underwent surgical intervention, of which 749 (55.0%) patients had PTR, 548 (40.2%) patients had MTR, and 66 (4.8%) patients had PMTR.

Impact of surgery intervention on survival outcomes in stage IV LUAD patients

Of all eligible patients, 1,363 underwent surgical intervention, while 31,134 did not. Statistical differences in age, race, sex, location, T stage, N stage, lymph node dissection (LND), chemotherapy, and metastatic site were noted between the surgery and no-surgery groups. After PSM, all baseline

Table 1 Baseline characteristics of patients with advanced LUAD

Variables	LUM n=4,600	BOM n=5,804	BRM n=3,538	LIM n=1,162	MOM n=10,030	OTM n=7,363	P value
Age (years)							<0.001
≤55	609 (13.2)	908 (15.6)	755 (21.3)	139 (12.0)	1,827 (18.2)	1,045 (14.2)	
56–75	2,547 (55.4)	3,472 (59.8)	2,162 (61.1)	694 (59.7)	6,179 (61.6)	4,098 (55.7)	
≥76	1,444 (31.4)	1,424 (24.5)	621 (17.6)	329 (28.3)	2,024 (20.2)	2,220 (30.2)	
Sex							<0.001
Male	2,136 (46.4)	3,221 (55.5)	1,759 (49.7)	591 (50.9)	5,172 (51.6)	3,756 (51.0)	
Female	2,464 (53.6)	2,583 (44.5)	1,779 (50.3)	571 (49.1)	4,858 (48.4)	3,607 (49.0)	
Race							<0.001
White	3,396 (73.8)	4,557 (78.5)	2,662 (75.2)	924 (79.5)	7,544 (75.2)	5,445 (74.0)	
Black	686 (14.9)	696 (12.0)	493 (13.9)	156 (13.4)	1,179 (11.8)	1,042 (14.2)	
Other	518 (11.3)	551 (9.5)	383 (10.8)	82 (7.1)	1,307 (13.0)	876 (11.9)	
Location							<0.001
Main bronchus	157 (3.4)	195 (3.4)	109 (3.1)	49 (4.2)	407 (4.1)	305 (4.1)	
Upper lobe	2,304 (50.1)	3,268 (56.3)	2,106 (59.5)	635 (54.6)	5,359 (53.4)	3,791 (51.5)	
Middle lobe	208 (4.5)	266 (4.6)	163 (4.6)	46 (4.0)	413 (4.1)	341 (4.6)	
Lower lobe	1,171 (25.5)	1,571 (27.1)	905 (25.6)	333 (28.7)	2,669 (26.6)	1,891 (25.7)	
Overlapping lesions	71 (1.5)	55 (0.9)	19 (0.5)	12 (1.0)	92 (0.9)	104 (1.4)	
NOS	689 (15.0)	449 (7.7)	236 (6.7)	87 (7.5)	1,090 (10.9)	931 (12.6)	
T stage							<0.001
T1	940 (20.4)	1,508 (26.0)	753 (21.3)	310 (26.7)	1,967 (19.6)	1,610 (21.9)	
T2	1,281 (27.8)	1,759 (30.3)	1,083 (30.6)	335 (28.8)	2,797 (27.9)	2,109 (28.6)	
T3	978 (21.3)	1,124 (19.4)	679 (19.2)	226 (19.4)	2,104 (21.0)	1,649 (22.4)	
T4	1,401 (30.5)	1,413 (24.3)	1,023 (28.9)	291 (25.0)	3,162 (31.5)	1,995 (27.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	LUM n=4,600	BOM n=5,804	BRM n=3,538	LIM n=1,162	MOM n=10,030	OTM n=7,363	P value
N stage							<0.001
N0	1,245 (27.1)	1,522 (26.2)	1,019 (28.8)	305 (26.2)	1,768 (17.6)	2,139 (29.1)	
N1	292 (6.3)	580 (10.0)	340 (9.6)	91 (7.8)	747 (7.4)	560 (7.6)	
N2	1,933 (42.0)	2,688 (46.3)	1,628 (46.0)	590 (50.8)	4,924 (49.1)	3,241 (44.0)	
N3	1,130 (24.6)	1,014 (17.5)	551 (15.6)	176 (15.1)	2,591 (25.8)	1,423 (19.3)	
Chemotherapy							<0.001
No/Unknown	1,994 (43.3)	2,321 (40.0)	7,695 (47.9)	547 (47.1)	4,335 (43.2)	3,157 (42.9)	
Yes	2,606 (56.7)	3,483 (60.0)	1,843 (52.1)	615 (52.9)	5,695 (56.8)	4,206 (57.1)	
LN dissection							<0.001
No/Unknown	4,452 (96.8)	5,721 (98.6)	3,496 (98.8)	1142 (98.3)	9,957 (99.3)	7,067 (96.0)	
Yes	148 (3.2)	83 (1.4)	42 (1.2)	20 (1.7)	73 (0.7)	296 (4.0)	
Surgery							<0.001
NS	4,339 (94.3)	5,636 (97.1)	3,323 (93.9)	1,134 (97.6)	9,806 (97.8)	6,896 (93.7)	
PTR	221 (4.8)	67 (1.2)	33 (0.9)	26 (2.2)	69 (0.7)	333 (4.5)	
MTR	29 (0.6)	95 (1.6)	167 (4.7)	1 (0.1)	151 (1.5)	105 (1.4)	
PMTR	11 (0.2)	6 (0.1)	15 (0.4)	1 (0.1)	4 (0.0)	29 (0.4)	

