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Title: Clinical Predictors of Successful and Earlier Pleurodesis of Tunneled Pleural Catheters in Malignant Pleural Effusions

Running head: *Predictors of TPC pleurodesis*

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Abbreviations list

BDI	Baseline dyspnea index
ECOG	European Cooperative Oncology Group
MT	Medical thoracoscopy
TDI	Transition dyspnea index
TPC	Tunneled pleural catheter

Abstract

BACKGROUND: Tunneled pleural catheters (TPCs) used to treat malignant pleural effusions may achieve pleurodesis. We aim to identify factors associated with higher pleurodesis rates, and earlier TPC removal.

METHODS: We reviewed a prospective database of TPCs inserted for confirmed malignant pleural effusions, including patients who underwent medical thoracoscopy. Clinical, radiologic, and pleural fluid data were recorded. Logistic regression and Cox regression were used to assess rates of and days to pleurodesis respectively.

RESULTS: Data from 1071 TPCs were analyzed. Increased rates of pleurodesis were associated with lymphoma (OR 3.49, 95% CI 1.93-6.33), ovarian cancer (OR 2.93, 95% CI 1.68-5.11), ECOG ≤ 2 (OR 2.79, 95% CI 1.79-4.34), medical thoracoscopy (OR 2.21, 95% CI 1.28-3.85), protein (OR 1.03, 95% CI 1.01-1.06), albumin (OR 1.07, 95% CI 1.03-1.12), and % eosinophils (OR 1.04, 95% CI 1.00-1.07). Reduced rates of pleurodesis were associated with gastrointestinal cancers (OR 0.41, 95% CI 0.19-0.87), hydropneumothorax on post-drainage chest x-ray (OR 0.62, 95% CI 0.41-0.94), and % other cells on cell count (OR 0.98, 95% CI 0.97-0.99). Earlier pleurodesis was associated with ovarian cancer (HR 1.48, 95% CI 1.06-2.08), medical thoracoscopy (HR 1.45, 95% CI 1.10-1.92), protein (HR 1.03, 95% CI 1.01-1.04), and % eosinophils (HR 1.02, 95% CI 1.00-1.04). Delayed pleurodesis was associated with breast cancer (HR 0.61, 95% CI 0.46-0.81), hydropneumothorax with <80% expansion (HR 0.55, 95% CI 1.93-6.33), and % other cells (HR 0.99, 95% CI 0.98-1.00).

INTERPRETATION: Clinicians should consider numerous factors to predict probability of and timing to TPC pleurodesis.

Tunneled pleural catheters (TPCs) are an alternative to chemical pleurodesis for managing recurrent malignant pleural effusions,[1] and are recommended by current international guidelines.[2,3] Patients can be treated as outpatients and avoid hospitalizations associated with chemical pleurodesis.[4] TPCs are also effective in the setting of trapped lung.5

Although approximately 45.6% of patients eventually achieve pleurodesis and their TPCs can be removed,[6] the mechanism is unclear. One study that assessed clinical factors that predict pleurodesis of TPCs in malignant pleural effusions found increased rates of pleurodesis with the absence of chest wall irradiation, cytology positivity, breast and gynecologic cancers, and complete re-expansion of the underlying lung.[7]

No studies have investigated factors associated with earlier pleurodesis. Recognizing clinical factors associated with earlier or delayed pleurodesis is important, allowing physicians to personalize treatment of malignant pleural effusions. Patients also frequently ask about the duration of TPC placement. Furthermore, there are economic implications of pleurodesis timing, because TPCs have ongoing drainage costs the longer they are in place.[8] The present study aims to identify clinical factors associated with higher TPC pleurodesis rates, and earlier TPC removal.

