The prognostic analysis of lung cancer patients with occult malignant pleural disease at thoracotomy

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Background: This study aims to determine the clinicopathological prognostic factors for occult malignant pleural disease (MPD) that were first detected in patients with non-small cell lung cancer (NSCLC) at thoracotomy and to assess the outcome of surgical intervention.

Methods: A total of 120 thoracotomy-patients with MPD were examined. The Kaplan-Meier test estimated survival curves, and Cox regression analysis was performed to validate the risk factors picked. In assessing surgical intervention, clinical and pathological parameters were matched by propensity score matching (PSM).

Results: With a median follow-up of 34 months, the 5-year overall survival of 120 patients was 28.0%. Multivariate analyses showed male (P=0.044), advanced T stages (P<0.001), advanced N stages (P=0.02), pleural invasion in image (P=0.005), pleural effusion (P=0.027), surgical intervention (P=0.008) and EGFR status (P=0.003) were independent predictors of survival. The 5-year survival rate and median survival time (MST) for 21 patients with lobectomy and pleurectomy were 71.6% and undefined, compared with 25.6% and 40.0 months in 46 patients with sublobectomy. When 53 patients only subjected to open-close surgery, their 5-year survival rate and MST were 23.4% and 30.2 months. After PSM, both 21 patients were included in lobectomy with the pleurectomy group and sublobectomy /open-close group. The overall survival of lobectomy with the pleurectomy group was better than the control group (P=0.046).

Conclusions: Age, stage, pleural invasion, pleural effusion, surgical intervention, and EGFR status affected the prognosis of the MPD patients first diagnosed at thoracotomy. Selective surgery gives better recovery, and additional studies are needed.

Keywords: Malignant pleural disease (MPD); lung cancer; EGFR; surgery

Introduction

The latest edition of the TNM classification for non-small cell lung cancer (NSCLC) affirmed the importance of the previously existing M1a descriptor definition featuring patients in this group with pleural/pericardial effusions (PE), contralateral or bilateral lung nodules, or pleural/pericardial nodules (PNs). There were no significant differences observed between the various groups set out in this M1a descriptor definition with poor prognosis as median survival time (MST) 11.5 months (1). However, occult malignant pleural diseases (MPD), including PN with/without PE, were occasionally only discovered at thoracotomy with relatively better outcomes as MST 34.0 months, and then the decision whether to remove or not remove the primary tumor lesion is regularly surrounded by controversy (2). The main tumor and visible pleural nodule resection were usually performed in minimal disease with less tumor burden, and open-close surgery was more likely to perform in advanced disease with multiple pleural nodules and pleural effusion, which was the primary selection bias in previous studies (3). This study's purpose was to ascertain the clinical and biological prognostic factors for occult MPD initially identified by thoracotomy and evaluate the results of surgical intervention using propensity score matching (PSM) analysis.

Methods

Patients

The subjects of this study were NSCLC patients who underwent surgery at the Department of Thoracic Surgery II, Peking University Cancer Hospital from January 2006 to October 2016. The 2,894 consecutive patients who had histologic diagnoses of NSCLC and received thoracotomy or video-assisted thoracic surgery were included in this study.

Computed tomography (CT) thorax scan, a full bone scan, a CT or magnetic resonance imaging (MRI) scan of the brain, and ultrasound scanning of the entire body's abdomen and supraclavicular lymph nodes or positron emission tomography (PET)/CT assisted in ruling out remote metastases. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or mediastinoscopy were used to identify preoperative N2-stage patients. All the patients underwent full oncological staging before surgery,

excluding clinical stage IV disease. However, among them, 123 patients (4.25%) were proven with pathological M1a disease based on the most recent (eighth edition) UICC staging system at the time the surgery was carried out, who had MPD including PN without or with PE. Three patients had incomplete clinical data. Therefore, we analyzed 120 patients in this study. We named the situation of those 120 patients as occult MPD.

Signed informed consent was collected from all patients before thoracotomy, including a statement of approval for their disease information that future retrospective studies could use. Approval for this study was granted by the Ethics Committee of Peking University Cancer Hospital.

