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Primary tumour resection showed survival benefits for non-small-cell lung cancers with unexpected malignant pleural dissemination

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Abstract

OBJECTIVES: Although non-small-cell lung cancer (NSCLC) with malignant pleural nodules is generally contraindicated for surgery, there is no consensus concerning on-site operative decisions for unexpected, intraoperatively encountered malignant pleural disseminations. The rationale underlying the primary tumour removal and other aggressive interventions remains controversial.

METHODS: All surgical NSCLC cases (9576) of Shanghai Pulmonary Hospital between January 2005 and December 2013 were reviewed. Among them, 83 cases (0.9%) met the definition of 'unexpected' macroscopic malignant pleural nodules, despite routine preoperative evaluations for tumour metastasis. No pleural effusion was visualized in 52 cases during operations, and 31 had pleural effusion in minimal volume (<300 ml). Survivals were calculated with the Kaplan–Meier method and risk factors were evaluated by the log-rank test.

RESULTS: The overall 3- and 5-year survival rates were 36.1 and 16.8%, respectively. The median survival time (MST) after surgery was significantly longer in the group without pleural effusion (37 months) compared with the group with pleural effusion (22 months, $P = 0.005$). Twenty-one cases had only biopsy, whereas 62 cases had primary tumour resection. Primary tumour resection had significantly better outcome compared with biopsy (MST: respectively, 35 vs 17 months, 3-year survival rate 45.8 vs 11.8%, $P = 0.001$). No baseline differences emerged in characteristics between biopsy and primary tumour resection groups including targeted therapy. Multivariate analysis showed that primary tumour resection (HR: 3.678, $P = 0.014$), no pleural effusion (HR: 3.409, $P = 0.001$) and adenocarcinoma (HR: 5.481, $P = 0.002$) were favourable prognostic factors in patients with malignant pleural nodules.

CONCLUSIONS: Patients with malignant pleural nodules but without pleural effusion had better survival compared with those with effusions. Primary tumour resection had survival benefits for patients with unexpected intraoperatively proven malignant pleural nodules.

Keywords: Lung cancer • Surgery • Malignant pleural dissemination • Prognosis

INTRODUCTION

Non-small-cell lung cancer (NSCLC) with malignant pleural disease, which includes malignant pleural effusion and malignant pleural nodules, has been believed to have poor outcomes, and it is generally contraindicated for operations [1–3]. The International Association for the Study of Lung Cancer (IASLC) Staging Project had stated that the median survival time (MST) and the 5-year survival rate of patients with malignant pleural disease were 8 months and 2%, respectively [3]. Therefore, NSCLC with confirmed malignant pleural disease was staged IV (M1a) in the new staging system of the Union for International Cancer Control (UICC) [4].

When malignant pleural disease is unexpectedly identified during operations, it causes a perplexing situation concerning whether to proceed with surgical removal of the primary tumour or even the pleural lesions. Supportive results had been proposed in several prior studies. Fukuse *et al.* [5] suggested that extensive surgical resection, including partial resection or lobectomy, resulted in satisfying 5-year survival rate at 45% for NSCLC cases with minor (less than 100 ml) malignant pleural effusion. Okamoto *et al.* [6] found that the prognosis of surgically detected and resected malignant pleural disease (5-year survival rate at 23.7%) was better than that of M1b patients. Iida *et al.* [7] found that patients with pleural carcinomatosis accounted for 2.9%, and macroscopic complete resection for them was associated with better survival.

Hence, in the present study, the authors aimed to summarize and compare the survival rates of different surgical manoeuvres for unexpected, intraoperatively confirmed malignant pleural dissemination cases and further evaluate related prognostic factors.

MATERIALS AND METHODS

The institutional review board of Shanghai Pulmonary Hospital approved the present study, and informed patient consent was waived because of the retrospective nature of the present study.

Inclusion criteria

From 1 January 2005 to 31 December 2013, 9576 registered NSCLC surgical patients of Shanghai Pulmonary Hospital were collected. The TNM staging was reclassified according to the seventh edition of the International Union Against Cancer-TNM staging system [4]. Among 9576 registered NSCLC surgical patients, 87 cases (0.9%) of macroscopic malignant pleural disseminations were confirmed during operations in Shanghai Pulmonary Hospital, despite preoperative evaluations for metastasis. After excluding 4 cases with neoadjuvant chemotherapies, 83 patients were enrolled into the present study.

