Original Article

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Factors Associated with Procedure-related Tumor Seeding in Advanced Stage Lung Cancer Patients with Malignant Pleural Effusions

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Abstract:

Objective: Pleural procedure-related tumor seeding detected by computed tomography (CT) is common in lung cancer patients with malignant pleural effusion. This study aimed to identify the incidence of tumor seeding and the associated factors among lung cancer patients with malignant pleural effusions.

Material and Methods: This retrospective cohort study was conducted on 146 lung cancer patients with malignant pleural effusions, diagnosed between 2010 and 2017, who underwent at least 1 pleural procedure and had at least 2 series of CT images. The potential factors were categorized into clinical characteristics, pleural characteristics, treatment factors, and pleural procedures. Incidence rate ratios (IRR) were analyzed by Poisson regression to identify factors that were independently associated with tumor seeding.

Results: The incidence of procedure-related tumor seeding was 26%. Significantly increased IRRs of tumor seeding were found in relation to 1 time (IRR 5.653, 95% confidence interval [CI] 2.549 to 12.538) and ≥2 times of conventional intercostal chest drainage (ICD) insertion (IRR 5.837, 95% CI 1.768 to 19.266), 1 time (IRR 8.924, 95% CI 3.181 to 25.033) and ≥2 times of pleural biopsy (IRR 6.485, 95% CI 1.372 to 30.660), adenocarcinoma (IRR 8.329, 95% CI 2.804 to 24.747), and pleural thickening (IRR 12.458, 95% CI 1.360 to 114.152).

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Conclusion: Patients who had at least one pleural biopsy or ICD insertion, pleural fluid cytology positive or suspicious for malignancy, adenocarcinoma, or pleural thickening were found to be significantly at risk for tumor seeding.

Keywords: lung cancer, malignant pleural effusion, pleural procedure, track seeding, tumor implantation

Introduction

Malignant pleural effusion significantly reduces patient life expectancy and decreases their quality of life[1]. To determine the underlying etiology of pleural effusion, pleural fluid analysis is usually performed by thoracocentesis, with a pleural biopsy often done in cases with pleural nodules or abnormal pleural thickening. In cases with symptomatic pleural effusion, conventional intercostal chest drainage (ICD) or ultrasound-guided percutaneous catheter drainage (PCD) is performed to relieve the patient's symptoms or for further medical pleurodesis to prevent recurrent effusion.

The implantation of tumors along the track of a pleural procedure has been reported in up to 40% in malignant mesotheliomas[2–4]. However, it is rare in lung cancer and other malignancies. It has been described, mainly in case reports, after a percutaneous lung biopsy[5–8], a percutaneous pleural procedure[9–15], and surgical video-assisted thoracic surgery (VATS)[16–18]. Today, computed tomography (CT) is routinely used to monitor the treatment of lung cancer patients. Cases of track seeding have been increasingly reported in lung cancer patients[19,20]. To our knowledge, no study has investigated potential factors affecting tumor seeding in these patients. A recent study[19] conducted by our group found a relatively higher incidence rate of pleural procedure-related tumor seeding detected by CT than in previous studies. The same study found that once the tumor seeding had occurred, with a mean time of tumor seeding 2.9 months, the risk of death significantly increased (hazard ratios [HR] 3.35, 95% confidence interval [CI] 1.87 to 6.01). In addition, ICD insertion was identified as the only independent predicting factor for tumor seeding[19]. However, the study did not investigate other potential factors affecting tumor seeding. Consequently, this study extended the period of collecting data and investigated potential influencing factors that may be associated with tumor seeding.

There were two main purposes for this study. The first was to identify the incidence rate of procedure-related tumor seeding in lung cancer patients with malignant pleural effusion. The second purpose was to evaluate unadjusted incidence rate ratios (IRR) of procedure-related tumor seeding and their corresponding adjusted values regarding potential influencing factors, emphasizing clinical factors, pleural characteristics, treatment factors, and the type and number of pleural procedures performed.