Surgical procedures

All the thoracotomy and surgical resections were carried out by surgeons based at the Department of Thoracic Surgery II of Peking University Cancer Hospital. One hundred twenty individuals with occult MPD were classified into three groups based on different surgical interventions. As many as 53 patients only experienced exploratory thoracotomy with biopsy of metastasis focuses, which was defined as open-close surgery, and the other 67 patients experienced primary lesion resection including 46 sublobectomy with/without pleurectomy and 21 lobectomies with pleurectomy. No matter whether the primary tumor lesion was resected, we systematically sampled the lymph nodes for more precise N stages.

Statistical analysis

Our analysis explored the clinicopathological attributes, therapy statuses and survival outcomes of occult MPD patients. Survival was estimated by the life table method in different groups, including gender, age, smoking history, drinking history, neoadjuvant therapy, PET/CT scan, tumor location, T stage, N stage, pathological type, pleural invasion in the image, vascular thrombosis, and EGFR status. Multivariate analysis was carried out by applying the Cox regression (backward stepwise) method. Follow-up was taken from our outpatient files and statistical office. One September 2018 served as the follow-up cut-off date. The Kaplan-Meier method was applied to draw up estimates for survival curves, and the log-rank test assessed significances. The terminal event was death from any cause. Matching of individual propensity scores was carried out with the nearest-neighbor method, with no

replacement, and 0.1-caliper width. Ultimately, 21 patients from the lobectomy group and 21 matched patients from the sublobectomy/open-close group were involved in our analysis. Comparisons between the attributes of patients in the two groups took place prior to and following propensity scores being matched. Statistical significance was considered to exist when P<0.05. Each statistical comparison was calculated with the SPSS Statistics 22.0 software package (SPSS Inc.).

Results

There were 123 patients (4.25%) patients with MPD observed at thoracotomy. Of available for analysis 120 patients, 99 had preoperatively pleural invasions in CT images, which were defined as clinical stage T2a. Seventy-eight patients had only PN without PE. Forty-two patients had a light PE, including malignant or reactive PE (<100 mL) with PN diagnosed at thoracotomy which was occasionally suspected before surgery. There were 110 adenocarcinoma, 6 squamous carcinomas, 1 adenosquamous carcinoma, 2 large cell carcinoma and one other carcinoma. Of 120 MPD patients, 32 had EGFR mutation, 25 had wild-type tumors and the other 63 had unknown EGFR status. *Table 1* sets out patients' characteristics.

The MST and 5-year survival rate of the 120 patients were, collectively, 34 months and 28%, respectively. We estimated survival among distinct groups by Kaplan-Meier method, and the results were also presented in *Table 1* including MST and 5-year survival. Differences were statistically significant in different gender (P=0.008), smoking status (P=0.03), T stages (P<0.001), pleural invasion in image (P=0.022), pleural effusion (P=0.003), surgical interventions (P=0.02), pathological types (P=0.02) and EGFR status (P=0.001). Except for those variables, drinking status (P=0.057), N stages (P=0.079) and CEA levels (P=0.089) were also incorporated into multivariate analyses by applying the Cox proportional hazards model (*Table 2*). Male (HR 1.693, 95% CI: 1.015–2.826, P=0.044), advanced T stages (HR 3.937, 95% CI: 2.028–7.642, P<0.001), advanced N stages (HR 1.855, 95% CI: 1.104–3.116, P=0.02), pleural invasion in image (HR 3.188, 95% CI: 1.415–7.181, P=0.005), pleural effusion (HR 1.77, 95% CI: 1.067–2.936, P=0.027), surgical intervention (open-close *vs.* lobectomy HR 3.688, 95% CI: 1.409–9.655, P=0.008/ sublobectomy *vs.* lobectomy HR 3.275, 95% CI: 1.231–8.710, P=0.017) and EGFR status (HR 4.164, 95% CI: 1.645–10.541, P=0.003) persisted as independent predictors

of survival.

