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ORIGINAL ARTICLE

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Primary tumour resection in non-small-cell lung cancer patients with ipsilateral pleural dissemination (M1a): a population-based study

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Key question

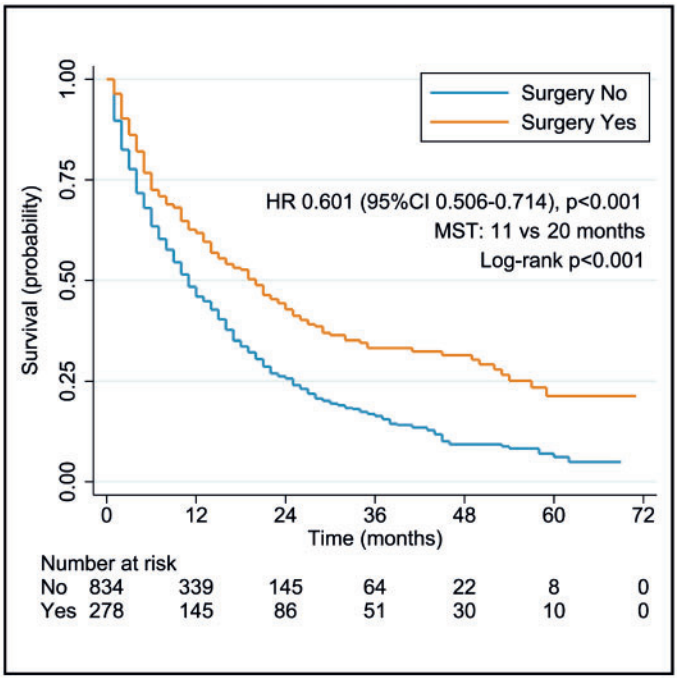
Can patients with non-small-cell lung cancer and ipsilateral pleural dissemination benefit from primary tumour resection?

Key finding(s)

Patients having surgery had better survival rates than those with nonsurgical treatment. Lobectomy was associated with the best survival rate.

Take-home message

Surgery could be used in the multimodal therapy of carefully selected patients with non-small-cell lung cancer and ipsilateral pleural disease.



Abstract

OBJECTIVES: Non-small-cell lung cancer (NSCLC) patients with ipsilateral pleural dissemination (M1a) are generally contraindicated for surgery. However, several small-sample studies have demonstrated that they might benefit from surgery. We investigated the effects of primary tumour resection on survival in these patients.

METHODS: Stage IV NSCLC patients with ipsilateral pleural dissemination were identified from the US National Cancer Institute Surveillance, Epidemiology and End Results database entries from 2010 to 2015. Survival analysis was performed before and after matching. Multivariable regression models were built to identify prognostic factors.

RESULTS: Of the 5513 patients with ipsilateral pleural dissemination, 309 underwent primary tumour resection. In the entire cohort, surgery was associated with improved overall survival (OS) in both the unmatched and matched cohorts (both log rank, $P < 0.001$). In the surgery-recommended cohort, patients treated with surgery also had significantly longer OS before and after matching. Multivariable

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regression models showed that surgery was an independent favourable prognostic factor for OS [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.48–0.65; $P < 0.001$] and lung cancer-specific mortality (subhazard ratio 0.60, 95% CI 0.51–0.70; $P < 0.001$). Surgery was independently associated with improved survival in all subgroups except for those with pericardial effusion ($P = 0.065$) or N3 disease ($P = 0.17$). In the surgical cohort, patients who underwent lobe/bilobectomy had significantly better OS than those who underwent sublobar resection (log rank, $P < 0.001$).

CONCLUSIONS: Inclusion of primary tumour resection in multimodal therapy of NSCLC was associated with improved survival in selected patients with ipsilateral pleural dissemination, except for those with pericardial effusion or N3 disease.

Keywords: Non-small-cell lung cancer • Ipsilateral pleural dissemination • Primary tumour resection • Surveillance Epidemiology and End Results database

INTRODUCTION

More than one-third of new cases of non-small-cell lung cancer (NSCLC) are diagnosed at stage IV [1]. Previously, patients with malignant pleural effusion were regarded as T4 in the 6th edition of tumour, node and metastasis (TNM) staging [2]. Because of extremely poor survival of those patients, patients with metastases within the chest cavity, including malignant pleural/pericardial effusion, pleural/pericardial nodules and contralateral pulmonary nodules, were defined as a new category of M1a in the 7th edition of TNM staging [3]. In 2017, the 8th edition of TNM staging subdivided M1a patients as stage IVA [4].

Recently, several studies have reported the favourable prognosis of patients with pleural dissemination treated by surgery. Liu *et al*. [5] reported that 80 surgical patients had a 5-year survival of 31% and a median overall survival (OS) of 34.3 months. Li *et al*. [6] found that patients with intraoperatively diagnosed pleural seeding who underwent tumour resection had a 3-year progression-free survival of 44.5% and a 3-year OS of 82.9%. However, the large majority of studies evaluating patients with pleural dissemination treated surgically are generally single-institution studies of likely highly selected patients. Thus, the question of which type of patient could benefit from surgery has yet to be clarified.

