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Primary tumour resection in non-small cell lung cancer patients with pleural dissemination unexpectedly detected during operation: a two-centre retrospective cohort study

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Abstract

Background There is no consensus regarding whether primary tumour resection (PTR) should be performed in non-small cell lung cancer (NSCLC) patients with unexpected pleural dissemination (PD) discovered at thoracotomy.

Materials and methods Consecutive NSCLC patients with surgically confirmed PD were retrospectively enrolled from two high-volume centres between January 2016 and December 2023. Patients were divided into the primary tumour resection (PTR) and exploratory thoracotomy (ET) group. PTR included wedge resection, segmentectomy and lobectomy. Patients in the ET group received biopsy only. Propensity score matching (PSM) was used to reduce selection bias from confounding factors. Disease-specific survival (DSS) and progression-free survival (PFS) were analysed using the Kaplan–Meier method, and comparisons were made using the log-rank test. Multivariate Cox regression analyses were performed to identify the independent prognostic factors.

Results A total of 223 patients were identified: 167 (74.9%) in the PTR group and 56 (25.1%) in the ET group. The median follow-up time and median survival time (MST) were 39.0 months and 49.0 months, respectively. The MST for the ET and PTR groups were 44.0 and 60.0 months, respectively (HR 0.80, 95% CI 0.51–1.24; $p=0.3097$). After PSM, there were no significant differences in terms of median disease-specific survival (DSS: 60.0 vs. 61.0 months, $p=0.3419$) or progression-free survival (PFS: 30.0 vs. 47.0 months, $p=0.5471$) between the two groups. Multivariate analysis revealed that smoking history and a tumour size ≥ 3 cm were independent risk factors for DSS and PFS, whereas targeted therapy was an independent protective factor.

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Conclusion Our results suggest that primary tumour resection does not improve long-term survival in NSCLC patients with unexpected PD discovered at thoracotomy. It is high time to re-evaluate the value of surgery for NSCLC patients with PD and avoid overtreatment, especially in the era of targeted therapy and immunotherapy.

Trial Registration ClinicalTrials.gov NCT06232967 (approval date: January 31, 2024).

Keywords Non-small cell lung cancer, Dry pleural dissemination, Primary tumour resection, Metastatic disease, Prognosis

Introduction

Non-small cell lung cancer (NSCLC) with pleural dissemination (PD) is classified as stage IVA according to the 8th edition of the TNM staging system and is generally contraindicated for radical surgery [1]. However, in clinical practice, unexpected PD is sometimes discovered during thoracotomy. For these affected patients, there is no consensus regarding whether primary tumour resection (PTR) should be performed. Actually, in comparison to malignant pleural effusion, dry pleural dissemination (DPD, defined as pleural seeding without effusion) represents a relatively early stage of pleural dissemination. Previous studies have shown that compared with exploratory thoracotomy (ET) alone, PTR is associated with a significantly greater survival rate [2–7]. Therefore, in clinical practice, PTR may be performed for those unexpected DPDs discovered during thoracotomy, according to surgeon experience and patient preference. However, the majority of these studies were single-centre case series with small sample sizes and were likely confounded by strong selection bias, as patients with good Eastern Cooperative Oncology Group performance status and low tumour burden were more likely to undergo PTR and thus have a positive outcome.

In addition, since erlotinib and nivolumab became the first approved targeted therapy and immunotherapy agents for the treatment of epidermal growth factor receptor (EGFR)- and programmed cell death ligand 1 (PD-L1)-positive advanced/metastatic NSCLC by the U.S. Food and Drug Administration in May 2013 and March 2015, respectively, the landscape for the treatment of advanced/metastatic NSCLC has rapidly evolved, and overall survival for these patients has significantly improved [8–13]. However, the aforementioned studies enrolled patients who underwent surgery prior to 2015. As a result, some potentially treatable patients have not had the opportunity to control their disease progression by using more effective targeted drugs, which may lead to a serious underestimation of the impact of drug treatment for NSCLC patients with DPD.

Consequently, a two-centre retrospective study was conducted on patients who underwent surgery between January 2016 and December 2023 to evaluate the impact of PTR on the long-term survival of NSCLC patients with DPD in the era of targeted therapy and immunotherapy.

Materials and methods

Patient eligibility

From January 2016 to December 2023, consecutive NSCLC patients with surgically confirmed DPD were retrospectively enrolled from two high-volume centers in China. The inclusion criteria were as follows: (1) pathologically confirmed primary NSCLC with malignant pleural dissemination, (2) no preoperative treatment, (3) aged 80 years or younger, and (4) complete clinicopathological data and follow-up data. Patients who met any of the following criteria were excluded: (1) had pleural effusion, contralateral lung metastasis or distant metastasis detected prior to surgery or (2) had a history of other malignant diseases. The data were obtained by reviewing medical records. The patient selection process is illustrated in Fig. 1. The disease stage was determined according to the general rules of the TNM classification of malignant tumours (8th edition) [1]. The study protocol was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Daping Hospital (approval number: 2024-01; approval date: January 17, 2024) and The First Affiliated Hospital of Chongqing Medical University (approval number: K2024-045-01; approval date: January 26, 2024). All patients signed the informed consent form prior to the surgery. The need for individual consent to the utilization of their clinicopathological data for scientific research purposes was waived by the committee.