Material and Methods

Patient selection

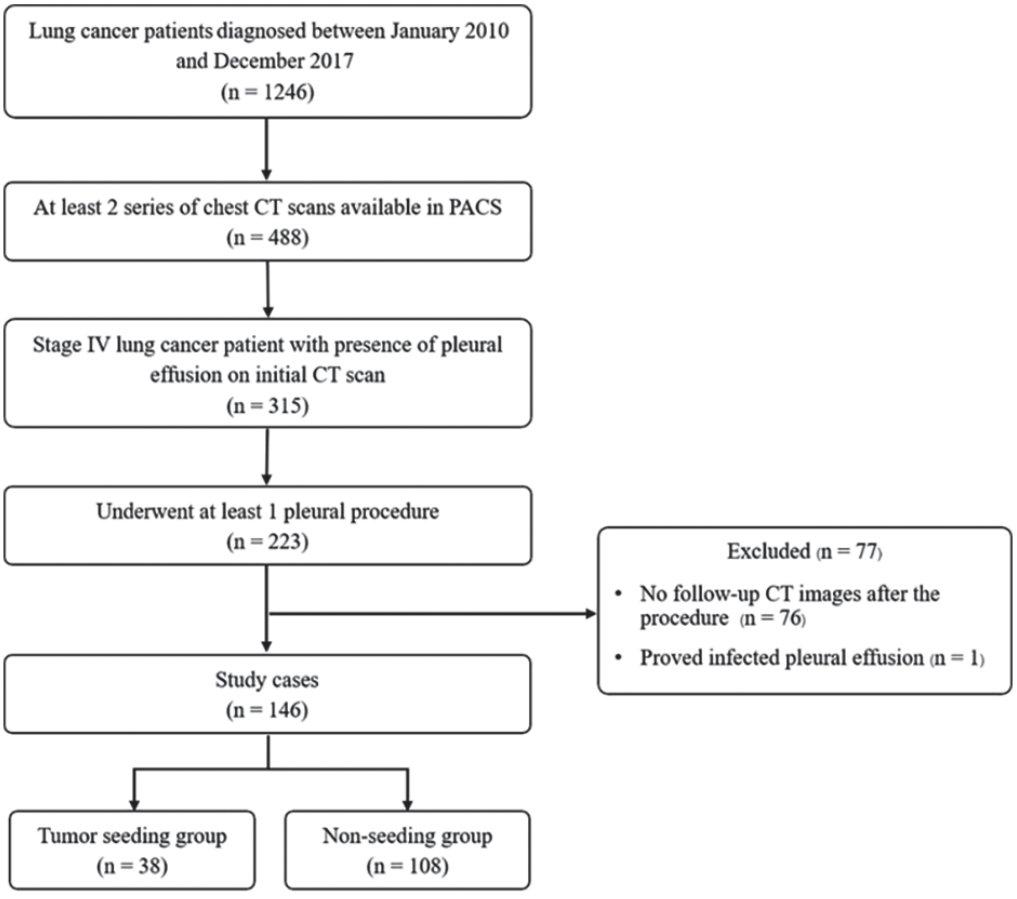
This retrospective cohort study was carried out with 1,246 patients who had been diagnosed with lung cancer between January 2010 and December 2017 in a tertiary care hospital. Informed consent from the study patients was waived with the approval of the faculty's Human Research Ethics Committee, with Institutional Review Board approval number 62-079-7-4. The estimated sample sizes for two independent proportions were 26 and 91 cases of patients with and without tumor seeding, respectively, according to our preceding study[19].

The inclusion criteria for the study were patients who had at least two available series of chest CT scans in the hospital picture archiving and communication system (PACS), and those with the presence of pleural effusion on the initial CT images and who had undergone at least one of thoracocentesis, chest drain insertion, or pleural biopsy. The

diagnosis of malignant pleural effusion was made by one of the following criteria: positive or suspicious malignant pleural fluid cytology analysis, histopathology confirmed by pleural biopsy, or suspicious findings of malignant pleural disease on initial CT images (including circumferential pleural thickening, nodular pleural thickening, pleural thickness greater than 1 cm, and mediastinal pleural involvement)[21]. The exclusion criterion was no follow-up chest CT images after the procedure. After reviewing the initial CT images, the selected patients were classified into the 2 groups noted above regarding pleural procedure-related tumor seeding (Figure 1).