Therefore, in this study, the US National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database was used to identify a large cohort of NSCLC patients with ipsilateral pleural dissemination and to evaluate outcomes associated with the surgical treatment of the primary tumour in this population.

MATERIALS AND METHODS

Study population

We used the US 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% of the US population. Cases diagnosed as malignant tumours of the lung and bronchus according to the 3rd edition of the International Classification of Disease for Oncology (ICD-O-3) between 2010 and 2015 were included in the eligibility screening process. Among these cases, we applied the following patient inclusion criteria: (i) pathologically confirmed NSCLC; (ii) stage IV M1a disease according to the 7th edition of the American Joint Committee on Cancer (AJCC) TNM classification; and (iii) the disease diagnosed as the first primary malignancy. Patients were excluded if (i) metastases in the contralateral lung were found at the time of diagnosis; (ii) information on survival month, cause of death or surgical status was unavailable; or (iii) the patients were younger than 18 years or had T0 disease. Finally, we used the item 'CS Mets at Dx' to identify patients with different metastatic patterns: (i) code 15 for ipsilateral pleural effusion; (ii) code 20 for pericardial effusion and (iii) code 24 for pleural nodules on the ipsilateral lung separated from direct invasion.

Baseline sociodemographic information, tumour characteristics and surgical information were collected. In this study, histological subtypes were classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma and adenosquamous carcinoma according to the ICD-O-3 histology codes. Surgical procedures were classified as local tumour destruction, sublobar resection, lobe or bilobectomy and pneumonectomy according to the SEER surgery codes for the lung. OS and lung cancer-specific mortality (LCSM) were the outcomes of interest. OS was defined as the time interval from diagnosis to all-cause death, whereas LCSM was defined as death attributed to lung cancer.

Statistical analysis

In this study, we compared the continuous variables using the Mann–Whitney *U*-test and categorical variables using the Pearson's χ^2 test. The Kaplan–Meier method with the log-rank test was performed to compare the survival curves. Propensity score matching (PSM) was carried out to reduce the selection bias. A logistic regression model was established to calculate the propensity score of the following covariates: age, sex, race, insurance, marital status, tumour location, histological subtype, T stage, N stage and metastatic pattern. Patients who underwent surgery were matched with non-surgical patients by 1:3 or 1:1 algorithm without replacement.

A multivariable Cox proportional hazards model was constructed to identify factors associated with OS. After the Cox model was built, proportional hazards assumption was tested by using the Schoenfeld residual method. Similarly, a multivariable competing risks regression model was built to recognize factors associated with LCSM. An analysis of the cumulative incidence of lung cancer-specific death considered non-cancer-specific death as competing events. The Fine–Gray competing risk regression was applied to estimate subhazard ratio (SHR). The multivariable regression model was also applied to adjust for covariates in the subgroup analysis.

All statistical analyses except for the PSM were performed using the Stata/SE 14.0 for Windows (StataCorp, College Station, TX, USA). PSM was performed using the SAS 9.4 (SAS Institute Inc., Cary, NC, USA). No correction for multiple testing was performed. All the statistical tests were 2-sided, and *P*-values of ≤ 0.05 were considered statistically significant.

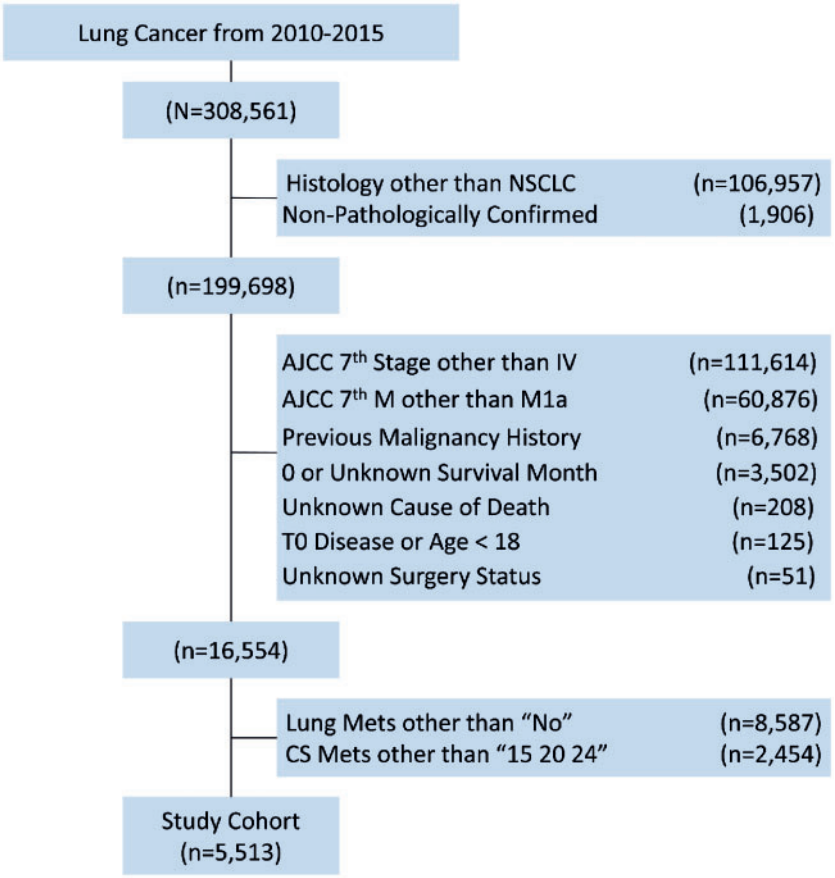

Figure 1: Flow diagram of the study. AJCC: American Joint Committee on Cancer; CS: collaborative staging; NSCLC: Non-small-cell lung cancer.