Patient management

Preoperative staging included chest computed tomography, bone emission computed tomography, brain computed tomography or magnetic resonance imaging, and whole-body positron emission tomography. All imaging studies were performed within 1 month prior to surgery, and all tumours were preoperatively staged as resectable. Surgical decisions to perform ET or PTR with wedge resection, segmentectomy, or lobectomy were based on surgeon experience and patient preference. The details of our surgical techniques are consistent with a previously published article [14]. After surgery, patients were recommended to receive platinum-based chemotherapy/chemoradiotherapy, targeted therapy, or immunotherapy based on the results of genetic and immunogenic testing.

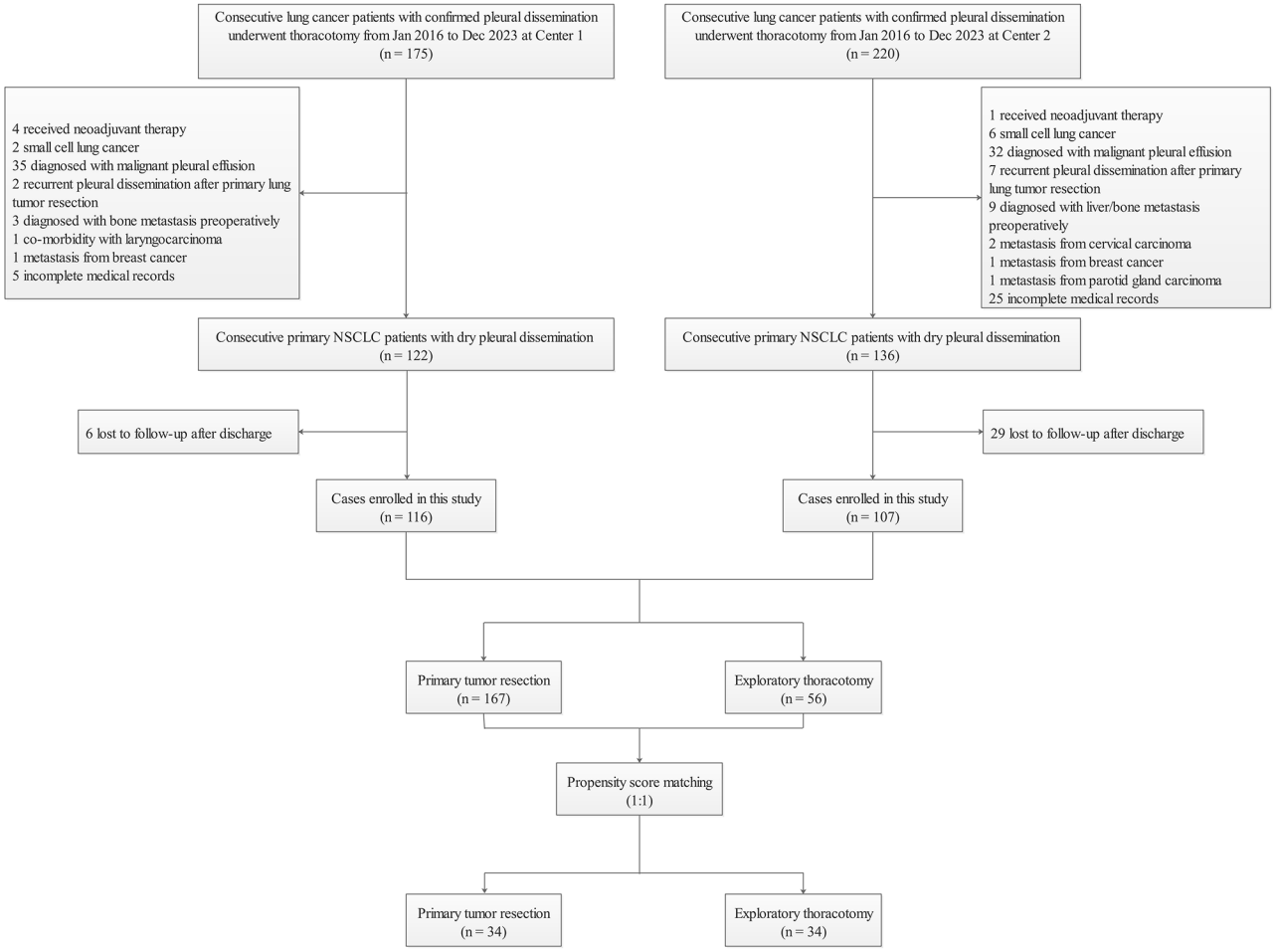

Fig. 1 Study flowchart

Patient follow-up

Patients underwent regular outpatient surveillance with physical examination, certain serum tumour markers, brain computed tomography or magnetic resonance imaging, and chest computed tomography every 3 months for 2 years. Patients were then followed regularly with similar assessments every 6 months. Complete follow-up information was available for all patients until death or January 2024.