Ninety-nine patients with pleural invasion in the image had worse prognosis with 5-year survival 24.3% and MST 38.3 months. In comparison, the 5-year survival of the 21 patients without the pleural invasion in the image was 55.9%, and the MST had not been achieved (P=0.022, *Figure 1A*). Seventy-eight PN patients without PE had a superior prognosis, with a 5-year survival rate of 37.6% and MST of 49.3 months, compared to 42 PN patients with PE, with a 5-year survival rate of 14.2% and MST of 34.7 months (P=0.003, *Figure 1B*). The EGFR mutation meant the patients could receive help from EGFR-TKI therapy. Thus the 32 patients with EGFR mutation had an exciting 72.7% 5-year survival rate and not reached MST. Furthermore, the 25 wild-type patients and 63 patients with unknown EGFR status had a 5-year survival rate of 23.0% and MST of 41.4 months (P=0.001, *Figure 1C*).

Twenty-one patients who underwent lobectomy had a 5-year survival rate of 71.6%, and the MST had not been achieved, in contrast with 25.6% and 40.0 months in 46 patients with sublobectomy (P=0.037). For 53 patients who received exploratory thoracotomy (open-close surgery), the 5-year survival rate and MST were 23.4% and 30.2 months, respectively (P=0.006, compared with lobectomy). No significant prognostic difference was observed when sublobectomy and open-close surgery were compared (P=0.255) (*Figure 1D*).

When PSM was carried out, both 21 matched cases from the lobectomy group and sublobectomy/open-close group were subjected to comparison and analysis. *Table 3* sets out the clinicopathological attributes of the two groups prior to and following PSM. The two groups were well balanced in terms of baseline characteristics, including sex, age, T stage, N stage, pleural invasion in the image, and pleural effusion after propensity scores were matched. *Figure 2* showed that the five-year survival rate and MST of the 21 patients with lobectomy were significantly better than those in the control group after PSM (P=0.046). The 5-year survival rate of the lobectomy group was 71.6%, and the MST was not achieved. In comparison, the 5-year survival rate of the control group was 40.8%, and the MST was 37.0 months.

Discussion

The seventh edition of the Union for International Cancer Control (UICC) oversaw the reclassification of patients suffering from MPD, which includes malignant pleural effusion and/or malignant pleural nodules, from having

Table 1 Characteristics of 120 occult MPD patients and median survival time (MST) and 5-year survival rate of a different subgroup

Characteristics	No. of patients (n=120) (%)	MST (months)	5-year survival rate (%)	P value
Sex				0.008*
Male	62 (51.7)	33.9	26.7	
Female	58 (48.3)	49.5	30.3	
Age				0.496
≤65	83 (69.2)	36.7	29.3	
>65	37 (30.8)	49.3	21.8	
Smoking status				0.03*
Never	70 (58.3)	49.3	27.3	
Smoker	50 (41.7)	30.2	25.4	
Drinking status				0.057*
Never	95 (79.2)	49	28.5	
Drinker	25 (20.8)	30.2	23.2	
T stages				<0.001*
T1–2	105 (87.5)	45.3	31.2	
T3–4	15 (12.5)	26.8	13.3	
N stages				0.079*
N0–1	77 (64.2)	45.3	30.1	
N2	43 (35.8)	33.3	23.7	
CEA level (ng/mL)				0.089*
≤5.0	44 (36.7)	49.3	40.2	
>5.0	76 (63.3)	38.7	22.3	
Pleural invasion in image				0.022*
Yes	99 (82.5)	38.3	22.3	
No	21 (17.5)	N/A	55.9	
Tumor location				0.128
Peripheral	91 (75.8)	38.7	25.8	
Central	29 (24.2)	55.6	41	
Pleural effusion				0.003*
Yes	42 (35.0)	34.7	14.2	
No	78 (65.0)	49.3	37.6	
Surgical intervention				0.02*
Open-close	53 (44.2)	30.2	23.4	
Sublobectomy	46 (38.3)	40	25.6	
Lobectomy	21 (17.5)	N/A	71.6	
Pathological type				0.02*
Adenocarcinoma	110 (91.7)	43.8	30.8	
Other	10 (8.3)	27.9	0	
Vascular embolism				0.119
Yes	30 (25.0)	34.9	23.4	
No	90 (75.0)	45.3	30.5	
EGFR status				0.001*
Mutation	32 (26.7)	N/A	72.7	
Wild type/unknown	88 (73.3)	41.4	23	

*, the clinicopathological features of these P values were included in further multivariate analysis. MPD, malignant pleural disease.