Medical record reviews

The selected patients' medical records were retrieved from an electronic hospital database which included the first visit date, last visit date or date of death, age at the first visit, gender, histopathologic subtype and current stage of lung cancer, pleural cytology results, and the treatments received, including systemic medical treatments (either chemotherapy, targeted therapy, and immunotherapy), radiotherapy sessions, and best supportive care or no specific treatment after the pleural procedure. Each patient's pleural procedures were also recorded, including thoracocentesis, pleural biopsy, and chest catheter



CT=computed tomography, PACS=picture archiving and communication system

Figure 1 Patient selection diagram

placement. The chest catheters were classified into two groups: ICD, usually performed using a large-bore catheter (28-36 Fr), and PCD, which used much smaller catheters (8-12 Fr).

Imaging analysis

Two thoracic radiologists (NK and WT, 12 and 25 years of experience, respectively) individually reviewed the initial CTs and all the available follow-up CT images, usually performed every 3-4 months. A consensus was reached in cases of initial disagreement.

The chest radiographs, CT images, and medical records were reviewed to determine the site of the procedures. For patients who underwent blind thoracocentesis or pleural biopsy, the standard landmark located just below the scapular tip at the posterior axillary line was deemed as the site. A seeding tumor was defined as present on a CT by a newly developed or growing enhancing mass or nodule

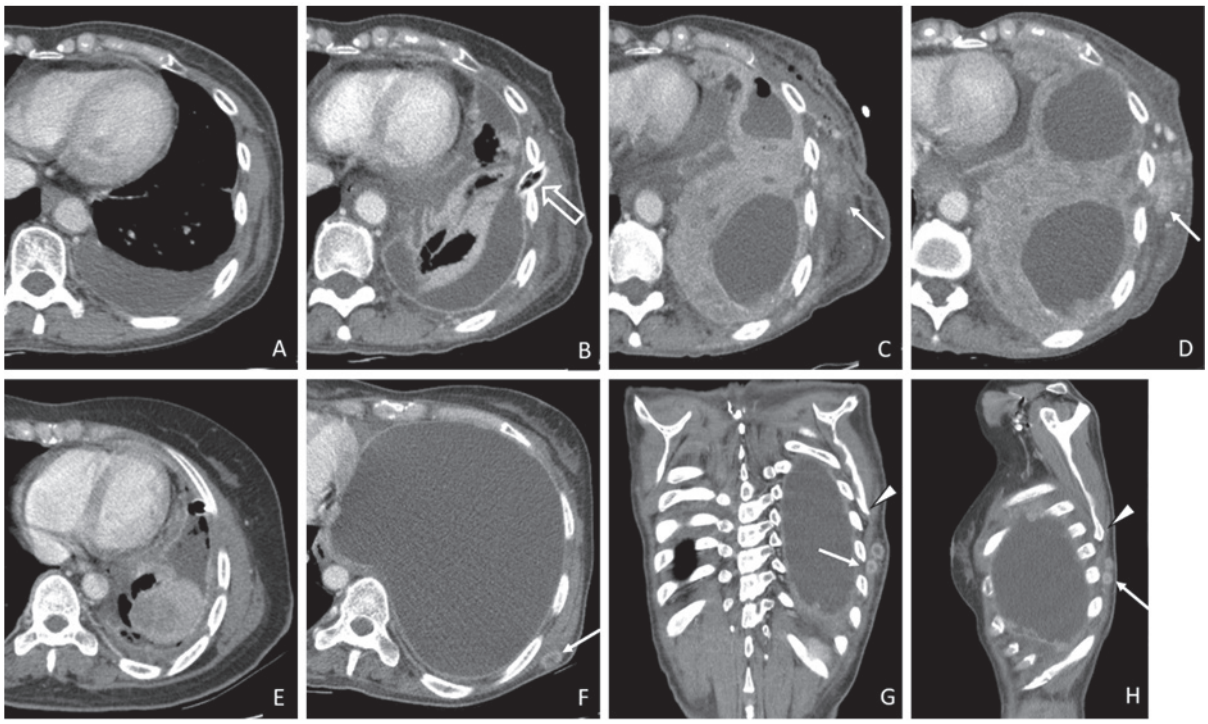


Figure 2 Enhanced chest computed tomography (CT) scans of an advanced stage lung cancer patient with pleural effusion who underwent intercostal chest drainage (ICD) and percutaneous catheter drainage insertions as well as thoracocentesis and pleural biopsy at initial scan (A) and follow-up scans which show progression of the disease (B-D). The ICD is observed (open arrow). After ICD removal, 2- (C) and 5-month (D) follow-up CT images show developed and growing enhanced chest wall nodules along the route of the removed ICD (arrows in C-D). Enhanced chest CT scans of another patient who underwent thoracocentesis and pleural biopsy at diagnosis (E) and 9 months later after the procedure (F-H). Note the large amount of left pleural effusion with two circumscribed heterogeneously enhanced nodules at the left posterior chest wall (arrows in F-H), just at the inferior tip of the scapula (arrowhead), which is a common location for a thoracocentesis or blind pleural biopsy.