Disease-specific survival (DSS) was defined as the duration from the day of surgery to the last follow-up visit or to death specifically caused by NSCLC. Progression-free survival (PFS) was defined as the duration without evidence of disease progression.

Statistical analysis

Continuous data were compared using Mann-Whitney U test, and categorical data were compared using Fisher's exact test or the X [2] test, as appropriate. Propensity score matching (PSM) was used to reduce selection bias due to confounding factors, including tumour size, cT stage, cN stage, and surgical approach. Matching was performed in a blinded manner (1:1 ratio, calliper distance = 0.02) without replacement using the nearest method in the MATCHIT package (version 3.0.2) of R software. Survival curves were generated using the Kaplan–Meier method, and comparisons were made using the log-rank test. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate Cox proportional hazards regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. P values less than 0.05 were considered to indicate statistical significance. All the statistical analyses and graphical presentations were performed using IBM SPSS 25.0 software (IBM, Inc.) and R (version 3.6.0).

RESULTS

Patient characteristics

Table 1 details the demographics of the patients who underwent PTR/ET during the study period. A total of 223 consecutive NSCLC patients with surgically confirmed DPD were identified, of which 167 (74.9%) patients underwent surgical resection of the primary tumour (PTR group), while 56 (25.1%) patients received

Table 1 Patients' characteristics before and after propensity score matching

Characteristics	Non-PSM			PSM		
	PTR (n = 167)	ET (n = 56)	*P*	PTR (n = 34)	ET (n = 34)	*P*
Age, yrs (IQR)	59 (50–66)	59 (52–67)	0.348	59 (47–68)	60 (52–67)	0.36
Sex, n (%)			0.757			0.807
Female	92 (55.1)	29 (51.8)		20 (58.8)	18 (52.9)	
Male	75 (44.9)	27 (48.2)		14 (41.2)	16 (47.1)	
Smoking status, n (%)			1			1
Yes	48 (28.7)	16 (28.6)		11 (32.4)	8 (23.5)	
No	119 (71.3)	40 (71.4)		23 (67.6)	26 (76.5)	
Comorbidities*, n (%)			0.719			0.59
Yes	39 (23.4)	15 (26.8)		10 (29.4)	8 (23.5)	
No	128 (76.6)	41 (73.2)		24 (70.6)	26 (76.5)	
Staging workup, n (%)			0.173			0.478
PET	68 (40.7)	30 (53.6)		14 (41.2)	19 (55.9)	
ECT + brain CT/MRI	80 (47.9)	23 (41.1)		16 (47.1)	12 (35.3)	
No	19 (11.4)	3 (5.4)		4 (11.8)	3 (8.8)	
Histology subtype, n (%)			0.916			0.356
Adenocarcinoma	153 (91.6)	52 (92.9)		30 (88.2)	33 (97.1)	
Squamous cell carcinoma	5 (3.0)	2 (3.6)		0 (0)	0 (0)	
Others	9 (5.4)	2 (3.6)		4 (11.8)	1 (2.9)	
Tumour size, cm (IQR)	3.6 (2.8–4.7)	2.5 (2.0-3.3)	**< 0.001**	3.0 (2.7–3.6)	3.0 (2.7–3.8)	0.753
Right-sided tumour, n (%)	80 (47.9)	33 (58.9)	0.167	18 (52.9)	21 (61.8)	0.624
Tumour location, n (%)			**0.002**			1
Periphery	162 (97.0)	47 (83.9)		33 (97.1)	32 (94.1)	
Center	5 (3.0)	9 (16.1)		1 (2.9)	2 (5.9)	
Clinical T stage, n (%)			**< 0.001**			1
T1	117 (70.1)	21 (37.5)		19 (55.9)	20 (58.8)	
T2	47 (28.1)	27 (48.2)		14 (41.2)	14 (41.2)	
T3	2 (1.2)	7 (12.5)		1 (2.9)	0 (0)	
Tx	1 (0.6)	1 (1.8)		0 (0)	0 (0)	
Clinical N stage, n (%)			0.771			0.47
N0	128 (76.6)	44 (78.6)		30 (88.2)	26 (76.5)	
N1	10 (6.0)	3 (5.4)		1 (2.9)	2 (5.9)	
N2	28 (16.8)	8 (14.3)		3 (8.8)	6 (17.6)	
Nx	1 (0.6)	1 (1.8)		0 (0)	0 (0)	
Surgical approach			0.079			0.493
VATS	161 (96.4)	50 (89.3)		34 (100)	32 (94.1)	
Thoracotomy	3 (3.6)	6 (10.7)		0	2 (5.9)	
Pleural nodule, n (%)			**0.029**			1
Localized	46 (27.5)	7 (12.5)		5 (14.7)	4 (11.8)	
Diffused	121 (72.5)	49 (87.5)		29 (85.3)	30 (88.2)	
Pleural involvement, n (%)			0.065			1
Visceral	25 (15.0)	3 (5.4)		3 (8.8)	3 (8.8)	
Partial	142 (85.0)	53 (94.6)		31 (91.2)	31 (91.2)	
Gene mutation, n (%)			0.34			1
EGFR/ALK	108 (64.7)	32 (57.1)		23 (67.6)	22 (64.7)	
Wild type/Unknown	59 (35.3)	24 (42.9)		11 (32.4)	12 (35.3)	
Adjuvant treatment, n (%)						
Targeted therapy	109 (65.3)	35 (62.5)	0.748	23 (67.6)	23 (67.6)	1
Chemotherapy	47 (28.1)	23 (41.1)	0.095	8 (23.5)	14 (41.2)	0.194
Immunotherapy	13 (7.8)	8 (14.3)	0.185	2 (5.9)	4 (11.8)	0.673
Postoperative complications						
Pneumonia	4 (2.4)	4 (7.1)	0.111	1 (2.9)	2 (5.9)	1
Hydrothorax	4 (2.4)	1 (1.8)	1	1 (2.9)	1 (2.9)	1