Materials and Methods

Overview

We performed a retrospective review of a prospectively collected database of TPCs inserted in The Ottawa Hospital for treating confirmed malignant pleural effusions. Our study was approved by the Ottawa Health Sciences Research Ethics Board. We evaluated TPCs that were consecutively inserted from May 2006 to June 2013. We assessed data for up to three years post TPC insertion to allow ample time for TPCs to achieve pleurodesis. Clinical data, baseline Eastern Cooperative Oncology Group (ECOG) score, baseline dyspnea index (BDI), transition dyspnea index (TDI), complications, pathology, pleural fluid analysis at the time of insertion, and chest x-ray data were collected. Chest x-rays were assessed at baseline, within 24 hours post-insertion, and at removal. The degree of lung expansion was recorded as >80%, 50-80%, 30-50%, or <30% expansion.

Definitions of outcomes:

The primary outcomes were rates of, and days to, pleurodesis. To meet our definition of pleurodesis, TPCs must have minimal drainage (<50mL) with two consecutive drainages, and a lack of increase in pleural effusion size on subsequent chest x-rays. Complete pleurodesis was defined as TPCs that had lung expansion of >80% at the time of TPC removal, versus <80% for partial pleurodesis. TPCs removed for another reason, such as dislodgement, were excluded from the final pleurodesis analysis. Failure of pleurodesis was defined as TPCs that did not meet pleurodesis criteria and the patient was deceased before TPC removal.

Clinical Practice

Patients with suspected or confirmed malignant pleural effusions were referred to our clinic and assessed for TPC insertion by Interventional Pulmonologists. TPCs in our center were inserted in an outpatient clinic, the inpatient wards, or at the time of medical thoracoscopy (MT) in the endoscopy suite. Pleural fluid was drained by vacuum bottles until there was no further drainage, or as tolerated by the patient. Home care nursing services were arranged to perform drainages three times a week up to 1L maximum. All patients were followed up in the pleural effusion clinic in two weeks and subsequent follow up was arranged every eight weeks. The TPC was kept in place until drainages were <50mL with two consecutive drainages, and there was no increase in pleural effusion size on follow up chest x-ray. At TPC removal, the skin was cleaned and draped in a sterile fashion. Lidocaine was used to anesthetize the insertion site, and the TPC was dissected out and removed.

Some patients underwent outpatient MT, for diagnosis or tissue acquisition for ancillary testing. These procedures were performed in the endoscopy suite with moderate conscious sedation. Ultrasound guidance was used to mark an appropriate entry site, the skin was anesthetized with lidocaine, Kelly forceps were used to dissect to the pleural space, and an 8mm disposable trocar was inserted. A semi-rigid pleuroscope (Olympus LTF-160) was inserted through the trocar and all the fluid was aspirated. Parietal pleural abnormalities were biopsied, and patients had a TPC inserted at the end of the procedure. The TPC was connected to a water seal suction device at -20cm H_20, followed by -40cm H_20. Patients were disconnected when no further air leak was noted. Patients were discharged home after two hours of observation and had a second post-procedure chest x-ray that was stable at 2 hours.

Statistical Analyses

Data was analyzed with SAS, version 9.4 statistical software. The associations of clinical variables with pleurodesis were determined by univariate and multivariate logistic regression for both categorical and continuous variables. Categorical variables were further assessed by X^2. Medians were compared by Mann-Whitney U-test. Significant continuous variables by multivariate analysis were assessed by receiver operating characteristic (ROC) analysis, and the highest predictive accuracy was used as the threshold value. The associations of clinical variables with days to pleurodesis were analyzed by Cox regression. Variables that were significant at a 5% significance level were retained in the final multivariate regression models. Adjusted ORs and 95% CIs were calculated for the final models.

Results

Baseline Demographics

A total of 1128 TPCs were reviewed. From the pleurodesis analysis, 43 were excluded due to removal for mechanical failure, kinking of the tube, chemical pleurodesis, or missing substantial data. 1071 TPCs were included in the final pleurodesis analysis. The baseline demographics are highlighted in Table 1.

Univariate Analyses

Rates of pleurodesis and days to pleurodesis by tumor type are shown in Table 2. The overall pleurodesis rate was 43%. Of these patients, 272 (59%) TPCs had complete pleurodesis, and 192 (41%) TPCs had partial pleurodesis. Only 15 (1%) TPCs had <50% lung expansion at removal. The median days to pleurodesis was 44 days (IQR 26 – 90). 607 (57%) TPCs were not removed before death. In patients who died prior to TPC removal, the median days to death was 38 days (IQR 18 – 80). In univariate logistic regression, ovarian cancer, lymphoma, and mesothelioma were associated with higher rates of pleurodesis when compared to other tumor groups. Gastrointestinal and non-small cell lung cancers were associated with lower rates of pleurodesis.