Preoperative evaluation

All patients underwent evaluations for both tumour resectability and metastasis before operations. Fibreoptic bronchoscopy was requested for all lung cancer candidates. Remote metastasis was excluded using brain MR, abdominal MR or sonography and bone scintigraphy or PET–CT scans. Pleural effusion, if measurable by ultrasonic probing, was drained and repeatedly (more than six times) sent for cytology. The diagnostic criterion for pleural dissemination without pleural effusion was defined as six or more pleural or uneven pleural or fissural thickening [8]. The radiological diagnostic criteria of pleural dissemination with pleural effusion included pleural effusion with the findings of circumferential pleural thickening, nodular pleural thickening, parietal pleural thickening of more than 1 cm or mediastinal pleural involvement [9].

Operations

Thoracic cavity was routinely accessed with standard posterolateral thoracotomies or video-assisted thoracoscopies. Initial exploration was performed and a frozen section of the pleural biopsy was taken if pleural metastasis was suspected. After pathological confirmation of the pleural malignancies, the extent of resection depended on surgeons' experiences and preferences. Palliative pneumonectomies were forbidden by the regulations of our department. Pleural biopsy, or removal of the primary lesion with pulmonary wedge resection, segmentectomy or lobectomy was optional to different surgeons depending on their respective therapeutic beliefs [10]. Parietal pleurectomy and lymphadenectomy were also preferred by a few treatment groups in our institution under the belief that these manoeuvres might help prolong survival and improve the quality of life.

Adjuvant treatment

All patients were referred to four to six cycles of platinum-based adjuvant chemotherapies. With the development of targeted therapy after 2009, patients with adenocarcinomas were sent for target gene analysis, and patients were recommended corresponding medications, including gefitinib or erlotinib.

Follow-up

The patients were scheduled for a first re-visit at 4 weeks after operations. Follow-up visit was then scheduled every 3–4 months after finishing chemotherapies. If the patients experienced disease progression, second-line chemotherapy or targeted therapy was recommended. For the present study, mail, phone call, internet message exchange or outpatient clinic re-visit records were the main methods of information collection. The end date of follow-up for the present study was November 2014.

Data collection and statistical analysis

All related clinical data were collected and subjected to subsequent statistical analysis. Fisher exact test and independent sample *t*-test were used to compare different patient groups. Survival curves were obtained using the Kaplan–Meier method and univariate comparisons were performed using the log-rank test. Zero time was the date of surgical treatment. Cox proportional hazards regression was used for survival analysis. A *P*-value of <0.05 was considered statistically significant.

RESULTS

General information

Overall, 83 patients, 44 males and 39 females, were enrolled in the present study, with an average age of 57 (95% CI = 54.6–59.0) years. Fifty-three patients had primary tumour on the right lung and 30 on the left. In 52 cases, no pleural effusion was noticed intraoperatively and preopreative examination; thus, these cases were then grouped as dry pleural nodule (DPN) whereas the remaining 31 cases were grouped as wet pleural nodule with minimal pleural effusion (WPN < 300 ml; Table 1). As mentioned above, all preoperative cytology tests (25 cases), if available, were negative of cancer cells.

Operations

Nineteen patients underwent video-assisted thoracoscopies and 64 had thoracotomies. Single pleural biopsy was performed in 14 cases and pleural biopsy plus lung biopsy was performed in 7 cases. Primary tumour removals were performed in 62 cases, which included 8 pulmonary wedge resections (3 right upper lobe, 3 left upper lobe and 2 right lower lobe), 43 lobectomies (9 left upper lobe, 10 left lower lobe, 16 right upper lobe, 3 right middle lobe and 5 right lower lobe) and 11 right mid-lower bi-lobectomies. All 62 resection patients were performed R0 resection. Parietal pleurectomies were performed in 24 cases. Thirty-eight patients had systematic mediastinal lymphadenectomy, 16 patients had lymph nodal sampling, and in the remaining 29 cases, no lymph nodes were removed. No baseline differences emerged in characteristics between biopsy and primary tumour resection groups, except the uncertain N status because of lacking of lymph node dissection in the biopsy group (Table 2).