Table 1 (continued)

Characteristics	Non-PSM			PSM		
	PTR (n = 167)	ET (n = 56)	*P*	PTR (n = 34)	ET (n = 34)	*P*
Pneumothorax	2 (1.2)	1 (1.8)	1	0	1 (2.9)	1
Prolonged air leak	1 (0.6)	0	1	1 (2.9)	0	1
Hemorrhage	1 (0.6)	0	1	0	0	NA
Pulmonary embolism	1 (0.6)	0	1	0	0	NA

*Comorbidities include hypertension, diabetes mellitus, coronary heart disease, chronic obstructive pulmonary disease. ECT, emission computed tomography; ET, exploratory thoracotomy; IQR, interquartile range; MRI, magnetic resonance imaging; PET, positron emission tomography; PTR, primary tumour resection; SD, standard deviation; VATS, video-assisted thoracoscopic surgery

exploratory thoracotomy only (ET group). Overall, patients in the ET group had significantly larger tumours (3.6 cm vs. 2.5 cm, $p < 0.001$) and more advanced clinical T stage ($p < 0.001$). In addition, there were significantly more patients with diffuse pleural metastasis (87.5% vs. 72.5%; $p = 0.029$) and a central location (16.1% vs. 3.0%; $p = 0.002$) in the ET group than in the PTR group.

In the PTR group, 126 (75.4%) patients underwent segmentectomy or wedge resection, and 41 (24.6%) patients underwent lobectomy. Moreover, 38 (22.8%) patients underwent systematic lymph node dissection, and 20 (12.0%) underwent sampling.

In addition, postoperative adverse events such as pneumonia (2.4% vs. 7.1%; $p = 0.111$), hydrothorax (2.4% vs. 1.8%; $p = 1.000$), pneumothorax (1.2% vs. 1.8%; $p = 1.000$), prolonged air leak (0.6% vs. 0%; $p = 1.000$), hemorrhage (0.6% vs. 0%; $p = 1.000$), and pulmonary embolism (0.6% vs. 0%; $p = 1.000$) did not differ significantly between the two groups.

Genetic testing was performed for 182 (81.6%) patients. Among these patients, 129 (70.9%) had targeted gene mutations, including 112 (54.9%) with epidermal growth factor receptor (EGFR) mutations, 11 (6.0%) with anaplastic lymphoma kinase (ALK) rearrangements, 2 (1.1%) with Kirsten rat sarcoma (KRAS) mutations, 2 (1.1%) with ROS proto-oncogene 1 (ROS1) mutations, and 1 (0.5%) with rearranged during transfection (RET) rearrangement. The remaining 37 (20.3%) were wild type.

After surgery, 144 (64.6%) patients received targeted therapy, 34 (23.6%) of whom received additional chemotherapy, radiotherapy, or immunotherapy after disease progression. In addition, 37 (16.6%) patients received platinum-based chemotherapy as first-line therapy, including 17 (45.9%) patients who were treated with additional radiation or immunotherapy after disease progression. In addition, 3 (1.3%) patients received immunotherapy as first-line therapy.