RESULTS

The patient selection process is presented in Fig. 1. A total of 5513 patients with ipsilateral pleural dissemination were identified in the study. Of these patients, 4209 (76.3%) had pleural effusion, 524 (9.5%) had pericardial effusion and 780 (14.2%) had pleural nodules. Patients with pleural nodules had the highest primary tumour resection rate (11.5%), followed by patients with pleural effusion (4.7%) and those with pericardial effusion (4.0%) (Supplementary Material, Fig. S1). Moreover, the survival outcome of patients with different metastatic patterns was assessed. Patients with pleural nodules also had significantly longer OS than patients with pleural or pericardial effusion ($P < 0.001$). No significant difference in survival was observed between patients with pleural and pericardial effusion ($P = 0.928$, Fig. 2).

In total, 309 (5.6%) patients with ipsilateral pleural dissemination underwent surgical resection of the primary tumour. Compared with those in the non-surgical group, patients in the surgery group were more likely to be young, married, have a tumour located in the lobe and have a lower T stage, lower N stage and pleural nodules (all $P < 0.05$, Table 1). After matching, 1112 patients in total were 1:3 matched in the 2 groups, and all covariates were well balanced (all $P > 0.05$, Table 1). Patients who underwent surgery had significantly longer OS than patients who had not undergone surgery in both the unmatched and matched cohorts (both log rank, $P < 0.001$, Fig. 3A and B).

Apart from the 309 patients who underwent surgery, 142 (2.6%) patients were recommended for surgical intervention by their physician originally but did not ultimately undergo surgery.

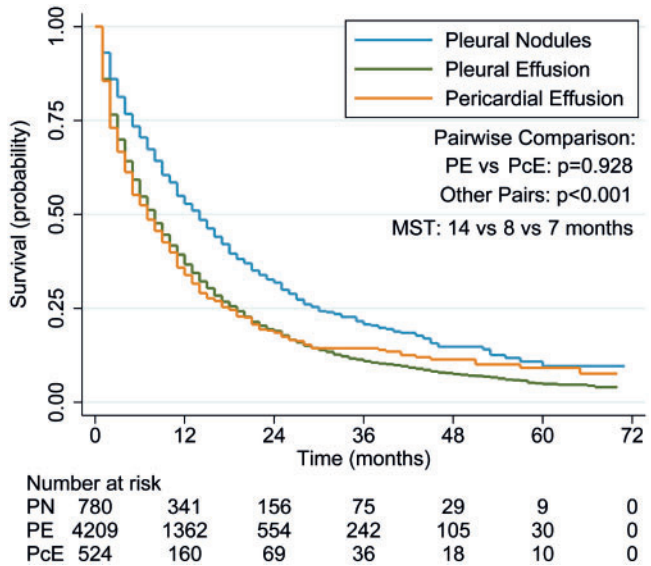

Figure 2: The Kaplan–Meier survival curves of overall survival stratified by metastatic pattern. MST: median survival time; PcE: pericardial effusion; PE: pleural effusion; PN: pleural nodules.

Of these patients, 10 (7.0%) patients died prior to surgery, 45 (31.7%) refused to undergo surgery and 87 (61.3%) did not undergo surgery for unknown reasons. To diminish the immortal time bias, we excluded patients who died prior to surgery and compared the OS of the remaining 132 non-surgical patients