Data presented as n (%). LUAD, lung adenocarcinoma; NS, no surgery; PTR, primary tumor resection only; MTR, metastatic tumor resection only; PMTR, both primary and metastatic tumor resection; LN, lymph node; LUM, lung metastases only; BOM, bone metastases only; BRM, brain metastases only; LIM, liver metastases only; MOM, multiple organ metastases; OTM, other metastases.

Table 2 Baseline characteristics of the no-surgery and surgery group before and after PSM

Variables	Before PSM			After PSM		
	No-surgery n=31,134	Surgery n=1,363	P value	No-surgery n=1,106	Surgery n=1,106	P value
Age (years)			<0.001			0.811
≤55	5,037 (16.2)	246 (18.0)		187 (16.9)	186 (16.8)	
56-75	18,288 (58.7)	864 (63.4)		707 (63.9)	696 (62.9)	
≥76	7,809 (25.1)	253 (18.6)		212 (19.2)	224 (20.3)	
Sex			0.313			0.470
Male	15,956 (51.2)	679 (49.8)		578 (52.3)	560 (50.6)	
Female	15,178 (48.8)	684 (50.2)		528 (47.7)	546 (49.4)	
Race			0.209			0.407
White	23,503 (75.5)	1,025 (75.2)		829 (75.0)	819 (74.1)	
Black	4,056 (13.0)	196 (14.4)		182 (16.5)	174 (15.7)	
Other	3,575 (11.5)	142 (10.4)		95 (8.6)	113 (10.2)	

Table 2 (*continued*)

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Table 2 (*continued*)

