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ORIGINAL ARTICLE

Primary tumor resection of non-small cell lung cancer patients with ipsilateral pleural dissemination (M1a) in the era of targeted therapy

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Keywords
Ipsilateral pleural dissemination; non-small-cell lung cancer; primary tumor resection; targeted therapy.

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Abstract

Background: Non-small cell lung cancer (NSCLC) patients with ipsilateral pleural dissemination (M1a) are generally contraindicated for surgery. Recently, several studies have demonstrated that these patients might benefit from primary tumor resection (PTR). However, whether PTR is beneficial for driver oncogene-positive patients treated with targeted therapy, remains unclear. Here, we investigated the effects of PTR on survival in the era of targeted therapy.

Methods: In total, 105 NSCLC patients with ipsilateral pleural dissemination were identified. The mode of systemic treatment was assessed in this study. Survival analysis was performed with the Kaplan-Meier method and Cox proportional hazards regression. The overall survival (OS) of patients with or without PTR was compared between propensity score-matched groups (caliper: 0.02).

Results: In the entire cohort, PTR was associated with improved OS in both unmatched (median survival time [MST]: 50.0 vs. 29.6 months, $P = 0.019$) and matched (MST: 50.0 vs. 34.4 months, $P = 0.052$) cohorts. Multivariate regression models showed that surgery was an independent favorable prognostic factor for OS. A total of 70 patients underwent genetic testing, and targeted therapies, such as EGFR-TKIs or ALK-TKIs, were used in the driver oncogene-positive patients. Subgroup analysis showed that PTR did not improve OS in the targeted therapy group (MST: 57.1 months vs. 50.4 months, $P = 0.840$). However, surgery significantly prolonged survival in the nontargeted therapy group (MST: 39.8 vs. 14.2 months, $P = 0.002$).

Conclusions: The results of this study indicated that PTR could prolong OS in stage IV NSCLC patients with ipsilateral pleural dissemination, especially in patients who are not candidates for targeted therapy.

Key points

- Non-small cell lung cancer patients with ipsilateral pleural dissemination can benefit from primary tumor resection.
- Primary tumor resection could prolong overall survival (OS) in non-small cell lung cancer patients with ipsilateral pleural dissemination who are not candidates for targeted therapy.

Introduction

Non-small cell lung cancer (NSCLC) patients with ipsilateral pleural dissemination, including malignant pleural/pericardial effusion and nodules, are defined as M1a in the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging.[1] Traditionally, these patients have

extremely poor survival, with median survival time (MST) of 4–11.5 months and a five-year survival rate of 3%–10%.[1, 2] Therefore, surgical intervention has generally been considered to be contraindicated for patients with pleural dissemination.[3, 4]

In the last few years, several retrospective studies have demonstrated that patients with pleural dissemination might benefit from primary tumor resection (PTR), with a five-year overall survival (OS) of up to 30%–40%.[5-7] In addition to those previous single-center studies, Ren and colleagues[8] showed that the prognosis of NSCLC patients with malignant pleural effusion were significantly improved after contraindicated surgery, using the Surveillance, Epidemiology, and End Results (SEER) database. Recently, our study based on the SEER database also supported a favorable prognostic effect of PTR for NSCLC patients with pleural dissemination.[9] However, the data from the SEER database does not include adjuvant therapeutic information or perioperative outcome.

In the last decade, new multimodality treatment options, especially targeted therapy for driver oncogene-positive patients, have significantly improved the survival of stage IV NSCLC patients.[10, 11] Recently, Li and colleagues[12] reported that patients with intraoperatively diagnosed pleural seeding who underwent PTR had a three-year progression-free survival (PFS) of 44.5% and a three-year OS of 82.9%. The extremely long survival may be related to the high adoption rate (approximately 76%) of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).

However, it is unclear whether PTR has a survival benefit for patients with pleural dissemination treated by targeted therapy. In the present study, we aimed to investigate whether resection of the primary tumor improved survival compared with pleural biopsy alone especially among patients who received targeted therapy.

Methods

Study population

The patient selection process is shown in Figure 1. From 1 January 2006 to 31 December 2016, a total of 5041 patients underwent surgical resection consecutively in the Department of Thoracic Surgery, Peking University People's Hospital, and 105 NSCLC patients with ipsilateral pleural dissemination receiving surgical treatment were included.

Assessment procedures included chest radiography, blood chemistry analysis, brain computed tomography (CT) or magnetic resonance imaging (MRI), chest CT, abdominal CT or ultrasound, positron emission tomography (PET) scanning or bone scanning, and pulmonary function testing.