Table 2 Multivariate analysis of prognostic factors of 120 MPD patients using the Cox proportional hazards model

Variable	HR	95% CI	P value
Male	1.693	1.015–2.826	0.044
T3–4 *vs.* T1–2	3.937	2.028–7.642	<0.001
N2 *vs.* N0–1	1.855	1.104–3.116	0.02
Pleural invasion in image	3.188	1.415–7.181	0.005
Pleural effusion	1.77	1.067–2.936	0.027
Surgical intervention			
Open-close *vs.* lobectomy	3.688	1.409–9.655	0.008
Sublobectomy *vs.* lobectomy	3.275	1.231–8.710	0.017
EGFR wild type/unknown	4.164	1.645–10.541	0.003

MPD, malignant pleural disease.
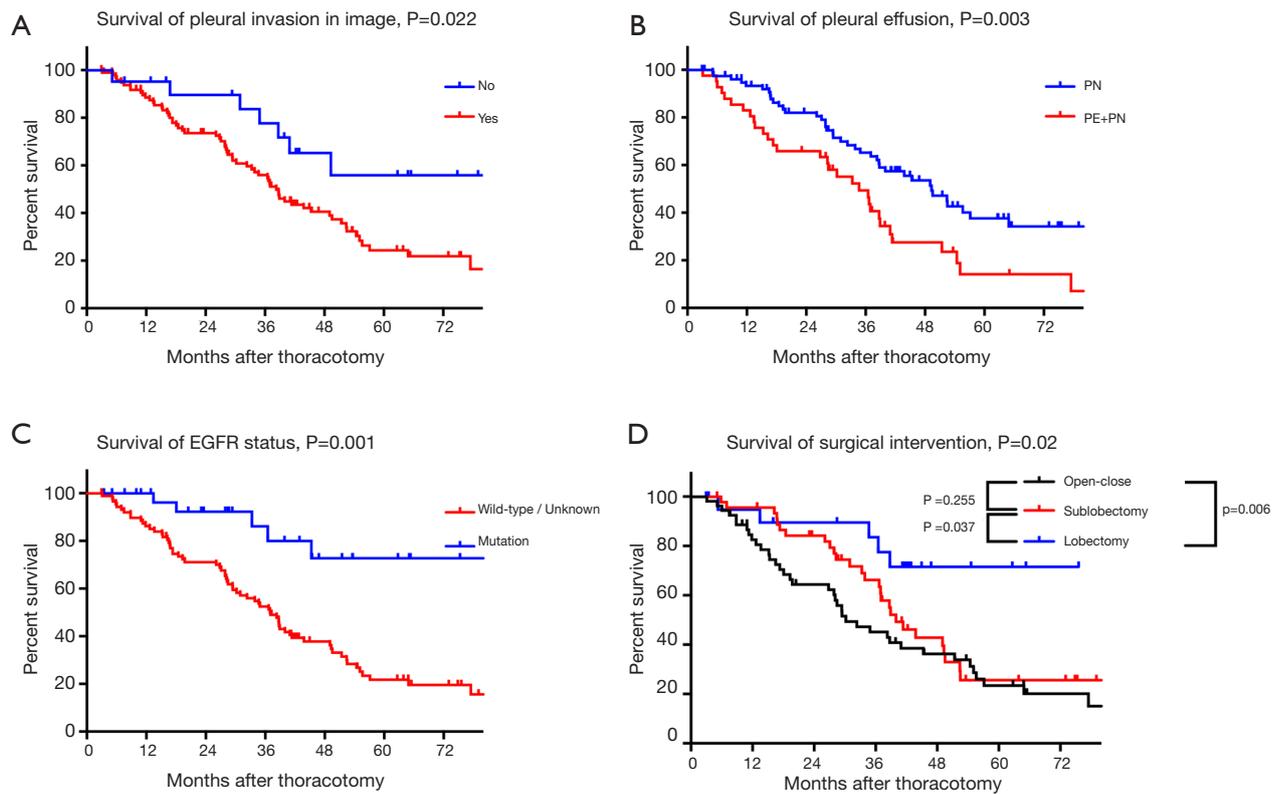
Figure 1 Curves of univariate survival analysis by Kaplan-Meier method. (A) Ninety-nine patients with pleural invasion in the image had a worse prognosis compared with 21 patients without pleural invasion. (B) Seventy-eight PN patients without PE had a significantly better prognosis than 42 PN patients with PE. (C) Thirty-two patients with EGFR mutation had an exciting prognosis compared to the other 88 patients with wild type/unknown EGFR status. (D) The prognosis of 21 patients with lobectomy and pleurectomy was better than 46 patients subjected to sublobectomy and 53 patients with open-close surgery, but no significant prognostic difference was found when sublobectomy was compared with the open-close surgery. PN, pericardial nodule.