Table 1: Baseline characteristics by surgery before and after PSM

	Entire cohort (*N* = 5513)							
	Non-PSM				PSM			
Variables	Total (5513)	No (5204)	Yes (309)	*P*-value	Total (1112)	No (834)	Yes (278)	*P*-value
Age (years),[a] mean ± SD	69.4 ± 11.1	69.6 ± 11.1	65.9 ± 10.8	**<0.001**	66.2 ± 10.4	66.3 ± 10.3	66.0 ± 10.7	0.827
Sex, *n* (%)				0.983				0.835
Male	2965 (53.8)	2799 (53.8)	166 (53.7)		606 (54.5)	456 (54.7)	150 (54.0)	
Female	2548 (46.2)	2405 (46.2)	143 (46.3)		506 (45.5)	378 (45.3)	128 (46.0)	
Race, *n* (%)				0.954				0.481
White	4124 (74.8)	3889 (74.7)	235 (76.1)		818 (73.6)	604 (72.4)	214 (77.0)	
Black	807 (14.6)	764 (14.7)	43 (13.9)		182 (16.4)	142 (17.0)	40 (14.4)	
Asian	558 (10.1)	528 (10.2)	30 (9.7)		109 (9.8)	86 (10.3)	23 (8.3)	
Other	24 (0.4)	23 (0.4)	1 (0.3)		3 (0.3)	2 (0.3)	1 (0.4)	
Insurance, *n* (%)				0.837				0.741
Uninsured/Medicaid	1099 (19.9)	1036 (19.9)	63 (20.4)		252 (22.7)	191 (22.9)	61 (21.9)	
Insured	4414 (80.1)	4168 (80.1)	246 (79.6)		860 (77.3)	643 (77.1)	217 (78.1)	
Marital status, *n* (%)				**0.003**				0.261
Unmarried	2841 (51.5)	2707 (52.0)	134 (43.4)		464 (41.7)	340 (40.8)	124 (44.6)	
Married	2672 (48.5)	2497 (48.0)	175 (56.6)		648 (58.3)	494 (59.2)	154 (55.4)	
Location, *n* (%)				**<0.001**				0.258
Lobe	4062 (73.7)	3796 (72.9)	266 (86.1)		977 (87.9)	740 (88.7)	237 (85.3)	
Bronchus	333 (6.0)	316 (6.1)	17 (5.5)		48 (4.3)	32 (3.8)	16 (5.8)	
Unknown	1118 (20.3)	1092 (21.0)	26 (8.5)		87 (7.8)	62 (7.4)	25 (9.0)	
Histological subtype, *n* (%)				**0.004**				0.123
Adenocarcinoma	3946 (71.6)	3737 (71.8)	209 (67.6)		778 (70.0)	588 (70.5)	190 (68.4)	
Squamous cell carcinoma	1415 (25.7)	1330 (25.6)	85 (27.5)		298 (26.8)	222 (26.6)	76 (27.3)	
Large cell carcinoma	79 (1.4)	75 (1.4)	4 (1.3)		20 (1.8)	16 (1.9)	4 (1.4)	
Adenosquamous carcinoma	73 (1.3)	62 (1.2)	11 (3.6)		16 (1.4)	8 (1.0)	8 (2.9)	
AJCC 7th edition, T stage, *n* (%)				**<0.001**				0.066
T1	379 (6.9)	354 (6.8)	25 (8.1)		104 (9.4)	80 (9.6)	24 (8.6)	
T2	1712 (31.1)	1617 (31.1)	95 (30.7)		378 (34.0)	284 (34.1)	94 (33.8)	
T3	1272 (23.1)	1177 (22.6)	95 (30.7)		242 (21.8)	174 (20.9)	68 (24.5)	
T4	1325 (24.0)	1242 (23.9)	83 (26.9)		302 (27.2)	221 (26.5)	81 (29.1)	
Tx	825 (15.0)	814 (15.6)	11 (3.6)		86 (7.7)	75 (9.0)	11 (4.0)	
AJCC 7th edition, N stage, *n* (%)				**<0.001**				0.468
N0	1876 (34.0)	1734 (33.3)	142 (46.0)		538 (48.4)	402 (48.2)	136 (48.9)	
N1	385 (7.0)	340 (6.5)	45 (14.6)		89 (8.0)	62 (7.4)	27 (9.7)	
N2	2316 (42.0)	2215 (42.6)	101 (32.7)		405 (36.4)	307 (36.8)	98 (35.3)	
N3	620 (11.3)	609 (11.7)	11 (3.6)		57 (5.1)	47 (5.6)	10 (3.6)	
Nx	316 (5.7)	306 (5.9)	10 (3.2)		23 (2.1)	16 (1.9)	7 (2.5)	
Ipsilateral pleural dissemination, *n* (%)				**<0.001**				0.178
Pleural nodules	780 (14.2)	690 (13.3)	90 (23.1)		299 (26.9)	220 (26.4)	79 (28.4)	
Pleural effusion	4209 (76.4)	4011 (77.1)	198 (64.1)		754 (67.8)	575 (68.9)	179 (64.4)	
Pericardial effusion	524 (9.5)	503 (9.7)	21 (6.8)		59 (5.3)	39 (4.7)	20 (7.2)	

Categorical variables were compared using the Pearson χ^2 test, and continuous variables were compared using the Mann–Whitney *U*-test. Statistically significant *P*-values are indicated in boldface.

[a]Continuous variable.

AJCC: American Joint Committee on Cancer; PSM: propensity score matching; SD: standard deviation.

with that of the 309 surgical patients. Baseline characteristics of this surgery-recommended cohort are described in the Supplementary Material, Table (*n* = 441). After PSM, a total of 138 patients were 1:1 matched in the 2 groups (all $P > 0.05$, Supplementary Material, Table). Patients who underwent surgery had significantly longer OS in both the unmatched (log rank, $P < 0.001$, Fig. 3C) and matched cohorts (log rank, $P = 0.022$, Fig. 3D).

For the entire cohort, multivariable regression models were established to identify factors associated with survival. No violation of the proportional hazard assumption was found in the Cox model ($P = 0.24$, Supplementary Material, Fig. S2). Primary tumour resection was independently associated with both improved OS [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.48–0.65; $P < 0.001$] and LCSM (SHR 0.60, 95% CI 0.51–0.70; $P < 0.001$). Moreover, other baseline characteristics, such as young age, female sex, Asian ethnicity, insured status, married status, lower T stage, lower N stage and pleural nodules, were also independent favourable predictors for both OS and LCSM (Table 2).