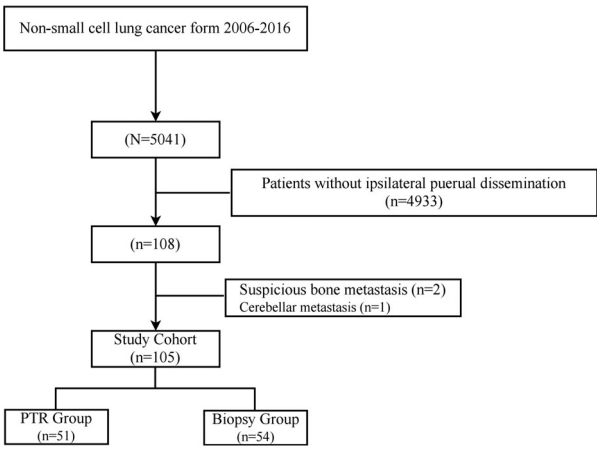

Figure 1 Flow diagram of the study.

For patients with preoperative ipsilateral pleural dissemination, surgical intervention was mainly performed for relieving symptoms and harvesting enough tumor tissue for pathology diagnosis and genetic testing. Each surgeon decided whether to perform PTR or pleural biopsy alone at his discretion in the whole cohort according to the intraoperative findings. A total of 51 patients underwent primary main tumor and visible pleural nodule resection (PTR group). Pleural nodule biopsy was performed in the other 54 patients (biopsy group). It should be noted that visceral pleural nodules were not totally resected, so both groups were considered as R1 resection. Stages were classified according to the AJCC TNM Classification for Lung and Pleural Tumors (eighth edition). Informed consent was waived for this retrospective study by the Research Ethics Committee of the Peking University People's Hospital.

The patients underwent follow-up adjuvant therapy in our center or at local hospitals. Results of follow-up evaluations were recorded every six months by phone call or review of outpatient clinic revisit records.

Statistical analysis

To compare the baseline characteristics between the PTR group and the biopsy groups, we used Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The Kaplan-Meier method with the log-rank test was used to compare the survival curves. Propensity score matching (PSM) was carried out to reduce patient selection bias. A logistic regression model was established to calculate the propensity score considering the following covariates: age, clinical M stage, pathological

T stage, N stage, state of malignant pleural effusion and pleural nodules, state of chemotherapy, radiotherapy and targeted therapy. Patients who underwent PTR were matched with patients who underwent biopsy by a 1:1 algorithm without replacement (caliper:0.02) (Figure S1). To access factors associated with OS, we constructed a multivariate Cox proportional hazards model, and no violation of the assumption was found in the Cox model.

All statistical analyses were performed using Stata/SE 15.1 for Windows (Stata Corp, College Station, TX, USA). *P*-values of 5% were considered to be statistically significant.

Results

Demographics and clinicopathological characteristics

We included a total of 105 patients diagnosed with NSCLC with ipsilateral pleural dissemination. The median follow-up time was 49.1 months. The mean age was 58.4 years (range 29–89 years). A total of 53 patients had suspicious pleural metastases according to radiographic evidence (clinical stage M1a, cM1a), seven with noted pleural effusion received thoracentesis and were confirmed to have malignant pleural effusion pathologically, and the remaining 52 patients were unexpectedly diagnosed with pleural seeding (clinical stage M0, cM0). Four patients in the biopsy group suffered from massive pleural effusion and pulmonary atelectasis, and thus we were unable to determine the clinical stage (clinical stage Tx in Table 1).

A total of 70 patients underwent genetic testing, and 50 patients were found to have *EGFR* mutation, three had *ALK* arrangement, and two were found to have *ROS1* arrangement. Driver mutations were not found in the other 15 patients. Malignant pleural effusion was found in 51 patients during surgery. A total of 93 patients (88.6%) had diffuse parietal pleural metastasis, and 12 patients (11.4%) only had localized parietal pleural metastasis. There were significantly more patients with malignant pleural effusion (59.3% vs. 37.2%; $P = 0.032$) and diffused parietal pleural metastasis (100.0% vs. 76.5%; $P < 0.001$) in the biopsy group compared with the PTR group. The clinical T, N and M stage were higher in the biopsy group than in the PTR group ($P = 0.004$/0.04/0.032). After PSM, a total of 52 patients were 1:1 matched to two groups, and all covariates were well balanced (all $P > 0.05$), Demographics and baseline characteristics before and after PSM are listed in Table 1.

Operative and perioperative results

Of the entire cohort, 99 patients (94.2%) underwent video-assisted thoracoscopic surgery (VATS), while six patients (5.7%) underwent thoracotomy. In the PTR group, 12 patients underwent lobectomy ($n = 11$) or pneumonectomy ($n = 1$) and systematic lymph node dissection. Sublobar resections were performed in the remaining 39 patients (37 wedge resections and two segmentectomies), 16 of whom underwent mediastinal lymph node sampling at the same time.