Variables	Before PSM			After PSM		
	No-surgery n=31,134	Surgery n=1,363	P value	No-surgery n=1,106	Surgery n=1,106	P value
Location			<0.001			0.363
Main bronchus	1,190 (3.8)	32 (2.3)		34 (3.1)	30 (2.7)	
Upper lobe	16,771 (53.9)	692 (50.8)		525 (47.5)	545 (49.3)	
Middle lobe	1,363 (4.4)	74 (5.4)		53 (4.8)	62 (5.6)	
Lower lobe	8,162 (26.2)	378 (27.7)		340 (30.7)	313 (28.3)	
Overlapping lesions	319 (1.0)	34 (2.5)		13 (1.2)	23 (2.1)	
NOS	3,329 (10.7)	153 (11.2)		141 (12.7)	133 (12.0)	
T stage			<0.001			0.849
T1	6,650 (21.4)	438 (32.1)		333 (30.1)	328 (29.7)	
T2	9,000 (28.9)	364 (26.7)		301 (27.2)	287 (25.9)	
T3	6,478 (20.8)	282 (20.7)		231 (20.9)	244 (22.1)	
T4	9,006 (28.9)	279 (20.5)		241 (21.8)	247 (22.3)	
N stage			<0.001			0.074
N0	7,414 (23.8)	584 (42.8)		426 (38.5)	422 (38.2)	
N1	2,470 (7.9)	140 (10.3)		75 (6.8)	96 (8.7)	
N2	14,520 (46.6)	484 (35.5)		421 (38.1)	440 (39.8)	
N3	6,730 (21.6)	155 (11.4)		184 (16.6)	148 (13.4)	
Metastatic site			<0.001			0.502
LUM	4,339 (13.9)	261 (19.1)		181 (16.4)	198 (17.9)	
BOM	5,636 (18.1)	168 (12.3)		164 (14.8)	154 (13.9)	
BRM	3,323 (10.7)	215 (15.8)		179 (16.2)	195 (17.6)	
LIM	1,134 (3.6)	28 (2.1)		27 (2.4)	20 (1.8)	
MOM	9,806 (31.5)	224 (16.4)		234 (21.2)	209 (18.9)	
OTM	6,896 (22.1)	467 (34.3)		321 (29.0)	330 (29.8)	
Chemotherapy			<0.001			0.307
No/Unknown	13,353 (42.9)	696 (51.1)		577 (52.2)	552 (49.9)	
Yes	17,781 (57.1)	667 (48.9)		529 (47.8)	554 (50.1)	
LN dissection			<0.001			1.000
No/Unknown	30,868 (99.1)	967 (70.9)		967 (87.4)	967 (87.4)	
Yes	266 (0.9)	396 (29.1)		139 (12.6)	139 (12.6)	

PSM, propensity score matching; LUM, lung metastases only; BOM, bone metastases only; BRM, brain metastases only; LIM, liver metastases only; MOM, multiple organ metastases; OTM, other metastases; LN, lymph node.
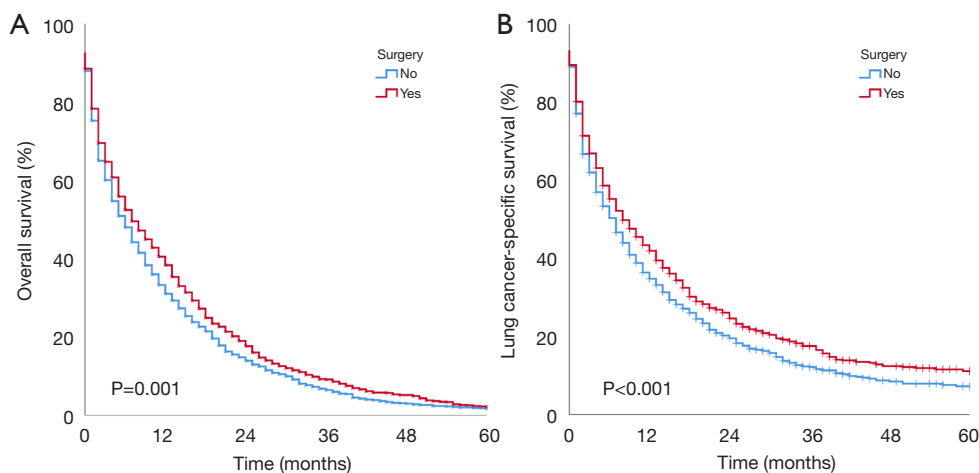
Figure 1 Kaplan-Meier curve of the no-surgery and surgery group. (A) Overall survival; (B) lung cancer-specific survival.

characteristics were well balanced (P>0.05; *Table 2*).