Subgroup analyses were performed with a multivariable regression model adjusting for covariates. Surgery was an independent favourable predictor of LCSM in patients with pleural nodules (SHR 0.48, 95% CI 0.35–0.67; $P < 0.001$, Fig. 4A) and pleural effusion (SHR 0.66, 95% CI 0.55–0.80; $P < 0.001$, Fig. 4B), whereas it was not independently associated with improved LCSM in patients with pericardial effusion ($P = 0.065$). In addition, subgroup analyses stratified by histological subtype, T stage and

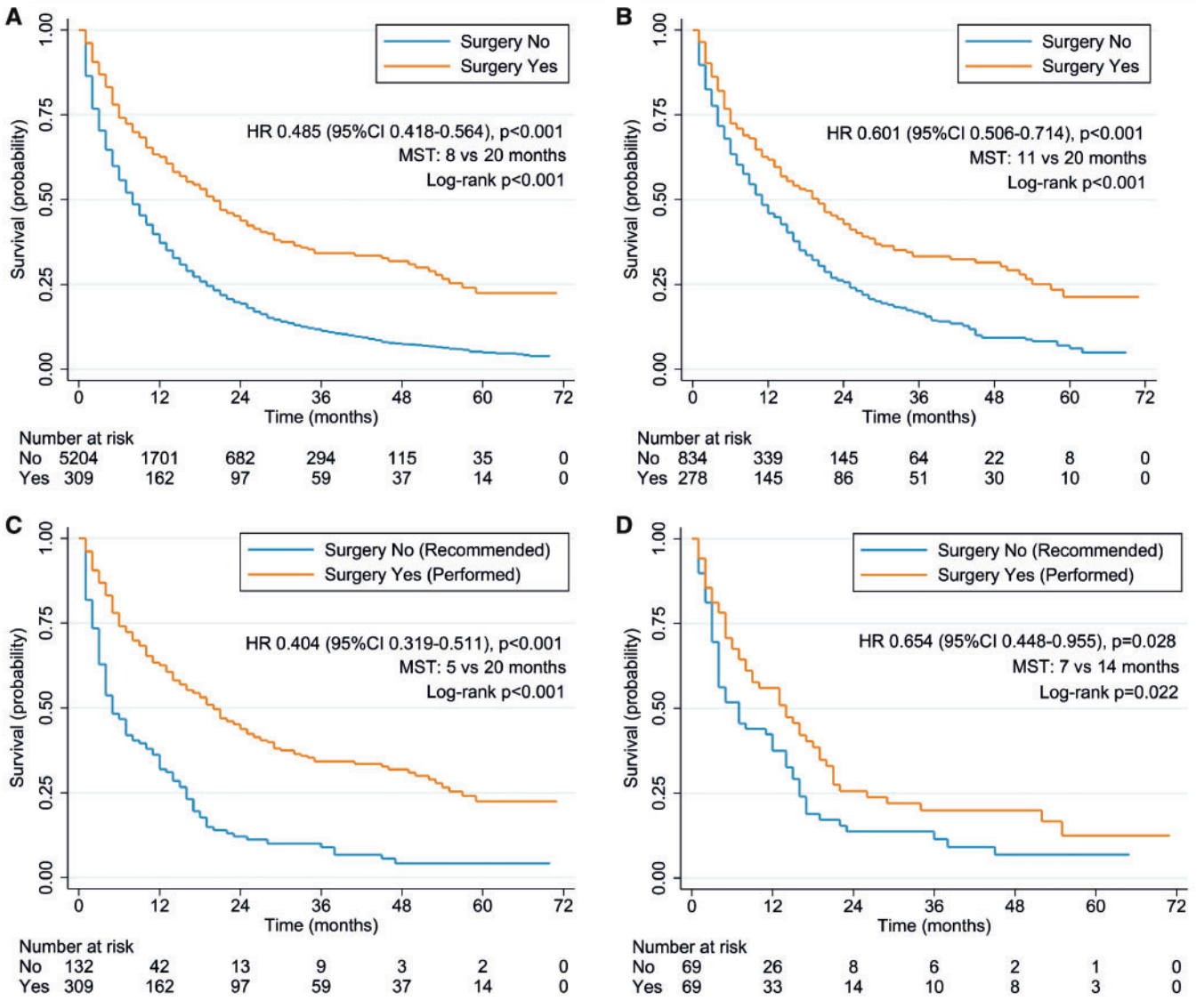

Figure 3: The Kaplan–Meier survival curves of overall survival stratified by surgery in the entire cohort before (**A**) and after (**B**) matching. The Kaplan–Meier survival curves of overall survival stratified by surgery in the surgery-recommended cohort before (**C**) and after (**D**) matching. CI: confidence interval; HR: hazard ratio; MST: median survival time.

N stage were also implemented. Surgery was an independent favourable predictor of LCSM in all subgroups except for patients with N3 disease ($P = 0.17$, Supplementary Material, Fig. S3).