Patients in the PTR group had longer operative time and more operative bleeding than those in the biopsy group (136 vs. 94 minutes, $P < 0.001$; 86 vs. 43 mL, $P = 0.045$). There were no other statistically significant between-group differences in perioperative outcomes, including chest tube duration (4.2 vs. 4.2 days; $P = 0.997$) and postoperative hospital stay ($P = 0.403$). Overall, four postoperative complications occurred. All four patients received conservative treatment and recuperated smoothly without reoperation. There was no perioperative deaths in the entire short term.

Neoadjuvant and adjuvant treatment

In the whole cohort, three patients underwent neoadjuvant platinum-based chemotherapy, and all remained as stable disease before surgery. Patients were recommended for gene mutation testing postoperatively since 2008. Targeted therapies were recommended for all driver mutation positive patients. Platinum-based chemotherapy within one month postoperatively was recommended for all patients with driver oncogenes (negative or unknown).

However, considering the patients' wishes and medical insurances, the actual situation was different from the recommendation. In fact, 10 patients in the whole cohort rejected all adjuvant treatment and received follow-up only. A total of 70 tumor specimens were tested for mutation. EGFR-TKIs, including gefitinib (Iressa), icotinib (Conmana), or erlotinib (Tarce-va), or ALK-TKIs, including crizotinib (Xalkori), were prescribed for all 55 driver oncogene-positive patients. One patient with ROS1 arrangement refused TKI therapy. In total, 54 patients received targeted therapy.

In the targeted therapy group, 36 patients received targeted therapy as first-line therapy, while the other 18 patients received 1–4 cycles of chemotherapy before commencing targeted therapy. A total of 34 of 54 patients experienced disease progression during follow-up, 21 of whom received a higher level of TKI treatment with drugs such as osimeritinib (Targisso) or lorlatinib (Lorbrena), as well as six patients who received salvage chemotherapy. Adjuvant radiotherapy was administered to seven patients for local tumor progression or distant metastasis control.

Survival analysis

The three-year OS and five-year OS rates for all patients were 55.5% and 29.2%, respectively. In the entire cohort,

Table 1 Baseline characteristics by surgery before and after propensity score matching

Variable	Entire cohort (*N* = 105)							
	Non-PSM				PSM			
	Total (105)	Biopsy (54)	PTR (51)	*P*-value	Total (52)	Biopsy (26)	PTR (26)	*P*-value
Age, mean ± SD, years	58.4 ± 11.9	59.9 ± 10.4	56.9 ± 13.3	0.183	57.2 ± 11.2	58.7 ± 9.7	55.6 ± 12.6	0.272
Sex								
Male	50 (47.6)	26 (48.1)	24 (47.0)	1	24 (46.2)	11 (42.3)	13 (50.0)	0.781
Female	55 (52.4)	28 (51.9)	27 (53.0)		28 (53.8)	15 (57.7)	13 (50.0)	
Smoking status								
Yes	37 (35.2)	19 (35.2)	18 (35.3)	1	14 (26.9)	8 (30.8)	6 (23.1)	0.755
No	68 (64.8)	35 (64.8)	33 (64.7)		38 (73.1)	18 (69.2)	20 (76.9)	
Comorbidities								
Yes	50 (47.6)	25 (46.3)	25 (49.0)	0.846	23 (44.2)	11 (42.3)	12 (46.2)	1
No	55 (52.4)	29 (53.7)	26 (51.0)		29 (55.8)	15 (57.7)	14 (53.8)	
Preoperative lung function								
Predicted FEV1, %	85.2 (66.1–95.2)	80.9 (63.0–93.9)	90.7 (74.4–98.1)	0.084	87.2 (71.4–95.2)	87.2 (68.6–95.0)	90.7 (71.7–98.2)	0.857
FEV1/ FVC, %	79.7 (74.7–84.0)	79.1 (74.4–83.4)	79.8 (75.2–84.5)	0.118	78.3 (74.7–83.3)	78.3 (74.2–81.4)	79.7 (76.0–84.4)	0.28
Neoadjuvant chemotherapy								
Yes	3 (2.8)	2 (3.7)	1 (2.0)	1	2 (3.8)	1 (3.8)	1 (3.8)	1
No	102 (97.1)	52 (96.3)	50 (98.0)		50 (96.2)	25 (96.2)	25 (96.2)	
Surgical approach								
VATS	99 (94.3)	53 (98.2)	46 (90.2)	0.106	50 (96.2)	26 (100.0)	24 (92.3)	0.49
Thoracotomy	6 (5.7)	1 (1.8)	5 (9.8)		2 (3.8)	0 (0.0)	2 (7.7)	
Operation time, minutes	100 (80–135)	85(70–110)	120 (90–150)	<0.001	110 (83.8–132.5)	90 (76.2–116.2)	115 (90–142.5)	0.081
Tube duration, day	4 (3–5)	4(3–5)	4 (3–5)	0.997	4(3–5.5)	4 (3–6)	3 (3–5)	0.283
Postoperative hospital stay, day	6 (5–7)	6 (5–7)	6 (5–7.5)	0.403	6(6–7)	6 (5–7)	6 (5–7.5)	0.852
Operative bleeding, mL	30 (20–50)	30 (10–50)	50 (20–100)	0.045	30 (20–50)	30 (12.5–50)	30 (20–100)	0.282
Histological subtype								
Adenocarcinoma	99 (94.3)	51 (94.4)	48 (94.1)	0.833	51 (98.1)	25 (96.2)	26 (100.0)	1
Squamous cell carcinoma	5 (4.8)	3 (5.6)	2 (3.9)		1 (1.9)	1 (3.8)	0 (0.0)	
Adenosquamous carcinoma	1 (0.9)	0 (0.0)	1 (2.0)					
Malignant pleural effusion								
Absent	54 (51.4)	22 (40.7)	32 (62.8)	0.032	21 (40.4)	8 (30.8)	13 (50.0)	0.258
Present	51 (48.6)	32 (59.3)	19 (37.2)		31 (59.6)	18 (69.2)	14 (50.0)	
Pleural nodule								
Localized	12 (11.4)	0 (0.0)	12 (23.5)	<0.001	0 (0.0)	0 (0.0)	0 (0.0)	/
Diffused	93 (88.6)	54 (100.0)	39 (76.5)		52 (100.0)	26 (100.0)	26 (10.0)	
Clinical T stage								
T1	36 (34.3)	12 (22.2)	24 (47.0)		20 (38.5)	8 (30.8)	12 (46.1)	
T2	28 (26.7)	14 (25.9)	14 (27.4)		17 (32.7)	11 (42.3)	6 (23.1)	
T3	10 (9.5)	4 (7.4)	6 (11.8)	0.004	5 (9.6)	1 (3.8)	4 (15.4)	0.239
T4	27 (25.7)	20 (37.0)	7 (13.7)		10 (19.2)	6 (23.1)	4 (15.4)	