Results of the univariate analysis on other clinical variables are shown in Table 3. Clinical factors significantly associated with higher rates of pleurodesis were ECOG, MT, protein, albumin, % lymphocytes, and % eosinophils. % Neutrophils, and % other cells on cell count were associated with lower rates of pleurodesis.

Lung expansion and hydropneumothorax

The interaction between degree of lung expansion and hydropnemothorax on post-insertion chest x-ray was further assessed by X^2 (Table 4). In TPCs with hydropneumothorax post insertion, the lower the degree of lung expansion, the lower the rates of pleurodesis. In patients with hydropneumothorax and less than 30% expansion, only 17% had pleurodesis. Interestingly, patients with hydropneumothorax with > 80% expansion had higher rates of pleurodesis (47/71, 66%), than patients with no hydropneumothorax with > 80% expansion (193/465, 42%, P=0.0001).

Medical thoracoscopy

Subgroup analysis of patients who underwent MT was performed (Table 5). More patients with TPCs inserted at MT had an ECOG ≤ 2, than patients with who did not undergo MT (60% vs 13%, P<0.0001). In patients with an ECOG ≤ 2, the pleurodesis rates were higher for patients who underwent MT than those who did not (87% vs 63%, P=0.0001); the days to pleurodesis in MT patients was 38 (IQR 16 – 91) days, and 56 (IQR 35 – 96) days in non-MT patients (P=0.039).

Multivariate Analyses

Results of multivariate logistic regression analysis to investigate the relationship between clinical factors and rates of pleurodesis are in Table 6. Increased rates of pleurodesis were significantly

associated with lymphoma, ovarian cancer, ECOG ≤ 2, MT, protein, albumin, and % eosinophils. Reduced rates of pleurodesis were associated with gastrointestinal cancers, the presence of hydropneumothorax on post-drainage chest x-ray, and % other cells on cell count. Threshold values for continuous variables with the highest accuracy for predicting pleurodesis were protein ≥ 44, albumin ≥ 25, % eosinophils ≥ 6, and % other cells = 0 (Table 7).

Results of the multivariate Cox regression analysis to investigate the relationship between clinical factors and days to pleurodesis are in Table 8. Factors significantly associated with earlier pleurodesis were ovarian cancer, MT, protein, and % eosinophils. Factors associated with delayed pleurodesis were breast cancer and % other cells on cell count. Hydropneumothorax was not significant in this model, and an alternate multivariate Cox regression was performed which combined hydropneumothorax with degree of lung expansion into one variable. In this final model, hydropneumothorax with <80% lung expansion was found to be associated with delayed pleurodesis (HR 0.55, *P*=0.0016).

Complications:

The study complications are listed in Table 9. The most common complications were loculations requiring fibrinolytic (4%), dislodged catheter (1.4%), and pleural infection (1.2%). Only one patient had a fractured and retained catheter, which occurred when the patient tried to remove it herself. There were no incidences of mortality associated with TPC insertion. Only 32 (3%) patients had recurrence of their pleural effusion after TPC removal and needed TPC re-insertion.

Interpretation

To our knowledge, this is the largest study of predictors of pleurodesis of TPCs, and the first study on predictors of early pleurodesis of TPCs in malignant pleural effusions. In addition, our study is also the first comparative study to report higher pleurodesis rates and earlier pleurodesis associated with combined MT and TPC insertion.