K-M analysis of the matched population found that patients who underwent surgical intervention had better OS and LCSS than those who did not. The median OS of the no-surgery group was 6.0 months (95% CI: 5.3–6.7 months), and the surgery group was 7.0 months (95% CI: 5.9–8.1 months). There was a statistical difference between the two groups (P=0.001) (*Figure 1A*). The median LCSS in the surgery group was better than the no-surgery group (surgery: 8.0 months, 95% CI: 6.7–9.3 months; no-surgery: 7.0 months, 95% CI: 6.1–7.9 months; P<0.001) (*Figure 1B*).

Prognostic factors for surgical intervention

Furtherly, we analyzed the prognostic factors of patients who underwent surgery in stage IV to determine the population who would benefit from surgical intervention (*Table 3*). We selected the matched cohorts that underwent at least one type of surgical strategy to conduct multivariate Cox regression analysis. Compared with PTR, MTR cannot benefit patients better (HR: 1.269, 95% CI: 1.091–1.475, P=0.002), and PMTR was not a prognostic factor related to OS (HR: 0.867, 95% CI: 0.613–1.224, P=0.416). Similar results also appeared in the patient's LCSS analysis. In terms of metastatic sites, LUM as a reference, BOM (HR: 1.516, 95% CI: 1.178–1.952, P=0.001), BRM (HR: 1.356, 95% CI: 1.048–1.754, P=0.021), LIM (HR: 1.725, 95% CI: 1.022–2.911, P=0.041) and MOM (HR: 1.426, 95% CI: 1.116–1.821, P=0.005) were adverse prognostic factors for the LCSS of patients, but isolated liver metastases (HR: 1.360, 95% CI: 0.853–2.167, P=0.196) were not statistically

related to OS. Male, advanced T stage, and N stage affected the patients' OS and LCSS. Meanwhile, chemotherapy and LND were favorable prognostic factors for patients.

Impact of lymph node dissection on survival outcomes in stage IV LUAD patients

According to multivariate Cox analysis in the matched population, LND was independently associated with better OS (HR: 0.767, 95% CI: 0.628–0.938, P=0.010) and LCSS (HR: 0.649, 95% CI: 0.508–0.829, P=0.001) (*Table 3*). We confirmed this result in the K-M analysis (*Figure 2*). The median OS was 6.0 months (95% CI: 5.1–6.9 months), and the median LCSS was 7.0 months (95% CI: 6.0–8.0 months) in the surgery without LND group. The median OS was 18.0 months (95% CI: 14.9–21.1 months), and the median LCSS was 20.0 months (95% CI: 16.2–23.8 months) in the surgery with LND group. Survival outcomes were better in the patients underwent surgery combined with LND (P<0.001 for OS and LCSS).

Correlation between different surgical intervention strategies and survival of stage IV LUAD

OS was evaluated based on whether the primary tumor or metastatic tumor surgery was performed in patients with LUM, BOM, BRM, and MOM. Before evaluation, PSM was used to eliminate possible confounders for different surgical strategies (PTR or MTR) in different metastatic sites (Tables S1-S8). Due to the limited number, the LIM and PMTR groups were excluded from these evaluations.

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Table 3 Multivariate Cox regression analysis for OS and LCSS in patients with surgery