Table 1 Continued

Variable	Entire cohort (*N* = 105)							
	Non-PSM				PSM			
	Total (105)	Biopsy (54)	PTR (51)	*P*-value	Total (52)	Biopsy (26)	PTR (26)	*P*-value
Tx	4 (3.8)	4 (7.4)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Clinical N stage								
N0	79 (75.2)	36 (66.8)	43 (84.3)		45 (86.5)	21 (80.8)	24 (86.5)	
N1	3 (2.9)	2 (3.7)	1 (2.0)	0.04	0 (0.0)	0 (0.0)	0 (0.0)	0.419
N2	17 (16.2)	10 (18.5)	7 (14.0)		6 (11.5)	4 (15.4)	2 (7.7)	
Nx	6 (5.7)	6 (11.1)	0 (0.0)		1 (1.9)	1 (3.8)	0 (0.0)	
Clinical M stage								
M0	52 (49.5)	21 (38.9)	31 (60.8)	0.032	27 (51.9)	14 (53.8)	13 (50.0)	1
M1	53 (50.5)	33 (61.1)	20 (39.2)		25 (48.1)	12 (46.2)	13 (50.0)	
Pathological T stage								
T1	11 (10.5)	4 (7.4)	7 (13.7)	0.003	4 (7.7)	2 (7.7)	2 (7.7)	0.36
T2	47 (44.8)	19 (35.2)	28 (54.9)		31 (59.6)	16 (61.5)	15 (57.7)	
T3	14 (13.3)	5 (9.3)	9 (17.6)		6 (11.5)	1 (3.8)	5 (19.2)	
T4	29 (27.6)	22 (40.7)	7 (13.7)		11 (21.2)	7 (26.9)	4 (15.4)	
Tx	4 (3.8)	4 (7.4)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Pathological N stage								
N0	16 (15.2)	4 (7.4)	12 (23.5)		6 (11.5)	3 (11.5)	3 (11.5)	
N1	5 (4.8)	2 (3.7)	3 (5.9)	0.006	2 (3.8)	1 (3.8)	1 (3.8)	0.733
N2	34 (32.4)	14 (25.9)	20 (39.2)		16 (30.8)	6 (23.1)	10 (38.5)	
Nx	50 (47.6)	34 (63.0)	16 (31.3)		28 (53.8)	16 (61.5)	12 (46.2)	
Radiotherapy								
Yes	7 (6.7)	3 (5.6)	4 (7.8)	0.711	5 (9.6)	3 (11.5)	2 (7.7)	1
No	98 (93.3)	51 (94.4)	47 (92.2)		47 (90.4)	23 (88.5)	24 (92.3)	
Targeted therapy								
Yes	54 (51.4)	24 (44.4)	30 (58.8)	0.173	31 (57.8)	15 (57.8)	15 (57.8)	1
No	51 (48.6)	30 (55.6)	21 (41.1)		22 (42.3)	11 (42.3)	11 (42.3)	
Chemotherapy								
Yes	57 (54.3)	28 (51.8)	29 (56.9)	0.696	31 (59.6)	14 (53.8)	17 (65.4)	0.572
No	48 (45.7)	27 (48.2)	23 (43.1)		21 (40.4)	12 (46.2)	9 (34.6)	