After PSM, there were no significant between-group differences with respect to tumour size, cT stage, tumour location, or extent of pleural nodule dissemination. In addition, no significant differences were observed between the two medical centres in terms of targeted therapy (66.7% vs. 69.2%, $p = 1.000$), chemotherapy (35.7% vs. 26.9%, $p = 0.595$) and immunotherapy (11.9% vs. 3.8%, $p = 0.395$). However, significant differences were identified in the rates of lobectomy (14.3% vs. 11.5%), limited resection (23.8% vs. 57.7%) and exploratory thoracotomy (61.9% vs. 30.8%, $p = 0.017$; not shown in Table).

Survival analysis

The median follow-up time was 39.0 months (standard deviation 2.8). A total of 91 deaths (40.8%) were observed: 30 (33.0%) in the ET group and 61 (67.0%) in the PTR group. Two of these deaths (0.2%) were due to other causes (cerebral infarction and traffic accidents). The overall 3-year and 5-year DSS rates were 60.3% and 42.8%, respectively, with a median survival time (MST) of 49.0 months. The median DSSs for the ET and PTR groups were 44.0 and 60.0 months, respectively (HR 0.80, 95% CI 0.51–1.24; $p = 0.3097$).

In addition, 107 patients (48.0%) were diagnosed with locoregional and/or distant recurrent disease—35 (32.7%) in the ET group and 72 (67.3%) in the PTR group. The overall 3-year and 5-year PFS rates were 53.8% and 29.7%, respectively, with an MST of 39.0 months. The median PFS times for the ET and PTR groups were 35.0 and 39.0 months, respectively (HR 0.78, 95% CI 0.52–1.17; $p = 0.2209$). (Fig. 2)

Furthermore, subgroup survival analysis revealed that there was no significant between patients who received sublobar resection or lobectomy in terms of DSS ($p = 0.43$) or PFS ($p = 0.24$) (Supplementary Figure S1).

After PSM, the differences between the two groups remained nonsignificant in terms of median DSS (PTR vs. ET: 60.0 and 61.0 months; HR 1.42, 95% CI 0.69–2.91; $p = 0.3419$) and PFS (PTR vs. ET: 30.0 and 47.0 months; HR 1.22, 95% CI 0.64–2.33; $p = 0.5471$). (Fig. 3)

Multivariate Cox regression analysis revealed that smoking history and a tumour size ≥ 3 cm were the independent risk factors for DSS (HR 3.17, 95% CI 1.46–6.89; $p = 0.004$; HR 2.78, 95% CI 1.19–6.51; $p = 0.018$, respectively) and PFS (HR 3.17, 95% CI 1.56–6.44; $p = 0.001$; HR 2.16, 95% CI 1.05–4.45; $p = 0.036$, respectively), whereas targeted therapy was the independent protective factor for DSS (HR 0.19, 95% CI 0.08–0.41; $p < 0.001$) and PFS (HR 0.34, 95% CI 0.17–0.67; $p = 0.002$; Table 2). The variance inflation factors (VIF) was less than 1.1, indicating the absence of multicollinearity among the final

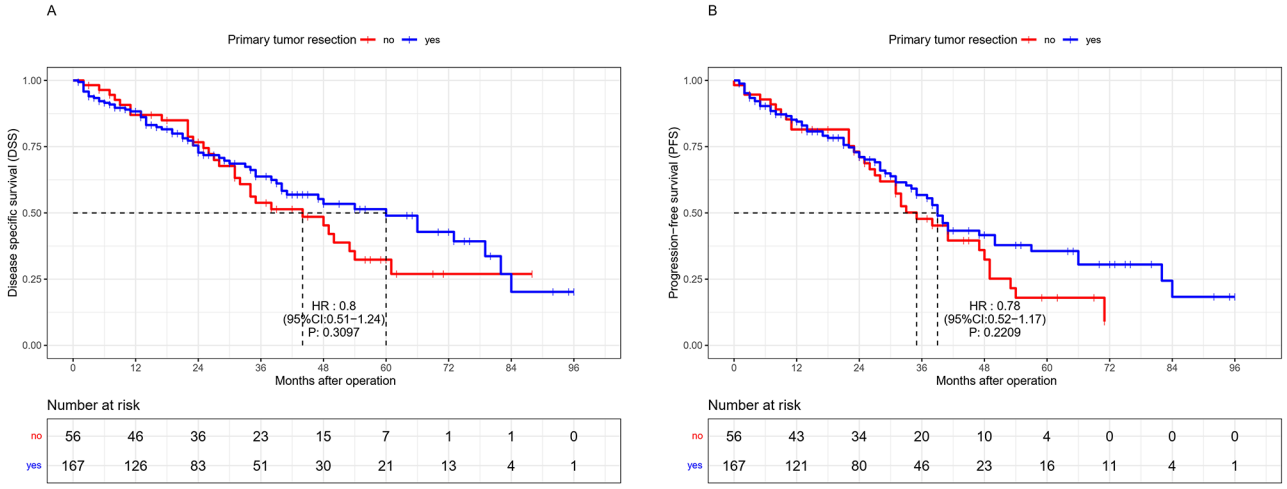

Fig. 2 Kaplan-Meier survival curves of disease-specific survival (**A**) and progression-free survival (**B**) of the study groups before propensity score matching