Variables	OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤55	1.00 (reference)	–	1.00 (reference)	–
56–75	1.153 (0.978–1.359)	0.089	1.317 (1.080–1.606)	0.007
≥76	1.361 (1.111–1.667)	0.003	1.650 (1.304–2.088)	<0.001
Sex				
Female	1.00 (reference)	–	1.00 (reference)	–
Male	1.164 (1.032–1.313)	0.013	1.128 (0.985–1.291)	0.081
T stage				
T1	1.00 (reference)	–	1.00 (reference)	–
T2	1.052 (0.893–1.239)	0.544	1.072 (0.890–1.291)	0.465
T3	1.329 (1.121–1.576)	0.001	1.425 (1.176–1.728)	<0.001
T4	1.376 (1.164–1.628)	<0.001	1.531 (1.270–1.846)	<0.001
N stage				
N0	1.00 (reference)	–	1.00 (reference)	–
N1	0.997 (0.792–1.254)	0.979	0.983 (0.755–1.279)	0.898
N2	1.130 (0.982–1.300)	0.088	1.222 (1.044–1.429)	0.013
N3	1.337 (1.097–1.629)	0.004	1.423 (1.141–1.773)	0.002
Metastatic site				
LUM	1.00 (reference)	–	1.00 (reference)	–
BOM	1.356 (1.087–1.691)	0.007	1.516 (1.178–1.952)	0.001
BRM	1.300 (1.037–1.629)	0.023	1.356 (1.048–1.754)	0.021
LIM	1.360 (0.853–2.167)	0.196	1.725 (1.022–2.911)	0.041
MOM	1.359 (1.097–1.683)	0.005	1.426 (1.116–1.821)	0.005
OTM	1.091 (0.911–1.306)	0.346	1.103 (0.889–1.367)	0.373
Chemotherapy	0.468 (0.410– 0.534)	<0.001	0.416 (0.358–0.483)	<0.001
LN dissection	0.767 (0.628–0.938)	0.01	0.649 (0.508–0.829)	0.001
Surgery				
PTR	1.00 (reference)	–	1.00 (reference)	–
MTR	1.269 (1.091–1.475)	0.002	1.298 (1.094–1.539)	0.003
PMTR	0.867 (0.613–1.224)	0.416	0.933 (0.616–1.414)	0.744

OS, overall survival; LCSS, lung cancer–specific survival; HR, hazard ratio; CI, confidence interval; PTR, primary tumor resection only; MTR, metastatic tumor resection only; PMTR, both primary and metastatic tumor resection; LN, lymph node; LUM, lung metastases only; BOM, bone metastases only; BRM, brain metastases only; LIM, liver metastases only; MOM, multiple organ metastases; OTM, other metastases.
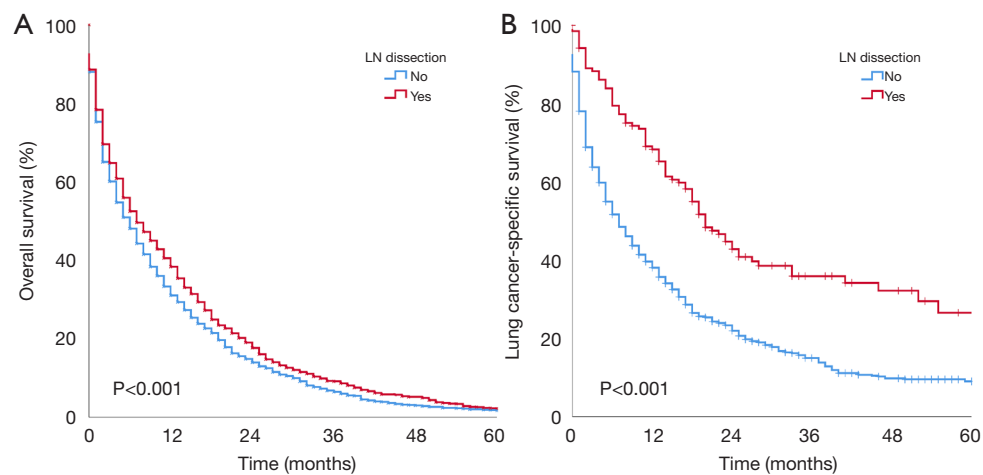
Figure 2 Kaplan-Meier curve based on whether or not lymph node dissection was performed. (A) Overall survival; (B) lung cancer-specific survival. LN, lymph node.

Patients with LUM and MOM benefited from PTR (LUM: P=0.041; MOM: P=0.003), while no survival benefits were observed for BOM and BRM (BOM: P=0.088; BRM: P=0.124) (*Figure 3*). On the other hand, no survival benefits were observed in MTR (LUM: P=0.402; BOM: P=0.696; BRM: P=0.951; MOM: P=0.365) (*Figure 4*).