Values are presented as mean ± SD, median (interquartile range) or n (%) (mean ± SD for normal variables or median, interquartile range for non-normal variables). FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PTR, primary tumor resection; SD, standard deviation.

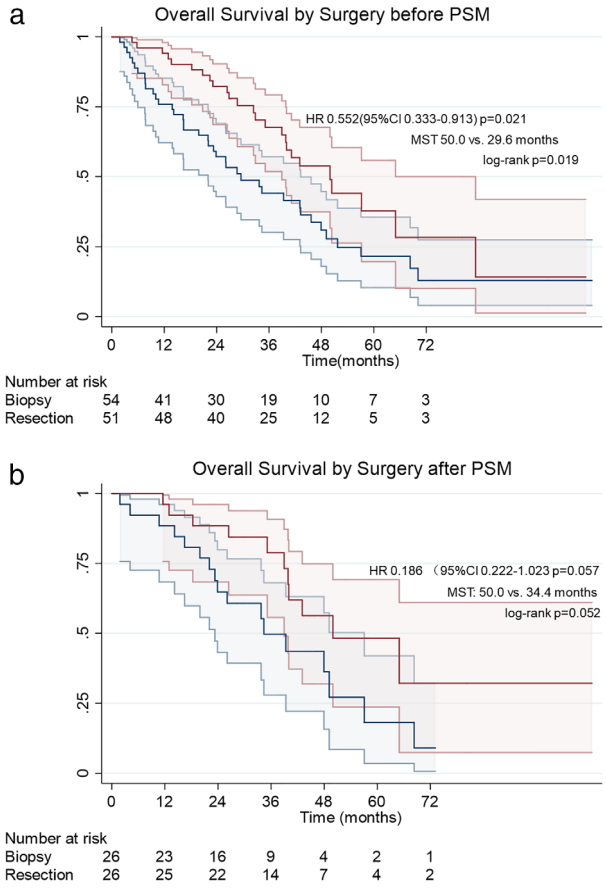

Figure 2 Kaplan-Meier survival curves of OS stratified by surgery in the entire cohort before, (**a**) and after, (**b**) matching. 95% CI, ——Biopsy, 95% CI, ——Resection. PTR, primary tumor resection; PSM, propensity-score. matched; CI, confidence interval; HR, hazard ratio; MST, median survival time.

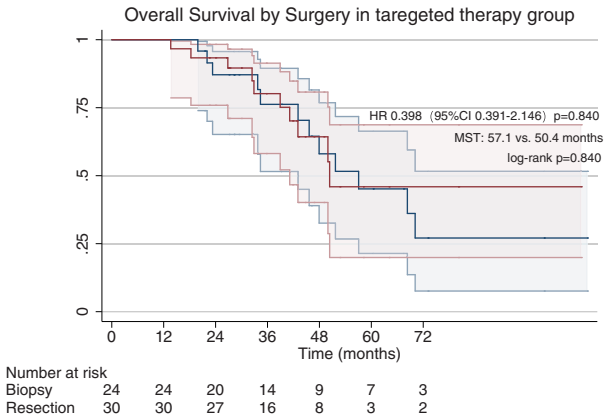

Figure 3 Kaplan-Meier survival curves of OS stratified by targeted therapy. 95% CI, ——Biopsy, 95% CI, ——Resection. CI, confidence interval; HR, hazard ratio; MST, median survival time.