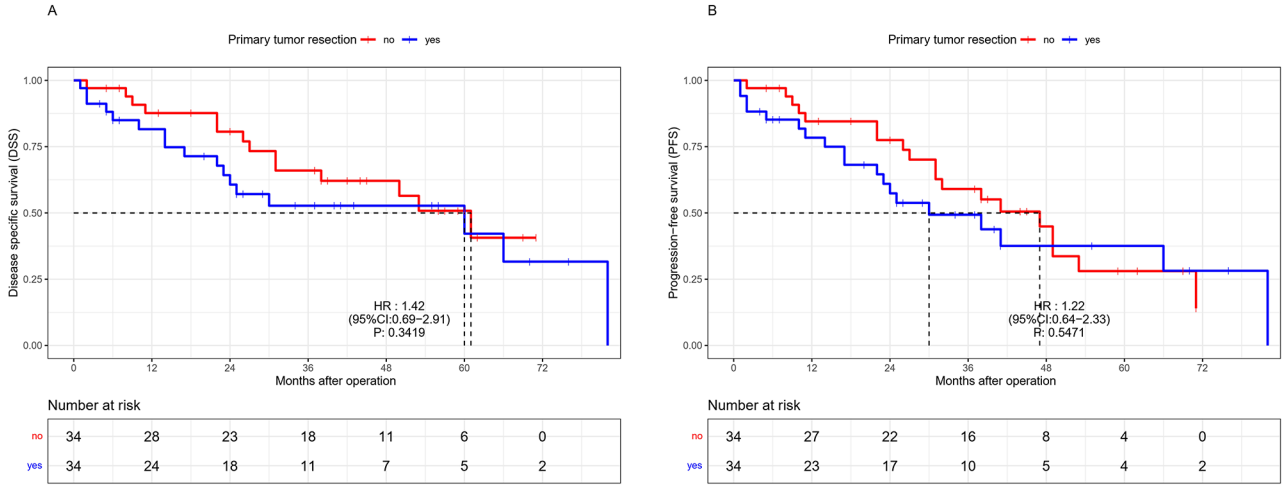

Fig. 3 Kaplan-Meier survival curves of disease-specific survival (**A**) and progression-free survival (**B**) of the study groups after propensity score matching

predictors (Supplementary Table S1). In addition, no significant differences were observed between the two medical centres in terms of DSS and PFS ($p = 0.341$; $p = 0.545$; respectively).

Further subgroup analysis showed that there was no significant difference between the two groups in wild-type patients (Supplementary Figure S2). In addition, multivariate cox regression analysis revealed that smoking history and tumour size were independent prognostic factors for DSS and PFS in these patients (Supplementary Table S2).

Discussion

The main findings of the present study were that PTR did not improve the long-term survival of NSCLC patients with DPD. Further multivariate Cox regression analysis revealed that smoking history and a tumour size ≥ 3 cm were independent risk factors for DSS and PFS, whereas targeted therapy was an independent protective factor.

NSCLC with DPD is classified as stage IVA according to the 8th edition of the TNM staging system and is generally contraindicated for radical surgery. However, in clinical practice, there has been no consensus regarding whether PTR should be performed in cases of unexpected DPD discovered at thoracotomy. A retrospective study performed by Kimura and colleagues [15] on 19 NSCLC patients with DPD who did not undergo any form of resection and who received platinum-doublet chemotherapy postoperatively revealed that the median PFS and OS were 10.4 months and 50.5 months, respectively, indicating a favourable survival prognosis for these patients. In 2002, Sawabata et al. [16] analysed 43 patients with MPE who underwent PTR or ET and found that there was no significant difference in survival between the two groups (MST: 13 vs. 17 months, $p = 0.8$). Recently, another retrospective study performed by Hu and colleagues [17] of 169 NSCLC patients with unexpected pleural dissemination revealed that PTR did not

Table 2 Univariable and multivariable analysis of prognostic factors for DSS and PFS