Postoperative complications

There was no intraoperative death. The 30-day postoperative mortality rate was 1.2% (1/83). One patient had acute respiratory failure subsequent to gastric aspiration on the second postoperative day and deceased 1 month later. The 30-day postoperative morbidity rate was 13.3% ($n = 11$). Major complications included pulmonary infection ($n = 3$), arrhythmia ($n = 3$) and prolonged air leak ($n = 5$), which were successfully managed conservatively.

Table 1: Characteristics of 83 patients with MPN

Factors	DPN (n = 52)	WPN (n = 31)	P-value
Age (years)			
≤60	28 (54)	18 (58)	0.708
>60	24 (46)	13 (42)	
Gender			
Male	26 (50)	18 (58)	0.476
Female	26 (50)	13 (42)	
Tumour size (cm), mean ± SD	3.2 ± 1.57	3.5 ± 2.48	0.592
Location			
Peripheral	47 (91)	30 (97)	0.277
Central type	5 (9)	1 (3)	
Histological type			
Adenocarcinoma	36 (69)	18 (58)	0.031
Squamous cell carcinomas	3 (6)	8 (26)	
Other type	13 (25)	5 (16)	
T status			
T1	15 (29)	9 (29)	0.271
T2	36 (69)	19 (61)	
T3	1 (2)	3 (10)	
Nodal status			
N0/1	13 (25)	10 (32)	0.284
N2	26 (50)	10 (32)	
Nx	13 (25)	11 (36)	
Procedure			
Biopsy	11 (21)	10 (32)	0.260
Primary tumour resection	41 (79)	21 (68)	
Pleurectomy			
Yes	15 (29)	9 (29)	0.986
No	37 (71)	22 (71)	
Lymphadenectomy			
No	16 (31)	13 (42)	0.419
Lymph nodal sampling	12 (23)	4 (13)	
Systematic mediastinal lymphadenectomy	24 (46)	14 (45)	
Adjuvant treatment			
No	14 (27)	11 (35)	0.506
Chemotherapy only	31 (60)	18 (58)	
Target therapy	7 (13)	2 (7)	

Data are numbers of patient, with percentages in parentheses.
DPN: dry pleural nodule; WPN: wet pleural nodule with minimal pleural effusion (<300 ml); MPN: malignant pleural nodule.

Table 2: Comparison of clinicopathological characteristics and postoperative treatment between patients with biopsy and primary tumour resection

Factors	Resection (n = 62)	Biopsy (n = 21)	P-value
Age (years)			
≤60	35 (57)	11 (52)	0.661
>60	27 (43)	10 (48)	
Tumour location			
Peripheral	58 (94)	19 (90)	0.638
Central type	4 (6)	2 (10)	
Histological type			
Ad	40 (65)	14 (67)	0.117
SCC	6 (10)	5 (24)	
Other type	16 (25)	2 (9)	
Pleural effusion			
WPN	21 (34)	11 (52)	0.260
DPN	41 (66)	10 (48)	
T status			
T1	19 (31)	5 (24)	0.363
T2	39 (63)	16 (76)	
T3	4 (6)	0 (0)	
N status			
N0–N1	22 (35)	1 (5)	0.000
N2–N3	34 (55)	2 (9)	
Nx	6 (10)	18 (86)	
Lung metastasis			
Yes	33 (53)	9 (43)	0.411
No	29 (47)	12 (57)	
Pleural metastasis			
Diffuse	58 (93)	21 (100)	0.233
2–3 metastasis	4 (7)	0 (0)	
Adjuvant treatment			
No	13 (21)	8 (38)	0.295
Chemotherapy only	42 (68)	11 (52)	
Target therapy	7 (11)	2 (10)	

Data are numbers of patient, with percentages in parentheses.
Ad: adenocarcinoma; SCC: squamous cell carcinoma; DPN: dry pleural nodule; WPN: wet pleural nodule with minimal pleural effusion (<300 ml).