Discussion

With advances in preoperative management and surgical techniques, the mortality rate associated with surgery has been declining. In the context of constant updates in systemic treatment, increasing awareness of clinical decision-making through multidisciplinary teams (MDT) also led to re-consideration of surgical intervention as part of treatment to advanced LUAD (12). In recent years, some evidence (3,13-15) supported the value of surgical intervention in patients with advanced NSCLC. Our study found that the surgery group had better OS and LCSS than the no-surgery group and that surgery combined with necessary LND prolonged the patient's survival significantly. These results may be related to the reduction of tumor burden in patients with advanced LUAD by surgical intervention on the basis of comprehensive treatment.

The most common single metastatic sites were bone, lung, brain, and liver in our data. In addition, MOM was more common than single-organ metastases. We reassessed the significance of PTR or MTR for different metastatic sites. Although the SEER database is not available for the specific number of metastatic lesions in a single metastatic organ, its considerable sample size helps us explain the effect of metastatic organ distribution on postoperative survival.

A study analyzing 1,206 patients who underwent PTR suggested that local tumor control strategies for NSCLC patients with distant metastases appear to prolong survival (4). Yang *et al.* (14) identified that receiving PTR is a prognostic factor for stage IV NSCLC. Local treatment of limited primary lung tumors is strongly associated with improved long-term survival (15). We found that surgical interventions for patients with LUM and MOM could prolong survival time to a certain extent. However, the effect was not significant for patients with BRM and BOM. Due to the small sample size and the possible confounding factors, prospective studies should be conducted in the future.

Previously, some single-center studies (16-18) demonstrated that surgical management of patients with oligometastatic NSCLC to the brain is associated with excellent long-term survival. Daniels *et al.* (18) retrospectively analyzed 15 NSCLC patients who underwent BRM resection, and 12 patients were resected entirely. Surprisingly, the 5-year OS after attempted radical resection of BRM and successful complete resection was 60% and 70%, similar to those only need to resect lung cancer completely. Nevertheless, in another study (19), 86 patients with metachronous BRM underwent surgery or radiation of their oligometastatic intracranial disease had a less 5-year survival rate of 22%, which indicated
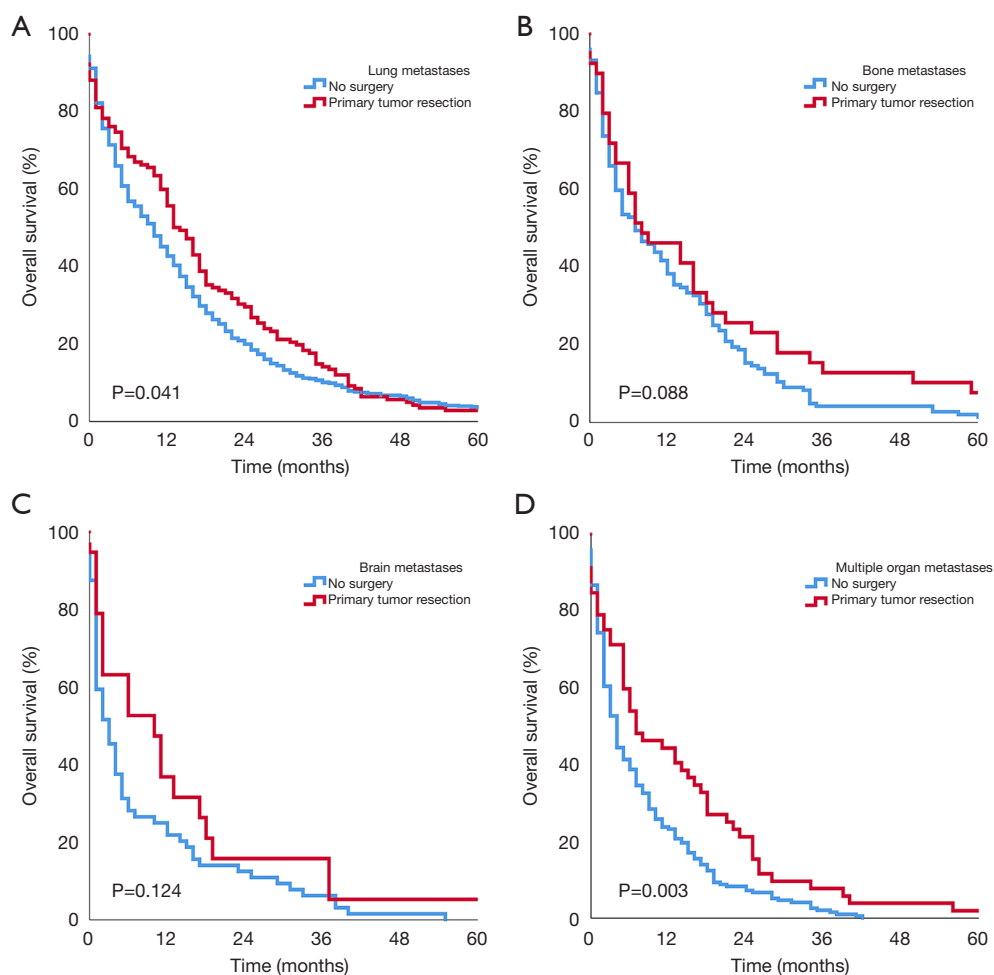
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Figure 3 Kaplan-Meier curve of overall survival based on whether or not primary tumor resection was performed. (A) Patients with isolated lung metastases; (B) patients with isolated bone metastases; (C) patients with isolated brain metastases; (D) patients with multiple organ metastases.