Table 3 Characteristics of 120 occult MPD patients before and after propensity score matching

Characteristics	Total cases			Matched group		
	Lobectomy (n=21)	Sublobectomy & open-close surgery (n=99)	P value	Lobectomy (n=21)	Sublobectomy & open-close surgery (n=21)	P value
Sex			0.683			0.757
Male	10 (47.6)	52 (52.5)		10 (47.6)	9 (42.9)	
Female	11 (52.4)	47 (47.5)		11 (52.4)	12 (57.1)	
Age			0.02			1
≤65	19 (90.5)	64 (64.6)		19 (90.5)	19 (90.5)	
>65	2 (9.5)	35 (35.4)		2 (9.5)	2 (9.5)	
T stages			0.318			0.378
T1–2	17 (81.0)	88 (88.9)		17 (81.0)	19 (90.5)	
T3–4	4 (19.0)	11 (11.1)		4 (19.0)	2 (9.5)	
N stages			0.082			1
N0–1	10 (47.6)	67 (67.7)		10 (47.6)	10 (47.6)	
N2	11 (52.4)	32 (32.3)		11 (52.4)	11 (52.4)	
Pleural invasion in image			0.67			0.679
Yes	18 (85.7)	81 (81.8)		18 (85.7)	17 (81.0)	
No	3 (14.3)	18 (18.2)		3 (14.3)	4 (19.0)	
Pleural effusion			0.092			1
Yes	4 (19.0)	38 (38.4)		4 (19.0)	4 (19.0)	
No	17 (81.0)	61 (61.6)		17 (81.0)	17 (81.0)	

MPD, malignant pleural disease.

stage IIIB (T4) to having stage IV (M1a) lung cancer (4). The classification of the 8th TNM allows the use of the existing category M1a. The IASLC Lung Cancer Staging Program indicated that 11.5 months of MST in patients with clinical MPD had a poor prognosis. While clinically diagnosed patients with MPD typically have a notable amount of malignant pleural effusion (5), MPD when observed with thoracotomy generally sees a lower amount of effusion or fewer pleural nodules, all of which have not been identified thorough pre-operative examination (6). Therefore, the progression of the disease in the pleural cavity among a subgroup of patients who have occult MPD could be at an earlier stage and as such, they may have a better prognosis than other M1 patients. The current study revealed an MST of 34 months as well as a 5-year survival rate of 28.0%. Furthermore, we analyzed prognostic factors for occult MPD initially identified by thoracotomy and found gender, advanced T stages, advanced N stages, pleural

invasion in the image, pleural effusion, surgery intervention, and EGFR status to be independent predictors of survival.