Characteristics	DSS			PFS	
	Uni.	*P*	Multi.	Multi.	*P*
	HR (95% CI)		HR (95% CI)	HR (95% CI)	
Age	0.98(0.94–1.03)	0.222			
Sex					
Male	Reference	0.189			
Female	0.61(0.29–1.27)				
Smoking status					
Nonsmoker	Reference	0.004	Reference	Reference	0.001
Smoker	2.94(1.41–6.11)		3.17(1.46–6.89)	3.17(1.56–6.44)	
Tumour size		0.05			0.036
< 3 cm	Reference		Reference	Reference	
≥ 3 cm	2.25(1.00-5.09)		2.78(1.19–6.51)	2.16(1.05–4.45)	
cN					
N0	Reference	0.439			
N1-2	1.39(0.59–3.26)				
PTR					
No	Reference	0.342			
Yes	1.41(0.69–2.91)				
Targeted therapy					
No	Reference	< 0.001	Reference	Reference	0.002
Yes	0.25(0.12–0.53)		0.19(0.08–0.41)	0.34(0.17–0.67)	

CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; PFS, progression-free survival; PTR, primary tumour resection; SD, standard deviation

improve OS in patients who received targeted therapy but was beneficial in patients who received adjuvant chemotherapy alone.

In contrast, several other previous studies have shown that these patients may benefit from PTR. Specifically, a nationwide retrospective study conducted by Iida and associates [3] of 329 patients with pleural carcinomatosis who underwent surgery in 2004 showed that the 5-year survival rate for patients with PTR was 37.1%, compared with 12.2% for patients with ET ($p < 0.001$). Of these, 180 (57.5%) patients received postoperative chemotherapy, but no information on targeted therapy was provided. Li and colleagues [4] analysed the US National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database of 5531 patients who underwent surgery between 2010 and 2015 and showed that patients who underwent PTR had significantly longer overall survival (OS) than those who received ET alone in both the unmatched (MST: 20 vs. 8 months, $p < 0.001$) and matched (MST: 20 vs. 11 months, $p < 0.001$) cohorts. However, postoperative therapeutic information such as driver gene mutations and individualized therapeutic regimens was limited in the SEER database. Recently, a study by Li et al. [5] involving 43 patients who underwent surgery between January 2006 and December 2014 showed that patients in the PTR group had better PFS (3-year survival: 44.5% vs. 0%; $p = 0.009$) and OS (3-year survival: 82.9% vs. 38.5%; $p = 0.013$) than did those in the ET group. Notably, differences in clinicopathologic characteristics, such as cT stage and neoadjuvant treatment, as well as small sample sizes, may have affected the difference in survival between the two groups.

With regard to the question of why PTR is unable to enhance the long-term survival prognosis of NSCLC patients with unexpected PDs discovered at thoracotomy, it is important to note that once lung cancer patients present with pleural metastasis, which are classified as M1a according to the AJCC stage system, radical resection cannot be achieved via pneumonectomy or pleurectomy, not to mention limited primary tumour resection. The pleural metastasis will continue to spread along the thoracic cavity and even transfer to distant organs postoperatively. In some cases, patients may receive timely pharmacological intervention due to complications arising from the surgical procedure itself, which can impact the efficacy of disease control. However, in comparison with surgical resection, chemotherapy, targeted therapy, and immunotherapy are capable of acting on systemic cancer cells, including primary tumours and metastasis lesions, and achieving the objective of disease control. In particular, recent years have seen significant advances in the development of targeted and immunotherapy drugs, which have led to enhanced efficacy in controlling the progression of such diseases. In 2017, the ALEX clinical trial demonstrated that alectinib had superior efficacy and lower toxicity than crizotinib in the first-line treatment of ALK-positive NSCLC [18]. The ALTA-1 L trial reported in 2018 showed that PFS was significantly longer in patients who received brigatinib than in those who received crizotinib [19]. The CROWN trial revealed that

patients who received lorlatinib had significantly longer PFS and a greater frequency of intracranial responses than did those who received crizotinib [20]. Regarding EGFR-positive agents, the FLAURA trial randomized 556 advanced NSCLC patients with an EGFR mutation to receive either osimertinib or one of two other EGFR TKIs (gefitinib or erlotinib) and showed that those who received osimertinib had longer overall survival than those in the other group [21]. For patients with locally advanced, unresectable NSCLC who did not experience disease progression after two or more cycles of platinum-based chemoradiotherapy, the PACIFIC clinical trial demonstrated that durvalumab can significantly prolong PFS [22]. However, the aforementioned studies enrolled patients who underwent PTR/ET prior to 2015. As a result, some potentially treatable patients do not have the opportunity to control their disease progression by using more effective targeted drugs, which may lead to a serious underestimation of the effect of drug treatment for NSCLC patients with DPD.