at the procedural site[19,20] (Figure 2). The management was independent of histologic confirmation for the tract seeding for all the patients with advanced-stage lung cancer in this hospital. Therefore, a biopsy was not done.

The characteristics of the pleural findings on initial CT images were analyzed. Pleural effusion was classified into loculated and free effusion. The presence of pleural thickening was recorded, defined by pleural thickness greater than or equal to 2 mm. The pleural thickening detected was further categorized into two distinct groups, thickening with and without mediastinal involvement. The maximal thickness of the pleura was recorded and measured on the axial scan.

Associated factors

The potential factors for procedure-related tumor seeding were reviewed and classified into four categories.

1. Clinical factors: staging of lung cancer before the start of treatment, histopathological type of lung cancer, and cytology result of pleural effusion.
2. Pleural factors: characteristics of the pleural effusion, the presence of pleural thickening, characteristics of the pleural thickening, and maximum pleural thickness.
3. Treatment factors: systemic medical treatment, thoracic radiation, and best supportive care or palliative or no further treatment following the procedure.
4. Pleural procedure factors: type and number of pleural procedures the patient underwent during observation.

Statistical analysis

Data gathered from the medical records and PACS were recorded using EpiData Entry (version 3.1), and the following statistical analyses were performed using Stata for Mac (version 16.1). For patient characteristics, continuous variables were described as means and standard deviations, while the categorical variables were described as numbers and percentages. The categorical variables were compared between groups using chi-squared test or Fisher exact test as appropriate, while the continuous variables were compared using t-test.

Both uni- and multivariable incidence rate ratios of tumor seeding were calculated using a Poisson regression model. We selected factors that could indicate a seeding risk to include in the multivariable model. A multivariable regression model was used to identify factors that were independently associated with the rate of tumor seeding by adjusting for other potential prognostic factors, including age, gender, subtype of lung cancer (adenocarcinoma vs non-adenocarcinoma), the presence of pleural thickening, pleural thickening characteristics, as well as number and type of pleural procedure that the patients underwent. A p-value less than 0.05 was considered statistically significant.

Results

Procedure-related tumor seeding

One hundred forty-six patients were selected for this study (Table 1). There were 38 patients (26.0%) who developed procedure-related tumor seeding. The incidence rate of developing tumor seeding was about 0.216 cases per person-year.

Clinical factors

The 38 patients in the tumor-seeding group consisted of 15 males and 23 females, with a mean age of 62.4 years. For the non-seeding group, there were 108 patients, consisting of 61 males and 47 females, with a mean age of 65.

Adenocarcinoma was the majority type of lung cancer in both groups, followed by squamous cell carcinoma. The distribution of histopathology types and stagings of lung cancer had no significant difference between groups. However, cytology-positive or suspicious-for-malignancy pleural fluid were more likely to be associated with tumor seeding than cytology-negative pleural fluid (p-value< 0.001).