that surgical intervention for patients with intracranial metastases might result in diminished survival. This study found that patients with BRM did not benefit from surgical resection. In clinical practice, most BRM of lung cancer choose gamma knife treatment locally. Given that radiotherapy cannot be well distinguished from surgery, we excluded patients treated with radiotherapy. The effects of radiotherapy on BRM are better than surgical resection with fewer postoperative complications (20).

There is no consensus on treating isolated metastatic diseases involving bone metastases, contralateral lung metastases, or other organ metastases (6,17,21-24). Patients with LUM, BOM, or MOM did not benefit from MTR in our study. We believe that surgical intervention for metastases without resection of the primary tumor cannot

fundamentally reduce the tumor burden of patients, nor can the potential risk of metastasis and recurrence be excluded. Therefore, MTR is not recommended for general use. Unfortunately, the number of patients who underwent PMTR was relatively small, so we could not analyze these patients further. But in the multivariate Cox proportional hazards regression analysis, PMTR was not an independent risk factor for patients in the surgery cohort, which is related to the impact of multi-organ surgery on patients' poor physical state and postoperative complications.

Currently, the NCCN guidelines suggest that patients with single brain or adrenal metastasis, but the primary tumor lesion is limited, local treatment for metastatic NSCLC lesions followed by resection of the primary tumor is recommended (3). A growing number of practice
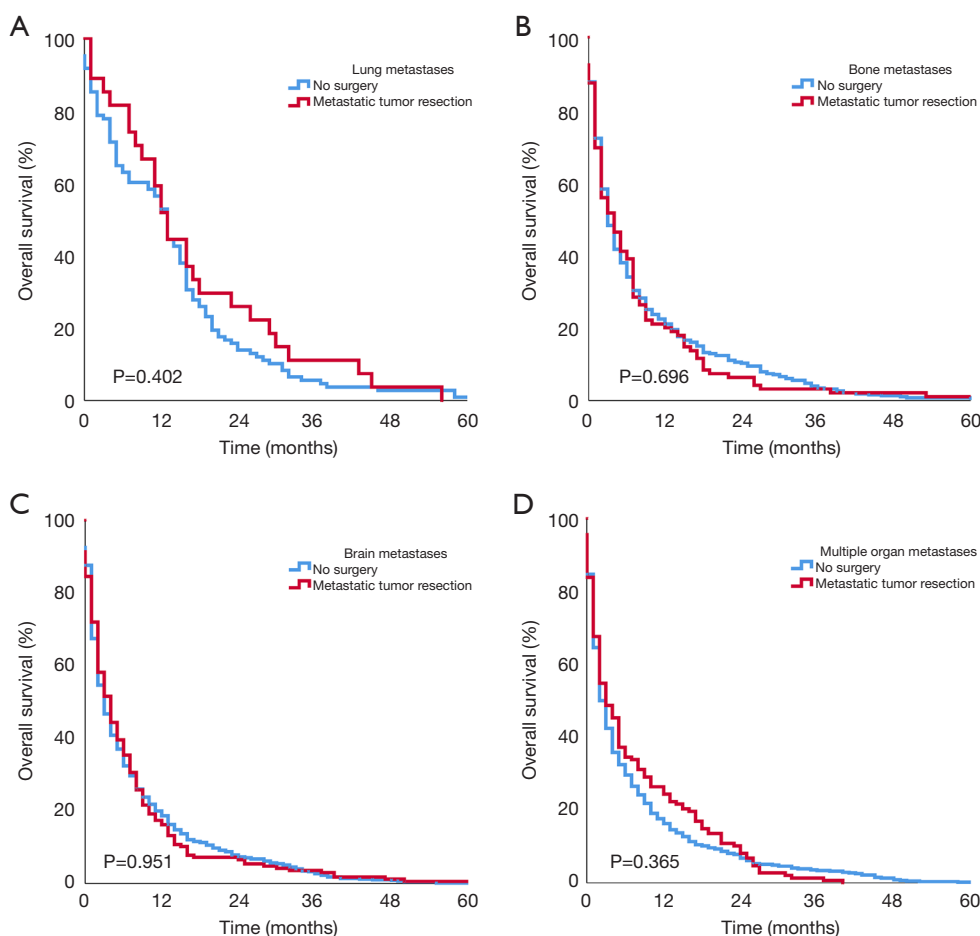
Figure 4 Kaplan-Meier curve of overall survival based on whether or not metastatic tumor resection was performed. (A) Patients with isolated lung metastases; (B) patients with isolated bone metastases; (C) patients with isolated brain metastases; (D) patients with multiple organ metastases.

guidelines have revised the recommendation for PTR as a treatment option for stage IV disease, especially those with limited extrathoracic metastatic disease and early-stage lung tumors. The reality is that few patients receive surgical interventions, and surgery in clinical practice often depends on the surgeon's judgment or the subjective consent of patients (4). Lack of standardized and systematic selection of individualized treatment is another reason that patients with LUM, BOM, BRM, or MOM could not benefit from MTR surgery.