Visceral pleura invasion (VPI) is mainly a pathological descriptor and confers a worse prognosis (7,8). At clinical staging, VPI can be assumed by the location of the tumor in relation to the surface of the lung and by its retraction, and despite the possibility of pathological confirmation (by true-cut biopsy, thoracoscopic biopsy, or wedge resection of tumor mass), it is not often confirmed, as it is inessential in the course of planning therapy. VPI is a key factor in prognosis and has been integrated into the latest IASLC lung cancer staging project (9). In this study, pleural invasion in CT image is also an independent prognostic factor in M1a patients, because it was the clinical feature of VPI. On the other hand, the patients with VPI were more easily suffered the MPD with/without pleural effusion (10,11). Our study also revealed malignant pleural nodule (MPN) patients without PE had a better prognosis

Survival of selective surgery, P=0.046
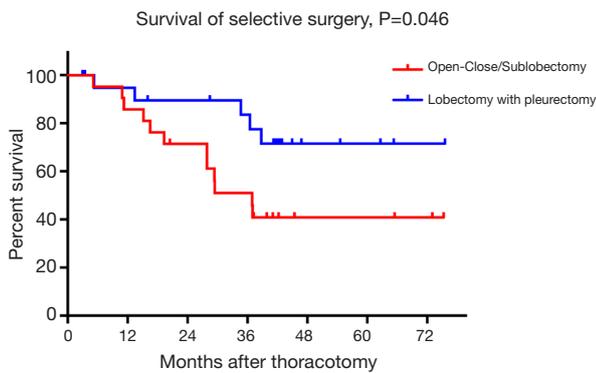
Figure 2 Following propensity score matching, 21 patients were included in lobectomy with the pleurectomy group and sublobectomy/open-close group. Overall survival of lobectomy was better for patients in the pleurectomy group than for their control group counterparts.

compared to MPN patients with PE, which was similar to the study of Okamoto *et al.* (12).

The incidence of occult MPD was ranged from 1.5–6.2%, according to earlier studies. Although the pulmonary resection was associated with better survival in selected patients with MPD, no current guidelines support surgery over conservative therapy and the previous studies were not strong enough to change this recommendation (12-22). It remained controversial whether surgery could ever be justified in NSCLC patients with an unexpected MPD at the surgery. Our results showed lobectomy with pleurectomy conferred to a better 5-year survival rate with 71.6% and MST with 62.6 months compared to sublobectomy and open-close surgery. However, no significant difference was found to exist between the prognostic abilities of sublobectomy and open-close surgery. There may be some reviewers who questioned our results and thought choosing the method of surgical intervention was not random, and those patients in good health, young, less severe disease was chosen to do lobectomy with pleurectomy. Therefore, we conducted a bias matching score analysis for lobectomy and sublobectomy/open-close surgery and found that the long-term survival of lobectomy was better than that of patients without lobectomy. Given the previous review (23,24) and this study, we concluded that lobectomy with pleurectomy or resection of greater range (such as extrapleural pneumonectomy) could improve the survival of occult MPD patients.

Recent data suggest that EGFR-TKIs (as opposed to standard first-line chemotherapy) should be used as first-line systemic treatment for patients in whom sensitizing EGFR mutations are recorded prior to first-line therapy (25-27). Our study showed that 32 patients with EGFR mutation had an exciting 5-year survival rate of 72.7% and had not reached MST. In contrast, 25 wide-type patients and 63 unknown of EGFR status patients had poor survival who had no chance to accept EGFR-TKIs therapy.

Of course, a number of limitations existed in our study. First, as a surgical-case study conducted retrospectively, the subjects of this analysis were specifically selected and did not represent all patients with pleural carcinomatosis. Second, this study duration ranged from 2006 to 2016; 53 adenocarcinoma patients had unknown EGFR mutation status and no chance to receive help from targeted therapy. Because of these limitations and the promising survival in selected MPD patients, the future study will explore to regard occult MPD patients as a subgroup of M1a and design a randomized controlled trial to explore whether surgical resection should be performed.

In sum, our data prove gender, T stages, N stages, pleural invasion in the image, pleural effusion, surgery intervention, and EGFR status were independent predictors of survival of occult MPD. Selective surgery such as lobectomy with pleurectomy confers better prognosis and randomized controlled studies are needed in the future to explore the value of the surgical intervention.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr.2020.02.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee approved this study of Peking University Cancer Hospital. Signed informed consent was collected from all patients before thoracotomy, including a statement of approval for their disease information that future retrospective studies could use.

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