Table 1 Patient characteristics

Factor	Tumor seeding n=38 (26%)	Non seeding n=108 (74%)	Total n=146 (100%)	p-value
Clinical factors				
Age, mean (S.D.)	62.4 (12.2)	65 (12.2)	64.3 (12.2)	0.510
Gender, n (%)				0.070
Male	15 (19.7)	61 (80.3)	76 (52.1)	
Female	23 (32.9)	47 (67.1)	70 (47.9)	
Histopathology, n (%)				0.890
Squamous cell carcinoma	2 (22.2)	7 (77.8)	9 (100.0)	
Adenocarcinoma	31 (26.0)	91 (74.0)	123 (100.0)	
Non-small cell lung cancer NOS*	2 (40.0)	3 (60.0)	5 (100.0)	
Small cell lung cancer and others	2 (22.2)	7 (77.8)	9 (100.0)	
Cytology, n (%)				<0.001
Positive/suspicious malignancy	33 (35.5)	60 (64.5)	93 (100.0)	
Negative	5 (16.1)	26 (83.9)	31 (100.0)	
Stage of lung cancer, n (%)				0.590
IV-A	23 (27.7)	60 (72.3)	83 (100.0)	
IV-B	15 (23.8)	48 (76.2)	63 (100.0)	
Pleural factors				
Loculated effusion, n (%)	10 (25.0)	30 (75.0)	40 (100.0)	0.860
Pleural thickening present, n (%)	37 (28.9)	91 (71.1)	128 (100.0)	0.030
Pleural characteristic, n (%)				0.110
Not thickening	1 (5.6)	17 (94.4)	18 (100.0)	
Spared mediastinal pleura	21 (29.2)	51 (70.8)	72 (100.0)	
Involved mediastinal pleura	16 (28.6)	40 (71.4)	56 (100.0)	
Treatment factors				
Systemic medical treatment, n (%)	35 (26.3)	98 (73.7)	133 (100.0)	0.800
Thoracic radiation, n (%)	3 (21.4)	11 (78.6)	14 (100.0)	0.680
Supportive/palliative care, n (%)	3 (23.1)	10 (76.9)	13 (100.0)	0.800
Pleural procedure factors				
Pleural biopsy, n (%)	32 (34.0)	62 (66.0)	94 (100.0)	<0.001
Number of pleural biopsies, n (%)				0.010
Never	6 (11.5)	46 (88.5)	52 (100.0)	
1 time	28 (35.4)	51 (64.6)	79 (100.0)	
≥2 times	4 (26.7)	11 (73.3)	15 (100.0)	
ICD, n (%)	24 (39.3)	37 (60.7)	61 (100.0)	<0.001
Number of ICDs, n (%)				<0.001
Never	14 (16.5)	71 (83.5)	85 (100.0)	
1 time	19 (35.8)	34 (64.2)	53 (100.0)	
≥2 times	5 (62.5)	3 (37.5)	8 (100.0)	
PCD, n (%)	9 (22.0)	32 (78.0)	41 (100.0)	0.480
Number of PCDs, n (%)				0.300
Never	29 (27.6)	76 (72.4)	105 (100.0)	
1 time	6 (17.6)	28 (82.4)	34 (100.0)	
≥2 times	3 (42.9)	4 (57.1)	7 (100.0)	
Thoracocentesis, n (%)	35 (27.8)	91 (72.2)	126 (100.0)	0.230
Number of thoracocenteses, n (%)				0.390
Never	3 (15.0)	17 (85.0)	20 (100.0)	
1 time	19 (25.7)	55 (74.3)	74 (100.0)	
≥2 times	16 (30.8)	36 (69.2)	52 (100.0)	

S.D.=standard deviation, NOS=not otherwise specified, ICD=conventional intercostal drainage, PCD=ultrasound-guided percutaneous drainage

Pleural effusion and pleural characteristics

The majority of the patients in both groups had free pleural effusion. A significant correlation with tumor seeding was observed in patients with an initial CT showing pleural thickening (28.9% vs. 5.6%, p-value=0.030).

Treatment factors

In the tumor-seeding group, 35 patients received systemic medical treatment, 3 received thoracic radiation, and 2 received no treatment during their end-of-life palliative care. For the non-seeding group, 98 patients received systemic medical treatment, 11 received thoracic radiation, and 10 received no treatment during their palliative care. There were no statistically significant differences in treatment modalities between the two groups.

Pleural procedure factors

Most patients in both groups underwent more than one pleural procedure, with some undergoing the same procedure more than one time. Among them, thoracocentesis was the most-performed procedure. In the tumor-seeding and non-seeding groups, 32 and 62 patients had a pleural biopsy done, 24 and 37 patients underwent ICD placement, 9 and 32 patients had a history of PCD insertion, and 35 and 91 patients underwent thoracocentesis, respectively. There were statistically significant differences in the number of pleural biopsies performed and ICD insertions performed.