Pathology

There were 11 (13.3%) squamous cell carcinomas, 54 (65.1%) adenocarcinomas and 18 (21.6%) others. A total of 516 nodes were harvested in 59 cases in the primary tumour resection group (90.3%, 56 of 62) and the biopsy group (14.3%, 3 of 21). Therefore, 15 patients were staged pN0, 8 were staged pN1 and 36 were staged pN2. EGFR mutation status was examined in 11 adenocarcinoma cases of which 7 were positive (19th exon mutation: 2; 20th exon mutation: 2; and 21st exon mutation: 3). There were 42 cases (50.6%) with gross residual lung metastasis. Seventy-nine cases (95.2%) had diffuse parietal pleural metastasis, and 4 (4.8%) cases only had two to three parietal pleural metastases.

Adjuvant treatment

Adjuvant chemotherapies were denied in 27 cases, and four to six cycles of platinum-based chemotherapies were performed in 54 patients. Two patients had targeted therapy at primary treatment. After disease progression, 44 patients had second-line chemotherapy and 7 patients had targeted therapy. Three patients with brain metastasis and 2 patients with bone metastasis had 30 Gy/10 fx dose of local chemoradiations.

Survivals

The median follow-up time was 32 (1–64) months. The main causes of death are lung cancer and metastases. The overall 3- and 5-year survival rates were 36.1 and 16.8%, respectively. The MST after surgery was significantly longer in the DPN group than in the WPN group (36.8 vs 22.4 months, $P = 0.005$). Primary tumour resection showed a prolonged MST compared with biopsy (37.3 vs 17.4 months, 3-year survival rate 45.8 vs 11.8%, $P = 0.001$) in all patients as well as in the DPN group (39.7 vs 23.3 months, $P = 0.044$) and the WPN group (27.1 vs 7.5 months, $P = 0.003$) (Figs 1–3). Major anatomical resections (lobectomies, $n = 54$) showed a prolonged MST compared with biopsy plus wedge resections (35.1 vs 23.7 months, 3-year survival rate 44.4 vs 26.6%, $P = 0.039$), whereas no significant survival benefit was observed comparing major anatomical resections with wedge resections in patients who had resection (35.0 vs 37.1 months, $P = 0.751$; Fig. 4). No significant survival benefit was observed concerning parietal pleurectomy only in patients who had resection (pleurectomy vs

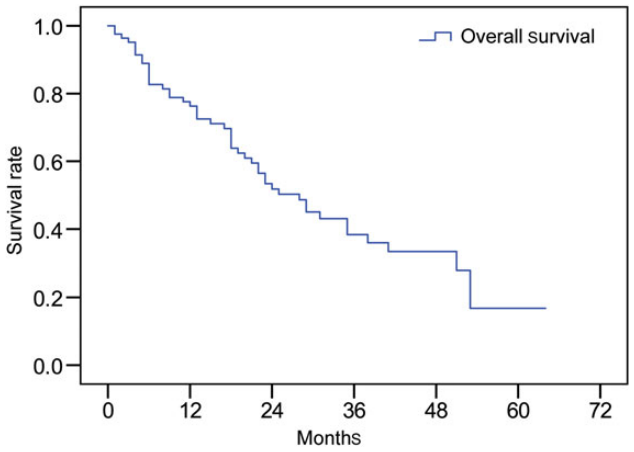

Figure 1: Kaplan–Meier survival curves of 83 patients with malignant pleural nodules. The overall 3- and 5-year survival rates were 36.1 and 16.8%, respectively.