Our cohort is unique because some of our patients had TPC insertion at the time of MT. Thus, we were able to simultaneously establish a tissue diagnosis and treat the patient's malignant pleural effusion. This approach has been described and facilitates safe discharge the same day of MT.[9,10] Our study found that patients who had combined MT and TPC insertion had significantly higher pleurodesis rates and earlier removal than patients with only TPC insertion. The rate of pleurodesis appears to be comparable if not greater than reported rates for chemical pleurodesis.[3] We believe that pleural biopsies, minor bleeding, and introduction of air into the pleural space result in inflammation and facilitate pleurodesis. MT may also be combined with talc pleurodesis[11] if earlier pleurodesis is desired, or delayed catheter removal is expected. Combined MT and TPC may also be a cost saving, since it can be performed as an outpatient, and is associated with decreased TPC duration. We believe that combined outpatient MT and TPC should be strongly considered as the diagnostic and therapeutic approach for patients suspected

to have a malignant pleural effusion and non-diagnostic cytology, or who require more tissue for ancillary testing.

As expected, patients with hydropneumothorax post TPC insertion have lower pleurodesis rates, likely due to the presence of trapped or entrapped lung. However, patients with hydropneumothorax and >80% lung expansion had higher pleurodesis rates than patients with no hydropneumothorax and >80% lung expansion in univariate analysis. One potential explanation for this finding is that the inflammatory pleural process that results in lung entrapment is also the same process that results in pleurodesis, and adequate lung expansion allows potential for adequate visceral and parietal pleural apposition. The mediastinum and diaphragm may shift slightly to facilitate pleural apposition. The simple presence of air in the pleural space may contribute to an inflammatory process to facilitate pleurodesis. Pneumothorax is a known etiology for eosinophilic effusions,[12] and pleural eosinophils were associated with successful pleurodesis in our study. Patients with hydropneumothorax and <80% lung expansion had delayed TPC removal. This finding may be explained by the fact that the pleural space of non-expanding lungs continues to re-accumulate fluid after fluid removal. Eventually there is partial pleurodesis, loculations may develop, and the TPC stops draining.

We found that lymphoma and ovarian cancer were associated with higher pleurodesis rates in multivariate analysis. Ovarian cancer was also associated with earlier removal. Although breast cancer was not associated with higher pleurodesis rates, it was associated with delayed pleurodesis. These findings may be reflective of varying tumor response to systemic therapy. For example, lymphoma and ovarian cancer may have effective and rapid response to therapy, while breast cancer may have a delayed response. We hypothesize that the type of systemic therapy may also have an impact. For example, patients with metastatic breast cancer are often treated with endocrine therapy, which may result in slower responses than chemotherapy.[13] Future studies on the effect of chemotherapy on TPC pleurodesis are needed.

Our finding that breast cancer and cytology positivity were not associated with increased pleurodesis rates is discrepant with another smaller study conducted between 1998 - 2006.[7] In fact, we found that breast cancer was associated with delayed TPC removal. The difference may be related to differences in our cohorts in the use of chemotherapy, or the advent of newer targeted therapies, such as trastuzumab.[14] Alternatively, the differences may be due to statistical chance. In our study, cytology approached statistical significance (p=0.077). The discrepancy in cytology may be because our study only included cytology results at the time of TPC insertion, and not prior thoracentesis. Also, the % other cells found in the cell count in our study was associated with reduced rates of pleurodesis and delayed pleurodesis. % other cells is non-specific but may suggest the presence of malignant cells in the pleural fluid, although insufficient in number to officially confirm pleural malignancy.

In regards to fluid analysis, we found that pleural protein level and % eosinophil predicted higher pleurodesis rates and earlier pleurodesis. Further characterization of the pleural fluid may

elucidate which specific proteins contribute to pleurodesis. The association of eosinophilic inflammation provides a clue to at least one cellular pathway to achieve pleurodesis.

The predictors of failed chemical pleurodesis in prior studies include low pH,[15,16] lung cancer, and tumor burden.[17] The differences in predictive variables between chemical and TPC pleurodesis suggest different mechanisms of pleurodesis.

Limitations:

Our study has several limitations. First, many patients were deceased before the endpoint of TPC removal was reached. In this way, true pleurodesis rates may be underestimated. This may explain why the pleurodesis rate of gastrointestinal malignancies was only 18%. Second, there were other variables that were not assessed that may impact pleurodesis, such as chemotherapy.