In the univariable analysis, patients who underwent a single pleural biopsy had a higher incidence rate ratio of developing pleural procedure-related tumor seeding (IRR 3.848, 95% CI: 1.550 to 9.295) than the patients who did not undergo this procedure. Patients with a history of one-time ICD insertion (IRR 2.644, 95% CI 1.326 to 5.263) and greater than or equal to two-time insertions (IRR 4.568, 95% CI 1.645 to 12.681) also had higher incidence rate ratios of tumor seeding. These factors remained significantly related to tumor seeding after multivariable analysis by Poisson regression. In addition, pleural biopsy ≥2 times (IRR 6.485, 95% CI 1.372 to 30.660), lung cancer with the adenocarcinoma subtype (IRR 8.329, 95% CI 2.804 to 24.747), and the presence of pleural thickening (IRR 12.458, 95% CI 1.360 to 114.152) were related with increased incidence rate ratios of tumor seeding, after adjustment for other factors (Table 2).

The adjusted predicted incidence rates of tumor seeding by each type and number performed of pleural procedures were about 0.082 (95% CI 0.012 to 0.152) for patients who never underwent a pleural biopsy, 0.742 (95% CI 0.292 to 1.191) for 1 time, and 0.573 (95% CI −0.176 to 1.322) for ≥2 times of pleural biopsies, and about 0.164 (95% CI 0.066 to 0.263) for patients who never underwent ICD insertion, 0.917 (95% CI 0.310 to 1.524) for 1 time and 0.907 (95% CI −0.081 to 1.895) for ≥2 times of ICD insertions. The predicted incidence rates of tumor seeding were calculated (Table 3), and the relationship between the predicted incidence rates of tumor seeding and the number of pleural procedures performed are shown in Figure 3.

Discussion

This is the first study to identify factors associated with procedure-related tumor seeding in lung cancer patients with malignant pleural effusions. Patients who had pleural fluid cytology positive or suspicious for malignancy, pleural thickening, or a history of pleural biopsy or ICD insertion were found to be significantly more likely to have tumor seeding. After adjustment for other factors, patients who underwent pleural biopsy or ICD insertion, or who had the adenocarcinoma subtype or pleural thickening were related to an increased incidence rate ratio of tumor seeding.

Table 2 Incidence rate ratio (IRR) for tumor seeding of potential factors

Variable	Univariate analysis		Multivariate analysis	
	IRR	95% CI	IRR	95% CI
Gender (male)	0.597	0.311, 1.143	0.286***	0.138, 0.593
Age	0.993	0.968, 1.019	1.006	0.973, 1.039
Cancer type (adenocarcinoma)	1.471	0.503, 3.566	8.329***	2.804, 24.747
Loculated pleural effusion	0.999	0.485, 2.057	1.273	0.572, 2.835
Pleural thickening	6.010	0.825, 43.803	12.458*	1.360, 114.152
Characteristic of pleural thickening				
Involved mediastinal pleura	6.085	0.807, 45.885	1.000	(omitted)
Spared mediastinal pleura	5.954	0.801, 44.263	1.417	0.669, 3.002
Maximal pleural thickness	1.009	0.969, 1.049	0.986	0.924, 1.052
Pleural biopsy				
1 time	3.848**	1.593, 9.293	8.924***	3.181, 25.033
≥2 times	2.312	0.652, 8.192	6.485*	1.372, 30.660
ICD				
1 time	2.644**	1.326, 5.263	5.653***	2.549, 12.538
≥2 times	4.568**	1.645, 12.681	5.837**	1.768, 19.266
PCD				
1 time	0.720	0.299, 1.735	0.689	0.278, 1.709
≥2 times	1.577	0.480, 5.176	1.016	0.251, 4.122
Thoracocentesis				
1 time	1.547	0.458, 5.227	1.381	0.375, 5.088
≥2 times	1.992	0.580, 6.836	1.330	0.349, 5.070