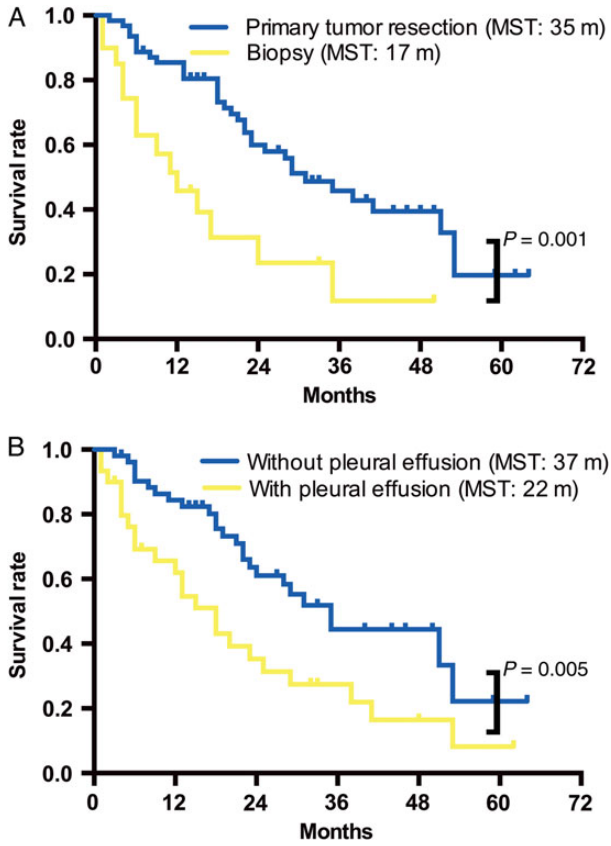

Figure 2: (**A**) Kaplan–Meier survival curves of primary tumour resection group ($n = 62$) and biopsy ($n = 21$) for patients with malignant pleural nodules. (**B**) Kaplan–Meier survival curves of 51 patients having malignant pleural nodules without pleural effusion and 32 patients having malignant pleural nodules with minimal pleural effusion (<300 ml). MST: median survival time.

no pleurectomy: 31.1 vs 36.1 months, $P = 0.533$) or systematic mediastinal lymphadenectomy within groups or subgroups.

Risk factors of 5-year survival rate

Multivariate analysis showed that primary tumour resection (HR: 3.678, $P = 0.014$), no pleural effusion (HR: 3.409, $P = 0.001$), N0/1 status (HR: 5.937, $P = 0.002$) and adenocarcinoma (HR: 5.481, $P = 0.002$) were independent prognostic indicators for patients with malignant pleural dissemination (Table 3).

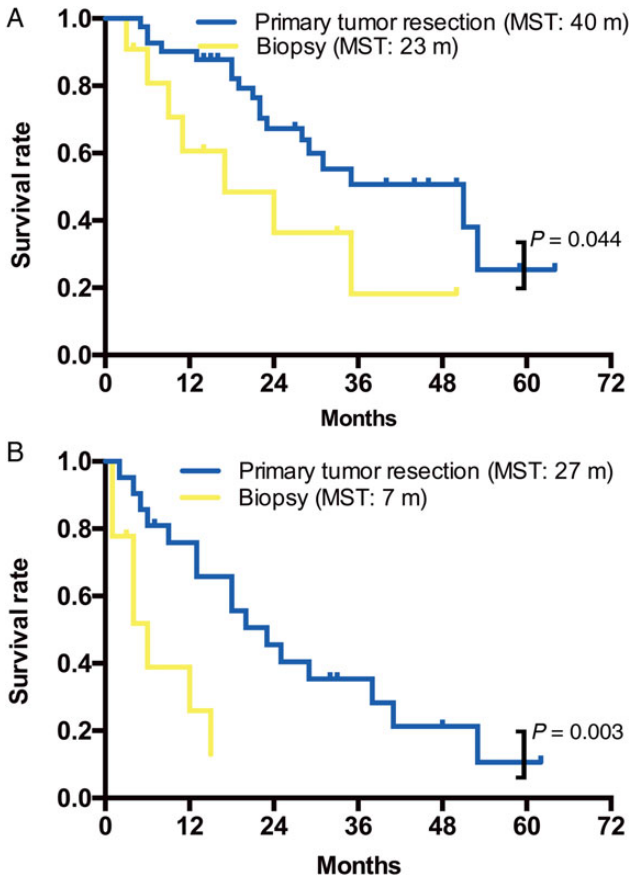

Figure 3: Survival differences were significant between primary tumour resection and biopsy for both patients having malignant pleural nodules without pleural effusion and with effusions. (**A**) Survival curves of patients without pleural effusion. (**B**) Survival curves of patients with minimal pleural effusions (<300 ml). MST: median survival time.