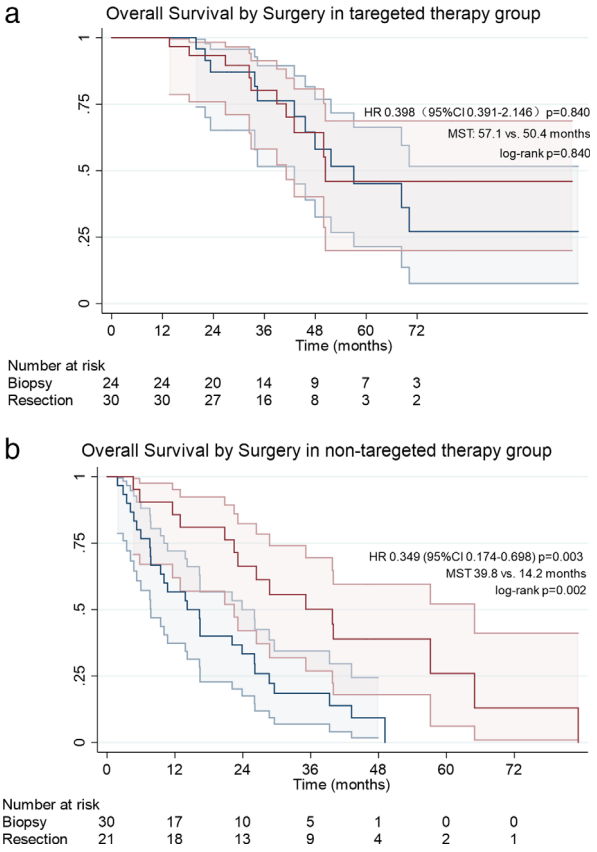

Figure 4 Kaplan-Meier survival curves of OS in patients stratified by surgery in targeted therapy group, (**a**) and nontargeted therapy group, (**b**); 95% CI, ——Biopsy, 95% CI, ——Resection. CI, confidence interval; HR, hazard ratio; MST, median survival time.

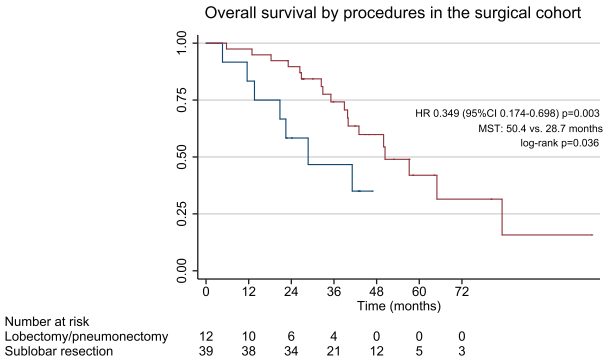

Figure 5 Kaplan-Meier survival curves of OS stratified by surgical procedure in the surgical cohort. —— Lobectomy/pneumonectomy, ——Sublobar resection. CI, confidence interval; HR, hazard ratio; MST, median survival time.

PTR was associated with significantly improved OS in the unmatched cohort (MST 50.0 vs. 29.6 months, P = 0.019, Fig 2a). After PSM, patients who underwent PTR tended

Table 2 Multivariate Cox proportional hazard regression of the entire cohort

	Univariate			Multivariate		
Variable	Crude HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Age						
<65	Reference		0.144	Reference		
≥65	1.447	0.882–2.377		1.008	0.55–1.845	0.979
Sex						
Male	Reference		0.379			
Female	0.8	0.486–1.316				
Smoking status						
No	Reference		0.232			
Yes	1.354	0.824–2.225				
Comorbidities						
No	Reference		0.049	Reference		
Yes	0.606	0.368–0.999		0.641	0.342–1.201	0.165
Neoadjuvant chemotherapy						
No	Reference					
Yes	1.718	0.536–5.508	0.363			
Clinical M stage						
M0	Reference			Reference		
M1	2.232	1.334–3.732	0.002	1.316	0.6–2.888	0.493
Primary tumor resection						
No	Reference			Reference		
Yes	0.552	0.333–0.913	0.021	0.515	0.28–0.946	0.033
Pleural nodule						
Localized	Reference					
Diffused	0.937	0.446–1.971	0.86			
Malignant pleural effusion						
Absent	Reference			Reference		
Present	2.238	1.337–3.745	0.002	1.853	0.901–3.771	0.089
Surgical approach						
VATS	Reference			Reference		
Thoracotomy	2.639	1.132–6.151	0.025	3.649	1.14–11.679	0.029
Histologic subtype						
Adenocarcinoma	Reference			Reference		
Squamous cell carcinoma	6.058	2.341–15.676	<0.001	6.821	1.674–27.793	0.007
Adenosquamous carcinoma	1.527	0.210–11.117	0.676	2.201	0.232–20.904	0.492
Pathological T stage						
T1	Reference			Reference		
T2	0.888	0.380–2.076	0.785	1.186	0.421–3.339	0.747
T3	1.431	0.541–3.732	0.475	1.134	0.337–3.815	0.839
T4	1.731	0.753–3.98	0.196	1.763	0.564–5.508	0.329
Tx	4.112	1.202–14.067	0.024	3.379	0.659–17.328	0.144
Pathological N stage						
N0	Reference			Reference		
N1	0.813	0.154–5.204	0.807	0.508	0.612–4.22	0.513
N2	2.672	1.013–7.044	0.047	1.779	0.566–5.595	0.324
Nx	2.002	0.777–5.156	0.151	1.348	0.464–3.911	0.583
Radiotherapy						
No	Reference					
Yes	1.014	0.406–2.532	0.976			
Targeted therapy						
No	Reference			Reference		
Yes	0.255	0.151–0.432	<0.001	0.21	0.107–0.414	<0.001
Chemotherapy						
No	Reference			Reference		
Yes	0.688	0.413–1.145	0.15	0.461	0.315–0.895	0.022

CI, confidence interval; HR, hazard ratio; VATS, video-assisted thoracoscopic surgery.

to have longer OS in the matched cohort (MST 50.0 vs. 34.4 months, $P = 0.052$, Fig 2b), but there was no significant difference. These results suggested that PTR was a beneficial prognostic factor for M1a NSCLC patients.