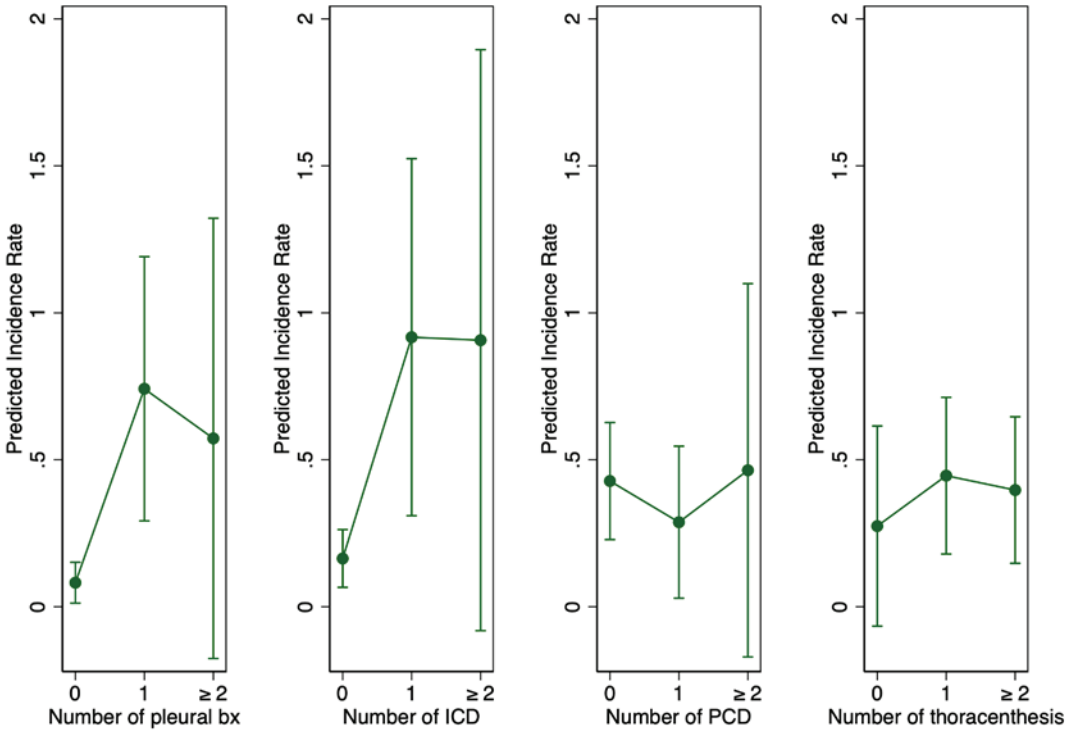
*p-value<0.05, **p-value<0.01, ***p-value<0.001

CI=confidence interval, CD=conventional intercostal drainage, PCD=ultrasound-guided percutaneous drainage

Table 3 Predicted incidence rate for tumor seeding by each type and number of performed pleural procedures

Procedure type	Number	Predicted incidence rate	95% CI
Pleural biopsy	Never	0.082	0.012, 0.152
	1 time	0.742	0.292, 1.191
	≥2 times	0.573	-0.176, 1.322
ICD insertion	Never	0.164	0.066, 0.263
	1 time	0.917	0.310, 1.524
	≥2 times	0.907	-0.081, 1.895
PCD insertion	Never	0.428	0.229, 0.627
	1 time	0.288	0.029, 0.546
	≥2 times	0.464	-0.171, 1.099
Thoracocentesis	Never	0.274	-0.066, 0.615
	1 time	0.446	0.179, 0.712
	≥2 times	0.397	0.148, 0.646

CI=confidence interval, ICD=conventional intercostal drainage, PCD=ultrasound-guided percutaneous drainage



bx=biopsy, CT=computed tomography, ICD=conventional intercostal chest drainage, PCD=ultrasound-guided percutaneous catheter drainage

Figure 3 Relationship between predicted incidence rate of tumor seeding and numbers of each separate pleural procedures performed

In lung cancer patients with malignant pleural effusion, pleural procedure-related tumor seeding is common. In this study, the incidence of tumor seeding was 26.0% (38/146), which is relatively close to a previous report (22.4%)[19]. However, it is higher than in other published literature that has only been described in case reports[9–12], probably because it was a CT-based assessment, which is more sensitive than a clinical-based assessment. This result is consistent with malignant mesothelioma reports in which the incidences of track seeding was higher in radiological than clinical evaluations[2,22].

The seeded tumors can develop along the track of an ICD, PCD, or pleural biopsy or thoracocentesis procedure (Figure 2). The pathogenesis of track seeding is mainly unknown. A pleural defect may be created at the location of an intervention site, leading to tumor infiltration of the thoracic wall by contaminated pleural fluid. Several hypotheses suggest that tumor seeding may occur due to the cancer itself being penetrated, improper tissue handling while doing a biopsy, or repeated penetration during the needle procedure[23]; the hematogenous spread of cancerous cells to a tissue undergoing repair following a biopsy[24]; or the influence of unknown genetic factors[25]. One possible pathogenesis hypothesizes that port-site recurrences after laparoscopic oncology may be due to contamination from the instruments and trocars with tumor cells[26,27]. This hypothesis has been confirmed in a porcine model[28–30].