DISCUSSION

In the seventh edition of TNM staging for NSCLC, pleural dissemination is defined as M1a [11]; therefore, it is generally not recommended for surgery. This is occasionally challenged when malignant pleural metastasis is unexpectedly identified only during operations, especially when primary tumour removal seems easy and does not add overloaded invasions to the patients. Moreover, Ohta *et al.* [12] documented that for 42 surgically resected malignant pleural dissemination cases, the 3- and 5-year survival rates were 31.4 and 13.1%, respectively, and MST was 17 months. Okamoto *et al.* [6] found that the 5-year survival rate of surgically detected malignant pleural nodules of N0/1 status was 27.3% after pulmonary resection. Iida *et al.* found that the MST and 5-year survival rate of 313 pleural carcinomatosis patients without other metastatic disease were 34.0 months and 29.3%, respectively. Primary tumour resection was performed in 256 (81.8%) patients, and macroscopic complete resection was achieved in 152 (48.6%) patients, with 5-year survival rates of 33.1 and 37.1%, respectively [7]. In addition, prior results of extensive surgical interventions concerning this special disease category provided additional evidence for tumour removal [10, 13]. Therefore, it remains

controversial whether attempts should be made to remove the cancerous lesions when confronting an unexpected pleural dissemination case.

The present study was an initial attempt to review previous studies that utilized various practices with an aim to standardize an optimal operative protocol for this disease. The data showed that primary tumour resection, if associated with least morbidity, had a significantly more favourable prognosis compared with biopsy or exploratory thoracotomy (HR: 3.678, $P = 0.014$). The underlying reason was possible reduction of the tumour burden. Clinical support might be found in Iida *et al.*'s study. They found that the 5-year survival rate for pleural carcinomatosis patients with macroscopic complete resection was 37.1%, whereas it was 22.7 and 12.2% in patients with macroscopic incomplete resection ($P = 0.009$) and exploratory thoracotomy ($P < 0.001$), respectively. Theoretical support might be found in Rashid *et al.*'s study on metastatic breast cancer resection. The authors utilized bioluminescence technology to monitor overall breast cancer load under direct vision mouse model [14]. They found that only primary tumour resection significantly reduced tumour burden. Moreover, even when metastatic proliferation increased rapidly, the overall tumour burden after resection remained low.

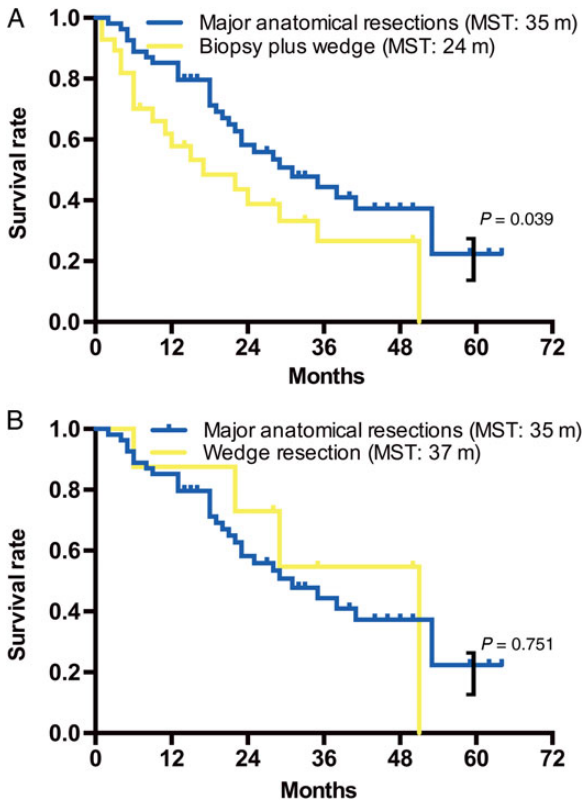

Figure 4: (**A**) Kaplan–Meier survival curves of major anatomical resections group (lobectomies, $n = 54$) and biopsy plus wedge resections group ($n = 29$). (**B**) Kaplan–Meier survival curves of major anatomical resections (lobectomies, $n = 54$) and wedge resections ($n = 8$) in patients who had resection.