Targeted therapy also improved OS significantly (MST 51.7 vs. 23.1 months, $P < 0.001$, Fig 3). To access the effect of PTR for patients receiving targeted therapy or not, a subgroup analysis was performed, which showed that PTR did not improve OS in the targeted therapy group (MST 57.1 vs. 50.4 months, $P = 0.840$, Fig 4a). However, surgery significantly prolonged survival in the nontargeted therapy group (MST:39.8 vs. 14.2 months, $P = 0.002$, Fig 4b). In addition, in the surgical cohort, patients who underwent sublobar resection had significantly better OS than those who underwent lobectomy/pneumonectomy ($P = 0.036$, Fig 5).

For the entire cohort, multivariate regression models adjusted for sociodemographic, tumor features, and therapeutic characteristics were established to identify factors associated with survival. Variables whose P-value <0.20 under univariate test were involved in the multivariate model. Factors independently associated with improved OS include PTR (HR: 0.515, 95% CI: 0.280–0.946, $P = 0.033$), targeted therapy (HR: 0.210, 95% CI: 0.107–0.414, $P < 0.001$) and chemotherapy (HR:0. 461, 95% CI: 0.315–0.895, $P = 0.022$). Factors independently associated with declined OS include thoracotomy (HR: 3.649, 95% CI: 1.140–11.679, $P = 0.029$) and squamous cell carcinoma (HR: 6.821, 95% CI: 1.674–27.793, $P = 0.007$). Further details are listed in Table 2.

Discussion

Owing to the extremely poor survival of NSCLC patients with pleural dissemination, the seventh edition of the Union for International Cancer Control (UICC) lung cancer staging system reclassified those patients from T4 to M1a (stage IV).[13, 14] Surgical intervention for the treatment of M1a NSCLC patients has traditionally been considered to be contraindicated according to guidelines.[3, 4] NSCLC patients with ipsilateral pleural dissemination have great heterogeneity regarding different pleural extension severities. In general, two clinical scenarios are encountered by thoracic surgeons. Some patients are preoperatively staged as resectable but are unexpectedly diagnosed intraoperatively with pleural dissemination (clinical stage M0, cM0). Another is that malignant pleural effusion or pleural seeding has already been detected in NSCLC patients by chest CT (clinical stage M1a, cM1a). Surgical intervention is mainly performed in these patients for diagnostic biopsy to harvest enough tumor tissue for pathology diagnosis and genetic testing.

The majority of studies on surgical intervention in M1a patients have focused on clinical stage M0 patients. In 2001, Ichinose *et al.*[15] first reported an unexpectedly good prognosis regarding the survival of patients with carcinomatous pleuritis found during thoracotomy with 100 patients undergoing main tumor resection with three- and five-year survival rates of 31.8% and 22.8%, respectively. However, Sawabata *et al.*[16] found that patients with malignant minor pleural effusion detected at thoracotomy, even with gross complete resection of the tumor, had a MST of only 13 months. In the last decade, several single-center retrospective studies with sample sizes ranging from 25 to 110 patients have shown favorable outcomes for M1a patients undergoing PTR, with MSTs ranging from 15 to 64 months and three-year OSs ranging from 34.2% to 82.9%, respectively.[6, 12, 17–22] A recent meta-analysis of nine retrospective studies[23] also suggested that PTR was a beneficial prognostic factor among cM0 and pM1a NSCLC patients.

Few studies on cM1a NSCLC patients have been reported. Liu *et al.*[5] retrospectively analyzed the effectiveness of PTR in 80 M1a patients and found that the five-year OS reached 31%. Recently, two studies using the SEER database also suggested that surgery was associated with improved OS for patients with M1a patients.[8, 9] Our study also demonstrated that patients who underwent PTR had significantly better OS than biopsy alone. After PSM, the PTR group tended to have longer OS but there was no significant difference.