Increasing attention has been given to whether PTR should be performed in patients with metastatic disease. In the field of stomach cancer, the REGATTA trial [23] enrolled advanced gastric cancer patients with a single unresectable factor confined to either the liver, peritoneum, or para-aortic lymph nodes and demonstrated that gastrectomy followed by chemotherapy did not confer a survival benefit over chemotherapy alone in these advanced gastric cancer patients. Further subgroup analysis revealed that gastrectomy plus chemotherapy was associated with significantly worse OS in patients in the upper third of the tumour and in patients in the cN0-1 stage due to decreased compliance with postoperative chemotherapy. In contrast, another randomized clinical trial showed that radical nephrectomy followed by immunotherapy improved the time to progression and OS compared to immunotherapy alone in patients with metastatic renal cell carcinoma [24]. However, to date, no randomized controlled trial has been conducted to investigate whether PTR confers a survival benefit over ET alone in NSCLC patients with DPD.

Similar to the findings of a previous study [25], our results also demonstrated that smoking history was an independent prognostic factor for DSS and PFS in NSCLC patients with DPD. Regarding the impact of smoking on the long-term survival of lung cancer patients, Carroll and colleagues [26] analysed 6813 lung cancer patients and reported that the MSTs for those who never smoked, formerly smoked, and currently smoked were 32.1, 25.9, and 23.3 months, respectively. Another prospective cohort study of 517 current smokers who were diagnosed with early-stage NSCLC revealed that smoking cessation after diagnosis significantly improved 5-year OS and PFS compared with those who continued smoking [27].

Our study had several limitations. There were significant differences among various centers regarding the choice of surgical modalities. However, due to the retrospective nature of this study, it is not possible to ascertain the surgical modalities chosen during the surgical process for each patient. It is our contention that a number of factors contribute to the discrepancy in surgical modalities selected by different centres. Firstly, as mentioned above, there is currently no consensus regarding whether PTR should be performed for NSCLC patients with PD. Consequently, the surgical methods (PTR or ET) employed by different doctors will vary according to their experience when confronted with this situation during the course of an operation. Secondly, in China, when confronted with cases of NSCLC with accidental PD during surgery, the attending surgeon will promptly engage in communication with the patient's family to ascertain their preferences regarding the surgical approach to be employed. In addition, PSM was performed according to tumour size, cT stage and cN stage. It is not possible to take into account the fact that surgical modalities differences among various centers. This also gives rise to the possibility that the matching data may exhibit discrepancies in surgical modalities selected by different centres. It is acknowledged that the potential impact of selection bias resulting from the variation in surgical modalities among various centers on the research outcomes is inevitable. Besides, although PSM was performed to improve the comparability between the two groups, the long-term survival comparison between the two groups may be affected by the small sample size after matching (34 pairs), which may further reduce the statistical power. In addition, the preoperative staging workup varies between centres, and clinical staging migration may exist, potentially affecting our final results. For instance, certain patients may harbour undetected distant organ metastases, which could lead to misdiagnosis as early-stage lesions due to the absence of PET scans and other imaging tests prior to surgery. However, follow-up examinations may reveal the presence of distant metastasis, leading to a diagnosis of disease progression. This can significantly impact the survival prognosis for the patient population. Therefore, in order to eliminate above limitations, a larger multi-institutional and larger patient populations need to be conducted.

In conclusion, our data suggest that PTR does not confer a survival benefit over exploratory thoracotomy alone in NSCLC patients with DPD. It is high time to re-evaluate the value of surgery for NSCLC patients with DPD, especially in the era of targeted therapy and immunotherapy. It is our view that the key to avoiding overtreatment is to enhance the diagnostic precision of

preoperative pleural metastasis through the utilization of artificial intelligence and other techniques. The proposed approach will facilitate the identification of patients for whom surgery may be contraindicated and thus help to prevent the unnecessary performance of procedures such as exploratory thoracotomy. Furthermore, for patients diagnosed with PDs preoperatively who may benefit from targeted and immunotherapy therapy, they have the right to choose to refuse surgery and receive drug therapy. This can also provide conditions for our prospective clinical research in the future.

Supplementary Information

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Supplementary Material 1

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none.

Author contributions
Wei Guo, Mingjian Ge, and Tao Bao conceived and designed the experiments. Tao Bao, Xiaolong Zhao, Xu Chen, Liang Zhang, Yingjian Wang, Xiandong He, Xiangshu Pu, Yan He, and Jun Yu recorded the follow-up data. Tao Bao, Yuanlin Deng, Liang Chen, and Weijie Sun analyzed the data. Tao Bao wrote the manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee of Ethics Committee of Daping Hospital Hospital (approval number: 2024-01; approval date: January 17, 2024) and The First Affiliated Hospital of Chongqing Medical University (approval number: K2024-045-01; approval date: January 26, 2024). All patients signed the informed consent form prior to the surgery. The need for individual consent to the utilization of their clinicopathological data for scientific research purposes was waived by the committee.

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Competing interests
The authors declare no competing interests.

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