This study also found that patients with a history of ICD insertion had a higher incidence rate and incidence rate ratio of tumor seeding than the patients who did not undergo this procedure. As suggested in a preceding study, these patients were likely to have more aggressive tumor behavior and require urgent large-bore chest tube insertion, thus were more likely to have tumor seeding[19]. Another suggestion is that a larger catheter size can cause a more significant pleural defect, increasing the possibility of tumor cells penetrating the chest wall. Earlier studies on malignant pleural mesothelioma have found that higher rates of chest wall intervention track metastases developed in more invasive procedures[2,31], providing supportive evidence that larger procedural track sizes may be related to tumor cell penetration through the chest wall, thereby increasing the likelihood of tumor seeding.

This study is the first to investigate the influence of the number of performed pleural procedures and tumor seeding. By multivariable Poisson regression analysis, we concluded that patients who underwent pleural biopsy or ICD insertion, either once or twice or more, had higher incidence rate ratios of tumor seeding. This finding could be useful for tumor seeding prediction after these procedures. However, a secondary analysis we did based on the predicted incidence rate instead of the incidence rate ratio found that only one pleural biopsy and ICD insertion were significantly related to tumor seeding; that finding might have been because only a small number of patients had the same procedure done twice or more.

Positive cytology means the presence of malignant cells in pleural effusion, indicating widespread disease and a worse prognosis than negative results[32]. This study found that pleural fluid cytology positive or suspicious for malignancy was more likely to be associated with tumor seeding than cytology-negative pleural fluid (p-value< 0.001). This could be explained by a greater number of malignant cells dispersed in the effusion, not only leading to cytomorphologic analysis with a positive result but also predisposing to malignant cell deposition throughout the procedure track. In the study, however, because of collinearity with the adenocarcinoma subtype, the pleural cytology results were not included in the final univariable and multivariable models.

Interestingly, only one out of 38 patients in the tumor seeding group lacked pleural thickening for pleural variables. In addition, regardless of mediastinal pleural involvement or maximal pleural thickness, pleural thickening was independently related to a higher incidence rate ratio of tumor seeding, which could be related to the deposition of malignant cells within the thicker pleura, making percutaneous intervention potentially hazardous, as malignant cells may deposit along the needle path into the overlying subcutaneous tissue when pleural nodules or thickened pleura are biopsied for diagnosis either under imaging guidance at the thickest point of the pleura with percutaneously accessible or by blind biopsy at a location just under the scapular tip in the posterior axillary line. That may explain why tumor seeding was higher among individuals with pleural thickening who underwent pleural biopsies.

This study had some limitations. First, it was a retrospective study; pleural procedures may be under-reported in some cases, particularly in the number of thoracocenteses performed at referring community hospitals; some factors that may be related to potential seedings, such as the number of pleural punctures, may not have been documented. Second, the study had various follow-up CT intervals. To address these limitations, prospective studies with regular-interval follow-up CT scans are needed. Third, this study did not include indwelling pleural catheter insertions, as the institute had limited cases of this type due to financial restrictions. Additional research should be done if sufficient cases occur in the future. Finally, due to ethical considerations in advanced disease, none of the

cases diagnosed as procedure-related tumor seeding in this study were confirmed by histopathology. However, this is not different from many studies in the prior literature, in which diagnoses of track seeding relied on serial CT studies[3,20,33].

Conclusion

This study successfully identified some factors that might be associated with pleural procedure-related tumor seeding in advanced stage lung cancer patients with malignant pleural effusions. Patients who had at least one pleural biopsy or ICD insertion, pleural fluid cytology positive or suspicious for malignancy, adenocarcinoma, or pleural thickening were found to be significantly at risk for tumor seeding. However, it should be noted that the presence of any of these factors is not a contraindication or discouragement for a pleural procedure because the benefits of this procedure are far greater than the risk of possible complications.

Conflict of interest

The authors declare there are no conflicts of interest.

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