Conclusions

In summary, MT, ECOG ≤ 2, lymphoma, ovarian cancer, protein, albumin, and % eosinophil count predicted higher pleurodesis rates. Gastrointestinal cancers, hydropneumothorax on post-drainage chest x-ray, and % other cells on cell count predicted lower pleurodesis rates.

Earlier pleurodesis was associated with MT, ovarian cancer, higher pleural protein, and % eosinophil count. Delayed removal was associated with breast cancer, hydropneumothorax with <80% lung expansion, and % other cells on cell count.

This study provides important information for the clinician to help personalize malignant pleural effusion management. In patients that require tissue biopsies, we favor combined outpatient MT and TPC insertion. In patients expected to have lower probability of pleurodesis or who are expected to keep their TPC for a longer duration, such as in breast cancer patients, chemical pleurodesis could be considered. We recommend individual consideration of each case. Clinicians must consider numerous factors to predict the likelihood of and timing to pleurodesis after TPC insertion. By recognizing these predictive factors, management of malignant pleural effusions can be better personalized.

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References

(1) Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012 Jun 13;307(22):2383-2389.

(2) Simoff MJ, Lally B, Slade MG, Goldberg WG, Lee P, Michaud GC, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013 May;143(5 Suppl):e455S-e497S.

(3) Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010 Aug;65 Suppl 2:ii32-40.

(4) Fysh ETH, Waterer GW, Kendall PA, Bremner PR, Dina S, Geelhoed E, et al. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. Chest 2012 Aug;142(2):394-400.

(5) Pien GW, Gant MJ, Washam CL, Sterman DH. Use of an implantable pleural catheter for trapped lung syndrome in patients with malignant pleural effusion. Chest 2001 Jun;119(6):1641-1646.

(6) Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. J Gen Intern Med 2011 Jan;26(1):70-76.

(7) Warren WH, Kim AW, Liptay MJ. Identification of clinical factors predicting Pleurx catheter removal in patients treated for malignant pleural effusion. Eur J Cardiothorac Surg 2008 Jan;33(1):89-94.

(8) Penz ED, Mishra EK, Davies HE, Manns BJ, Miller RF, Rahman NM. Comparing cost of indwelling pleural catheter vs talc pleurodesis for malignant pleural effusion. Chest 2014 Oct;146(4):991-1000.

(9) DePew ZS, Wigle D, Mullon JJ, Nichols FC, Deschamps C, Maldonado F. Feasibility and safety of outpatient medical thoracoscopy at a large tertiary medical center: a collaborative medical-surgical initiative. Chest 2014 Aug;146(2):398-405.

(10) Kyskan R, Li P, Mulpuru S, Souza C, Amjadi K. Safety and Performance Characteristics of Outpatient Medical Thoracoscopy and Indwelling Pleural Catheter Insertion for Evaluation and Diagnosis of Pleural Disease at a Tertiary Center in Canada. Canadian Respiratory Journal 2017;2017:6.

(11) Reddy C, Ernst A, Lamb C, Feller-Kopman D. Rapid pleurodesis for malignant pleural effusions: a pilot study. Chest 2011 Jun;139(6):1419-1423.

(12) Adelman M, Albelda SM, Gottlieb J, Haponik EF. Diagnostic utility of pleural fluid eosinophilia. Am J Med 1984 Nov;77(5):915-920.

(13) Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev 2003;(2)(2):CD002747.

(14) Harries M, Smith I. The development and clinical use of trastuzumab (Herceptin). Endocr Relat Cancer 2002 Jun;9(2):75-85.

(15) Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure: analysis of primary data. Chest 2000 Jan;117(1):87-95.

(16) Yildirim H, Metintas M, Ak G, Metintas S, Erginel S. Predictors of talc pleurodesis outcome in patients with malignant pleural effusions. Lung Cancer 2008 Oct;62(1):139-144.

(17) Bielsa S, Hernandez P, Rodriguez-Panadero F, Taberner T, Salud A, Porcel JM. Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung 2011 Apr;189(2):151-155.