The management of advanced lung cancer has changed dramatically since the development of targeted therapy, especially given the excellent efficacy of EGFR/ALK-TKIs for patients harboring *EGFR/ALK* mutations.[10] Therefore, should the surgical strategy used for M1a NSCLC patients be changed according to the tumor genotype is a new question. In 2015, Yun *et al.*[6] reported a similar rate (approximately 50%) of *EGFR* mutation and EGFR-TKI treatment between a resection and an exploration group in patients with localized pleural seeding first detected during surgery. In the most recent study by Li *et al.*[12] approximately 67% of patients with adenocarcinomas ($n = 29$) received EGFR-TKI therapy, which contributed, in part, to the surprising surgical outcomes of patients with lung adenocarcinoma with intraoperatively diagnosed pleural seeding. However, the question remains whether main tumor resection still needs to be performed among *EGFR* mutation-positive patients who could have excellent survival receiving only EGFR-TKI therapy. Therefore, in our study, we further compared the survival effect of PTR among the targeted therapy group and the nontargeted therapy group. The results showed that PTR did not improve OS in the targeted therapy group, owing to the excellent survival benefit of targeted therapy regardless of the type of surgery. However, PTR significantly prolonged survival in the nontargeted therapy group. The possible

reason for this survival effect of PTR might be reduction in tumor burden and the cytoreduction of possible drug-resistant lesions. These results suggested PTR as a valuable treatment for oncogene-negative M1a patients who cannot receive targeted therapy.

Of note, following the development of minimally invasive thoracic surgery, the decreasing rate of perioperative mortality and morbidity have made it more cost-effective for surgical intervention of primary tumors. In 2018, Li *et al.*[12] performed PTR in 30 M1a patients using VATS. No other statistically significant differences in perioperative parameters except longer operative times in the PTR group were observed. In the PTR cohort of our study, the rate of VATS was almost 90% among patients (46 of 51, 90.2%). The PTR group had a longer operation time and more bleeding, but there were no significant differences between the two groups in chest tube duration and postoperative hospital stay. These results may provide evidence that in the era of thoracoscopic surgery, PTR for M1a patients will not cause more harm than biopsy alone.

We further analyzed the prognostic effect of different surgical procedures among the PTR group of patients who underwent sublobar resection and they had significantly better OS than those who underwent lobectomy/pneumonectomy ($P = 0.036$). This result was opposite to that compared with our previous SEER-based study.[9] It may be because of the limited sample size of our retrospective study. On the other hand, differences such as the stage of pleural nodules and systemic therapy between the two groups may also bring bias to survival (Table S1). A greater percentage of patients who underwent lobectomy/pneumonectomy were stage T3/T4 (58.3%) than those who received sublobar resection (23.1%). The heavier tumor burden among patients who received lobectomy/pneumonectomy was probably related to their worse survival. Which procedure is better for M1a NSCLC patients still requires more evidence.

Taken together, previous studies and our present study suggest the following surgical therapeutic strategy for M1a NSCLC patients. (i) For patients with "unexpected" pleural dissemination during surgery, surgeons should try to resect the main tumor to prolong patient survival. (ii) For cM1a patients with ipsilateral pleural dissemination, such as malignant pleural effusion confirmed by pathology, surgery should be carefully considered as an important option in multimodal therapy regimens, especially for patients negative for driver mutations. (iii) To ensure patients receive systemic therapy sooner, the VATS technique is preferable to thoracotomy.

Several inherent limitations were identified due to the retrospective nature of this study. First, time-trend bias and patient selection bias were inevitable in this single-institution retrospective study considering only one decade. We set the inclusion period of this study to begin in 2006 to cover most of the targeted therapy era and to achieve the maximum sample size at the cost of increasing the time-trend bias. However, we adopted the PSM method to reduce patient selection bias between the PTR group and the biopsy group as much as possible. Patient selection bias still existed in the subgroup analysis of both the targeted therapy cohort and the nontargeted therapy cohort. These biases could influence the statistical survival outcome. Another limitation of this study was the small number of enrolled patients due to the low incidence of pleural dissemination at the surgical center. Such concerns should be considered in future multi-institutional randomized controlled studies.

In conclusion, this single-institution retrospective study demonstrated that PTR could prolong OS in stage M1a NSCLC patients with ipsilateral pleural dissemination, especially in patients who are not candidates for targeted therapy. PTR should be included as an important option in the multimodal therapeutic strategies for carefully selected patients with ipsilateral pleural dissemination.

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Disclosure

All authors declare that there are no conflicts of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. Histogram of propensity scores for patients between PTR and biopsy groups; b: Standardized differences of variables between PTR and biopsy groups. Propensity matching effectively reduced heterogeneity among variables between two groups. State of pleural nodules was linearly dependent with surgery, so it was not showed in the figure. PTR: primary tumor resection; Targeted: Targeted therapy; Chemo: Chemotherapy; Radio: Radiotherapy; PE: State of pleural effusion.

Table S1. Baseline characteristics of surgery group