Finally, of the 309 surgical patients, 23 (7.4%), 132 (42.7%), 124 (40.1%) and 30 (9.7%) patients underwent local tumour destruction, sublobar resection, lobe/bilobectomy and pneumonectomy, respectively. Compared with sublobar resection and local tumour destruction, lobe/bilobectomy led to significantly longer OS (log rank, $P < 0.001$, Fig. 5). No significant difference in survival was observed between lobe/bilobectomy and pneumonectomy (log rank, $P = 0.065$).

DISCUSSION

In this population-based analysis of NSCLC patients with ipsilateral pleural dissemination in the SEER database, patients who underwent primary tumour resection were found to have significantly better OS than those treated without surgery both before and after PSM. The multivariable Cox proportional hazard analysis showed that primary tumour resection was independently associated with improved OS and LCSM. The multivariable competing risk analysis revealed that surgery was an independent favourable predictor for LCSM in all subgroups except for patients with pericardial effusion or N3 disease. In the surgical cohort, patients who underwent lobe/bilobectomy had significantly better OS than those who underwent sublobar resection (log rank, $P < 0.001$).

Traditionally, NSCLC patients with pleural dissemination have extremely poor survival, with an median survival time (MST) of 4 months and a 5-year survival rate of 3.1% [7]. Thus, those patients were reclassified as stage IV (M1a) in the 7th edition of the Union for International Cancer Control (UICC) lung cancer staging system [2]. Systemic chemotherapy was the standard therapy, and surgical intervention was considered to be contraindicated for patients with malignant pleural extension [8, 9].

Ichinose *et al.* [10] first reported an unexpectedly good prognosis for patients with carcinomatous pleuritis of minimal disease

Table 2: Multivariable Cox proportional hazard regression and multivariable competing risks regression

	Overall survival			Lung cancer-specific mortality		
Variables	HR	95% CI	*P*-value	SHR	95% CI	*P*-value
Age (per 1 year increased)	1.023	1.020–1.027	**<0.001**	1.018	1.015–1.021	**<0.001**
Sex						
Male	Reference			Reference		
Female	0.821	0.771–0.874	**<0.001**	0.832	0.781–0.886	**<0.001**
Race						
White	Reference			Reference		
Black	1.002	0.918–1.093	0.965	0.931	0.852–1.018	0.118
Asian	0.666	0.596–0.745	**<0.001**	0.718	0.646–0.797	**<0.001**
Other	0.615	0.356–1.062	0.081	0.624	0.335–1.164	0.138
Insurance						
Uninsured/Medicaid	Reference			Reference		
Insured	0.814	0.753–0.880	**<0.001**	0.846	0.781–0.916	**<0.001**
Marital status						
Unmarried	Reference			Reference		
Married	0.829	0.779–0.883	**<0.001**	0.868	0.815–0.924	**<0.001**
Location						
Lobe	Reference			Reference		
Bronchus	1.086	0.957–1.232	0.201	1.079	0.948–1.229	0.251
Unknown	1.098	1.013–1.191	**0.023**	1.061	0.976–1.154	0.163
Histological subtype						
Adenocarcinoma	Reference			Reference		
Squamous cell carcinoma	1.076	1.000–1.158	0.050	0.992	0.920–1.069	0.836
Large cell carcinoma	1.005	0.787–1.283	0.967	0.999	0.779–1.282	0.995
Adenosquamous carcinoma	1.141	0.884–1.473	0.311	1.217	0.956–1.550	0.110
AJCC 7th edition, T stage						
T1	Reference			Reference		
T2	1.238	1.082–1.415	**0.002**	1.188	1.041–1.355	**0.011**
T3	1.321	1.149–1.518	**<0.001**	1.237	1.078–1.419	**0.002**
T4	1.352	1.176–1.554	**<0.001**	1.316	1.146–1.510	**<0.001**
Tx	1.391	1.197–1.617	**<0.001**	1.312	1.128–1.526	**<0.001**
AJCC 7th edition, N stage						
N0	Reference			Reference		
N1	1.036	0.914–1.175	0.578	1.016	0.891–1.158	0.811
N2	1.096	1.020–1.176	**0.012**	1.120	1.043–1.203	**0.002**
N3	1.184	1.065–1.316	**0.002**	1.172	1.053–1.303	**0.004**
Nx	1.125	0.981–1.290	0.091	1.034	0.888–1.204	0.669
Ipsilateral pleural dissemination						
Pleural nodules	Reference			Reference		
Pleural effusion	1.313	1.196–1.442	**<0.001**	1.298	1.187–1.418	**<0.001**
Pericardial effusion	1.391	1.220–1.586	**<0.001**	1.337	1.168–1.529	**<0.001**
Primary tumour resection						
No	Reference			Reference		
Yes	0.561	0.482–0.653	**<0.001**	0.598	0.513–0.697	**<0.001**

Statistically significant *P*-values are indicated in boldface.