TABLE 1] Baseline demographics at tunneled pleural catheter insertion	
Characteristic	Value
Patients, no.	956
TPCs, no.	1071
Age, mean ± SD, yr	68 ± 12
Gender	
Male, no. (%)	437 (41)
Female, no. (%)	634 (59)
Side of TPC, no. (%)	
Left	466 (44)
Right	605 (56)
ECOG*, no. (%)	
0	1 (0)
1	43 (4)
2	173 (16)
3	395 (37)
4	459 (43)
BDI†, mean ± SD, no.	2.2 ± 1.9
TDI‡, mean ± SD, no.	6.4 ± 1.6
Fluid drained, mean ± SD, L	1.6 ± 0.77
Cytology positive, no. (%)	399 (37)
Baseline pleural effusion above the hilum, no. (%)	585 (55)
Hydropneumothorax after drainage, no. (%)	228 (21)
Medical thoracoscopy at insertion, no. (%)	158 (15)

*Eastern Cooperative Oncology Group
†Baseline dyspnea index
‡Transition dyspnea index

TABLE 2] Rates of pleurodesis and days to pleurodesis by tumor type in univariate logistic regression analysis						
Tumor type	N (%)	Pleurodesis, no. (%)	Odds ratio (95% CI)	*P* Value	Days to pleurodesis, median (IQR)	*P* Value*
Non-small cell lung cancer	384 (36)	151 (39)	0.77 (0.60 – 0.998)	0.048	42 (25 – 77)	0.47
Breast	213 (20)	90 (42)	0.95 (0.70 – 1.28)	0.73	65 (35 – 144)	0.0003
Ovarian	83 (8)	56 (67)	2.95 (1.83 – 4.75)	<0.0001	41 (29 – 66)	0.30
Lymphoma	76 (7)	48 (63)	2.39 (1.47 – 3.87)	0.0004	48 (29 – 100)	0.43
Gastrointestinal†	66 (6)	12 (18)	0.27 (0.14 – 0.51)	<0.0001	35 (28 – 46)	0.37
Mesothelioma	53 (5)	32 (60)	2.07 (1.18 – 3.63)	0.012	39 (16 – 87)	0.44
Other	196 (18)	75 (38)	0.77 (0.56 – 1.06)	0.11	42 (21 – 62)	0.08
TOTAL	1071	464 (43)			44 (26 – 90)	

TABLE 3] Univariate logistic regression analyses of clinical factors predicting rates of pleurodesis		
Variable	Odds ratio (95% CI)	*P* Value
Clinical factors		
Age	0.994 (0.985 – 1.004)	0.27
ECOG ≤ 2	5.078 (3.639 – 7.087)	<0.0001
Medical thoracoscopy	5.435 (3.639 – 8.041)	<0.0001
Pleural infection	2.645 (0.792 – 8.837)	0.11
Chest x-ray data		
Hydropneumothorax	1.091 (0.812 – 1.464)	0.56
Lung expansion < 80%	0.887 (0.696 – 1.131)	0.33
Pleural fluid analysis		
pH	1.499 (0.882 – 2.547)	0.13
Protein, g/L	1.07 (1.054 – 1.086)	<0.0001
Albumin, g/L	1.147 (1.118 – 1.178)	<0.0001
LDH, IU/L	1 (1 – 1)	0.19
RBC count, 10^6 cells/L	1 (1 – 1)	0.45
Total nucleated cell count, 10^6 cells/L	1 (1 – 1)	0.71
% Neutrophils	0.99 (0.984 – 0.997)	0.0026
% Lymphocytes	1.016 (1.011 – 1.021)	<0.0001
% Monocytes	0.996 (0.99 – 1.002)	0.18
% Mesothelial cells	0.999 (0.988 – 1.011)	0.93
% Eosinophils	1.045 (1.015 – 1.076)	0.0031
% Other cells on cell count	0.986 (0.979 – 0.993)	0.0001
Cytology positive	0.797 (0.62 – 1.025)	0.077