The other surgical manoeuvres, including extensive lymph node dissection and parietal pleurectomy, showed no significant survival effect, according to the present data. Pleurectomy decreased the local recurrence rate in patients with malignant pleural effusion, as reported by Martini *et al.* [15] and Harvey *et al.* [16]. Larger-scale studies should be developed to evaluate the role of pleurectomy and lymph node dissection in controlling pleural malignancies.

Other than primary tumour removal, lymph node status also showed prognostic significance. In accordance with previous research, N2 status was significantly associated with worse outcome compared with N0/1 status (3-year survival rate 22.7 vs 60.9%, $P = 0.007$). Okamoto *et al.* [6] reported 5-year survival rate of 27.3% in a study conducted with 41 N0/1 cases. Furthermore, Albain *et al.* [17] proposed that N0/N1 cases with malignant pleural nodules could still be candidates for surgery by demonstrating that N0/N1 is the strongest predictor of long-term survival after operation. However, since most of our biopsy group patients lack pathological lymph node status, we do not regard lymph node status as a prognostic factor according to the existing evidence.

The negative prognostic effect of pleural effusion had also been previously documented. In 98 cases series of malignant pleural dissemination patients, MST was significantly longer if there was no pleural effusion (38 vs 13 months, $P < 0.001$) [18]. Patients without pleural effusion had less tumour burden, which, consistent with the theory of Kim *et al.* [18], may be one of the causes of superior survival in these conditions. This evidence suggests that more comprehensive preoperative examinations of the pleural

Table 3: Univariate and multivariate analyses of prognostic factors by using the Cox proportional hazards model

Factors	Univariate analysis		Multivariate analysis	
	Hazard ratio (95.0% CI)	*P*-value	Hazard ratio (95.0% CI)	*P*-value
Age (≤60 vs >60)	1.025 (0.572–1.837)	0.933		
Gender (male versus female)	0.649 (0.366–1.150)	0.139		
Location (left versus right)	1.128 (0.622–2.046)	0.692		
Malignant pleural effusion (DPN versus WPN)	2.177 (1.233–3.843)	**0.007**	3.409 (1.724–6.741)	**0.001**
Procedure (resection versus biopsy)	2.843 (1.495–5.405)	**0.001**	3.678 (1.308–10.347)	**0.014**
Pleurectomy (yes versus no)	1.092 (0.564–2.113)	0.794		
Lymphadenectomy (none versus SL)	0.661 (0.343–1.275)	0.217		
Histological type (Ad versus SCC)	2.759 (1.278–5.957)	**0.010**	5.481 (1.910–15.725)	**0.002**
Lung metastasis (yes versus no)	1.048 (0.591–1.859)	0.872		
N factor (N0/N1 versus N2)	2.700 (1.223–5.959)	**0.014**	5.937 (1.882–18.733)	**0.002**
Postoperative chemotherapy (yes versus no)	2.295 (1.558–3.032)	0.260		

SL: systematic mediastinal lymphadenectomy; Ad: adenocarcinoma; SCC: squamous cell carcinoma; DPN: dry pleural nodule; WPN: wet pleural nodule with minimal pleural effusion (<300 ml).
Bold values shows *P*-values ≦ 0.05.

effusions should be performed, including molecular biomarkers. Although primary tumour resection might still help prolong survival for these patients, a previous recognition of pleural dissemination and timely multidisciplinary intervention might be then warranted, as recognized previously.

Our study has some limitations. First, because this is a retrospective study of surgical cases, patients included in this analysis were highly selected and not representative of all patients with pleural dissemination. Secondly, because our dataset was not integrated for unexpected pleural dissemination, interesting information, such as the functional status, lung function, low usage rate of PET–CT and perhaps the intraoperative burden of disease. Because of these limitations, the question whether surgical resection should be performed for patients with unexpected intraoperatively proven malignant pleural nodules remains unanswered.

Briefly, the results of this study revealed that primary tumour resection had survival benefits for patients with unexpected intraoperatively proven malignant pleural nodules. However, due to its retrospective nature, a more complete prospective cohort study or a retrospective study after propensity score matching with more cases is warranted to confirm the role of surgery in NSCLC patients with malignant pleural nodules. Also, a study on how to enhance the sensitivity of detecting preoperative pleural metastasis using improved criteria combining CT, ultrasound and PET–CT is quite significant in the future.

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