AJCC: American Joint Committee on Cancer; CI: confidence interval; HR: hazard ratio; SHR: subhazard ratio.

after surgery, with 3-year and 5-year survival rates of 31.8% and 22.8%, respectively. In 2002, however, Sawabata *et al*. [11] demonstrated the opposite result that tumour resection was not beneficial for the survival of NSCLC patients with minor malignant pleural effusion. However, in the last few years, some single-centre retrospective studies with sample sizes ranging from 25 to 110 patients have shown promising survival outcomes for patients with pleural dissemination who underwent primary tumour resection since 2011 [8, 9, 12–18]. In a multicentre study performed by the Japanese Clinical Oncology Group in 2015, Iida *et al*. [19] reported that 256 patients with pleural carcinomatosis who underwent primary tumour resection had a 5-year survival rate of 33.1%, and macroscopic complete resection was associated with better survival. Recently, a meta-analysis, including 9 retrospective studies, also indicated that resection of a primary tumour was a beneficial prognostic factor among NSCLC patients with malignant pleural disease unexpectedly discovered during surgery [20]. Most of the above studies focused on localized pleural carcinomatosis, especially intraoperatively diagnosed pleural seeding. In 2016, Ren *et al*. [21] analysed the prognosis of NSCLC patients with malignant pleural effusion after surgery using SEER database entries from 2004 to 2012. The results showed that patients who underwent primary tumour resection had better OS and lung cancer-specific survival after PSM. However, this study did not include patients with pleural nodules or malignant pericardial effusion. In fact, when a malignant pleural nodule is unexpectedly identified during operations, it causes a perplexing situation regarding whether to proceed with resection of primary

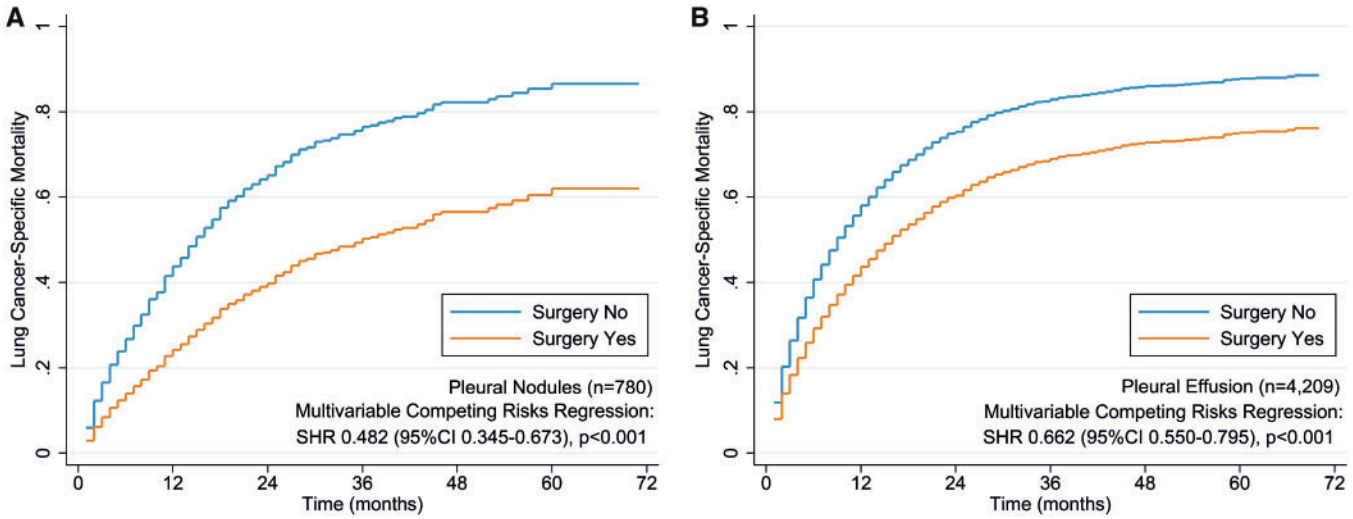

Figure 4: Adjusted subgroup analysis of cumulative incidence of lung cancer-specific mortality stratified by surgery in patients with (**A**) pleural nodules and (**B**) pleural effusion. CI: confidence interval; SHR: subhazard ratio.

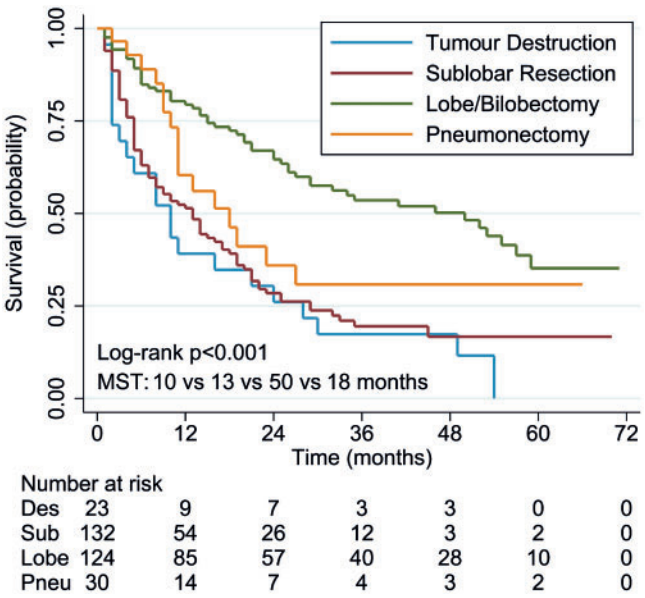

Figure 5: The Kaplan–Meier survival curves of overall survival stratified by surgical procedure in the surgical cohort. MST: median survival time.

tumour or just pleural biopsy. Furthermore, the study by Ren *et al*. only matched the surgery cohort with the non-operation cohort containing a large number of inoperable patients, which could cause selection bias. To reduce this bias, we further conducted an analysis of the cohort recommended for surgery.