TABLE 4] Relationship of hydropneumothorax (HP) on post drainage chest x-ray with pleurodesis of tunneled pleural catheters			
Variable	No.	Pleurodesis, no. (%)	*P* Value*
HP and > 80% expansion	71	47 (66)	0.0002
HP and 50 – 80% expansion	94	37 (39)	0.59
HP and 30 – 50% expansion	39	8 (21)	0.0056
HP* and < 30% expansion	24	4 (17)	0.011

**P* Value when compared to all other inserted catheters

TABLE 5] Relation of medical thoracoscopy and ECOG ≤ 2 with pleurodesis			
	ECOG ≤ 2		
	Medical thoracoscopy (N=95)	Non-medical thoracoscopy (N=122)	*P* Value
Pleurodesis, no. (%)	83 (87)	77 (63)	0.0001
Median days to pleurodesis, days (IQR)	38 (16 – 91)	56 (35 – 96)	0.039

TABLE 6] Multivariate logistic regression of clinical factors predicting rates of pleurodesis		
Variable	Odds ratio (95% CI)	*P* Value
Lymphoma	3.49 (1.93 – 6.33)	<0.0001
Ovarian cancer	2.93 (1.68 – 5.11)	0.0002
Gastrointestinal cancer	0.41 (0.19 – 0.87)	0.0208
ECOG ≤ 2	2.79 (1.79 – 4.34)	<0.0001
Medical thoracoscopy	2.21 (1.28 – 3.85)	0.0048
Hydropneumothorax	0.62 (0.41 – 0.94)	0.0238
Protein	1.03 (1.01 – 1.06)	0.0082
Albumin	1.07 (1.03 – 1.12)	0.0007
% Eosinophils	1.04 (1.004 – 1.07)	0.0272
% Other cells	0.98 (0.97 – 0.99)	<0.0001

TABLE 7] Optimal threshold values by ROC curve analysis of continuous variables predicting pleurodesis*

Variable	Value	AUC* (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV†	NPV‡	+LR	-LR
Protein, g/L	≥ 44	0.69 (0.65-0.72)	0.45 (0.41-0.50)	0.81 (0.77-0.84)	0.63 (0.57-0.68)	0.67 (0.64-0.71)	2.35	0.68
Albumin, g/L	≥ 25	0.71 (0.68-0.75)	0.47 (0.42-0.52)	0.82 (0.79-0.85)	0.65 (0.59-0.71)	0.69 (0.65-0.72)	2.64	0.65
% Eosinophils	≥ 6	0.55 (0.52-0.58)	0.09 (0.07-0.12)	0.96 (0.94-0.97)	0.61 (0.49-0.73)	0.60 (0.57-0.63)	2.22	0.95
% Other cells	= 0	0.55 (0.51-0.58)	0.60 (0.55-0.65)	0.47 (0.43-0.51)	0.44 (0.40-0.49)	0.62 (0.57-0.67)	1.12	0.86

*All laboratory values wereperformed on pleural fluid. AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio.

TABLE 8] Multivariate Cox regression of clinical factors predicting days to pleurodesis		
Variable	Hazard ratio (95% CI)	*P* Value
Ovarian	1.48 (1.06 – 2.08)	0.0228
Breast	0.61 (0.46 – 0.81)	0.0005
Medical thoracoscopy	1.45 (1.10 – 1.92)	0.0079
Hydropneumothorax with <80% expansion	0.55 (0.38 – 0.80)	0.0016
Protein	1.03 (1.01 – 1.04)	<0.0001
% Eosinophils	1.02 (1.003 – 1.04)	0.0238
% Other cells	0.99 (0.98 – 0.996)	0.0026

TABLE 9] Tunneled pleural catheter related complications	
Complication	N (%)
Loculations needing fibrinolytic	45 (4)
Dislodged	16 (1.4)
Pleural infection	13 (1.2)
Symptomatic re-expansion pulmonary edema	13 (1.2)
Leak at catheter site	7 (0.6)
Cellulitis	6 (0.5)
Pain requiring removal	4 (0.4)
Mechanical failure	3 (0.3)
Plugged	3 (0.3)
Tumor seeding	2 (0.2)
Broken catheter valve	2 (0.2)
Syncope	1 (0.1)
Fractured catheter at removal	1 (0.1)