As far as we know, there has been limited study with the primary aim to the comparison of the survival outcomes of LUAD patients with surgical intervention strategies for different metastatic sites. Based on our analysis, we believe that surgical intervention should not be rejected outright for advanced LUAD but should be carried out when

necessary under the careful selection of patients to improve the survival outcomes of some patients. Females, earlier T stage and N stage, chemotherapy, and LND were more likely to benefit from surgical intervention strategies.

Although this analysis suggests survival benefit of surgical intervention strategies for patients with stage IV LUAD, there are several unavoidable limitations in the study, most of which are attributed to the insufficient information in the SEER database: (I) The database cannot list how many metastatic lesions are in a single organ, so it is impossible to study the impact of the metastasis number. (II) The study excluded patients with radiotherapy who influence the assessment of the surgical intervention. Thus, the role of radiotherapy may be overlooked. (III) Because the information of metastatic organs other than lung, bone, brain, and liver is missing, the impact of

surgery on other organs cannot be accurately assessed. (IV) Another limitation of the current research is that data on systemic therapies are unavailable; target therapies and immunotherapy, for example. Nonetheless, as the only comprehensive population-based database, the SEER database provides the ideal approach to study the survival of these patients with open access worldwide. Prospective randomized controlled trials with large sample sizes are needed to further validate the survival benefits of surgical intervention in patients with metastatic LUAD.

Conclusions

The poor prognosis of metastatic LUAD has prompted thoracic surgeons and oncologists to seek and evaluate a variety of treatment strategies to extend survival. This study demonstrates that surgical intervention may be an option to improve the survival of some LUAD patients with different metastatic sites after highly individualized selection.

Acknowledgments

Footnote

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