In fact, patients with M1a NSCLC have great heterogeneity regarding the extent of pleural disease. Some patients may have only a few small pleural nodules without pleural effusion, which are unexpectedly detected by thoracic surgeons intraoperatively, whereas other patients may already have massive malignant pleural effusion and multiple large pleural nodules, which can be detected using chest computed tomography. The survival benefit of primary tumour resection for M1a patients may vary from person to person according to the disease severity. In the subgroup analysis of our study, both patients with adenocarcinoma and those with squamous cell carcinoma could benefit from primary tumour resection. The survival benefit of surgery seemed to be greater in patients with a lower T stage and a lower N stage, which is consistent with previous studies [13, 15, 19–22]. More importantly, patients with pleural nodules seemed to have a more prominent survival gain from surgery than patients with pleural effusion. One likely explanation for this phenomenon is that patients with only pleural nodules may have a relatively limited pleural disease, which might be well controlled by comprehensive multidisciplinary management. The selection criteria for surgical intervention in M1a NSCLC patients should be further explored.

Of note, the non-surgical group of the study cohort may contain a large number of physically inoperable patients, which could result in selection bias. Therefore, we further analysed the surgery-recommended cohort based on the item 'NAACCR item #: 1340'. The survival of patients who underwent surgery (code 0) and patients who were recommended for surgery by their physician but did not ultimately undergo surgery (codes 5–7) was compared. To diminish the survival time bias, patients who died prior to the recommended surgery (code 5) were excluded. We speculated that physicians hold consistent selection criteria when making the surgical recommendation for their patients. Thus, in this highly selected surgery-recommended cohort, all patients might share a similar health condition (e.g. performance status and comorbidity index) preoperatively. Patients who underwent surgery still had significantly better OS than those who did not both before and after matching, further supporting the effect of surgical intervention in patients with pleural dissemination.

The prognostic effect of different surgical procedures among the 309 surgical patients was further analysed. Compared with patients who underwent sublobar resection, patients who underwent lobe/bilobectomy had the longest MST (50 months) and significantly longer OS ($P < 0.001$). One likely explanation for this result could be that patients who underwent sublobar resection

usually exhibited worse performance and cardiopulmonary function. Another reason might be the oncological benefit of the radical resection. Studies have shown that macroscopic complete resection, which is more likely to be achieved by lobectomy, is associated with better survival [19]. No significant difference in survival was observed between patients who underwent lobe/bilobectomy and those who underwent pneumonectomy in our study ($P = 0.065$). Yamaguchi *et al.* [23] reported a recurrence rate of 88.9% and a 3-year OS rate of 33.3% among patients at stage M1a who underwent extrapleural pneumonectomy. Therefore, the treatment goal of surgical intervention in patients with pleural dissemination would be primary tumour resection, rather than curative surgery, which involves the extensive resection of all uninvolved lung parenchyma.

Strengths and limitations

The strengths of this study are that it is the largest cohort of NSCLC patients with ipsilateral pleural dissemination reported in the literature and utilizes a PSM analysis. Specifically, we analysed the role of surgery in a highly selected surgery-recommended cohort to eliminate as much selection bias as possible. Nevertheless, this study has several inherent limitations due to its retrospective nature. First, selection bias was inevitable. Potential confounding variables that were not captured in the SEER database, such as performance status and comorbidity index, remained unbalanced and could still cause selection bias during the analysis. Second, therapeutic information other than surgical intervention is quite limited in the SEER database. Although it is fair to assume that most patients with stage IV disease received systemic treatment, individualized therapeutic regimens varied from person to person and may have had a great impact on survival. The OS may be especially long for patients harbouring driver gene mutations such as *epidermal growth factor receptor* and *anaplastic lymphoma kinase*. Unfortunately, we were not able to evaluate the effect of systemic therapy on survival in this study. Third, although the patients who underwent surgery had an outstanding survival rate, the appropriate time for surgical intervention during the multimodal management process remained unexplored. Moreover, whether ipsilateral pleural dissemination was incidentally detected at thoracotomy or was diagnosed before surgery remained unclear. Thus, the findings of this study are not comparable to those of previous studies focusing on either intraoperatively detected or preoperatively confirmed pleural disease. It is inappropriate to recommend surgery for M1a NSCLCs patients only on the basis of our study.

CONCLUSIONS

This real-world retrospective population-based study indicates that the inclusion of primary tumour resection in the multimodal therapy of NSCLC was associated with prolonged OS in carefully selected patients with ipsilateral pleural dissemination. Moreover, radical resection might further benefit these patients in conjunction with other cancer modalities.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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APPENDIX. CONFERENCE DISCUSSION

Dr J. Kużdżał *(Cracow, Poland):* We should congratulate you for the excellent study, showing that there are further limits that are not absolute and that we can try to extend the surgical treatment to the patients who classically would be deemed inoperable. I think it's a good sign for the future.