Pleural Touch Preparations and Direct Visualization of the Pleura during Medical Thoracoscopy for the Diagnosis of Malignancy

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Abstract

Rationale: During diagnostic thoracoscopy, talc pleurodesis after biopsy is appropriate if the probability of malignancy is sufficiently high. Findings on direct visual assessment of the pleura during thoracoscopy, rapid onsite evaluation (ROSE) of touch preparations (touch preps) of thoracoscopic biopsy specimens, and preoperative imaging may help predict the likelihood of malignancy; however, data on the performance of these methods are limited.

Objectives: To assess the performance of ROSE of touch preps, direct visual assessment of the pleura during thoracoscopy, and preoperative imaging in diagnosing malignancy.

Methods: Patients who underwent ROSE of touch preps during thoracoscopy for suspected malignancy were retrospectively reviewed. Malignancy was diagnosed on the basis of final pathologic examination of pleural biopsy specimens. ROSE results were categorized as malignant, benign, or atypical cells. Visual assessment results were categorized as tumor studding present or absent. Positron emission tomography (PET) and computed tomography (CT) findings were categorized as abnormal or normal pleura. Likelihood ratios were calculated for each category of test result.

Results: The study included 44 patients, 26 (59%) with a final pathologic diagnosis of malignancy. Likelihood ratios were as follows: for ROSE of touch preps: malignant, 1.97 (95% confidence interval [CI], 0.90–4.34); atypical cells, 0.69 (95% CI, 0.21–2.27); benign, 0.11 (95% CI, 0.01–0.93); for direct visual assessment: tumor studding present, 3.63 (95% CI, 1.32–9.99); tumor studding absent, 0.24 (95% CI, 0.09–0.64); for PET: abnormal pleura, 9.39 (95% CI, 1.42–62); normal pleura, 0.24 (95% CI, 0.11–0.52); and for CT: abnormal pleura, 13.15 (95% CI, 1.93–89.63); normal pleura, 0.28 (95% CI, 0.15–0.54).

Conclusions: A finding of no malignant cells on ROSE of touch preps during thoracoscopy lowers the likelihood of malignancy significantly, whereas finding of tumor studding on direct visual assessment during thoracoscopy only moderately increases the likelihood of malignancy. A positive finding on PET and/or CT increases the likelihood of malignancy significantly in a moderate-risk patient group and can be used as an adjunct to predict malignancy before pleurodesis.

Keywords: pleural effusion; pleural biopsy; medical thoracoscopy; malignant pleural effusion

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Pleural effusion is a common clinical problem, and approximately 1.5 million new pleural effusions are diagnosed in the United States each year (1). Malignant pleural effusion (MPE) occurs in 7–15% of lung cancer cases and complicates the course of many other types of cancer (2). In patients with cancer, involvement of the pleura signifies distant spread of tumor, so a finding of MPE has significant prognostic implications.

In general, the first step in determining the cause of pleural effusion is thoracentesis; however, cytologic examination of pleural fluid obtained by thoracentesis is diagnostic for malignancy in only approximately 40–60% of cases (3, 4). When the cause of pleural effusion cannot be determined by examination of pleural fluid, thoracoscopy

and pleural biopsies are the recommended next steps. Thoracoscopy allows for direct visualization of the pleura and direct examination of the lung, diaphragm, and visceral and parietal pleura and can identify appropriate areas for biopsy. The sensitivity of thoracoscopy in the detection of malignancy is 92.6–100% (5–10).

MPEs tend to recur in a majority of patients, requiring definitive management, such as pleurodesis with talc or other agents or the placement of an indwelling pleural catheter (11). A meta-analysis suggested that talc was the most effective sclerosing agent and that talc poudrage via thoracoscopy was more effective than application of talc slurry via chest tube (12, 13).

Given that thoracoscopy can be both diagnostic and therapeutic, it would be beneficial if diagnostic thoracoscopy could be combined with talc poudrage via thoracoscopy in appropriate cases. However, it is difficult to predict during diagnostic thoracoscopy whether a patient has an MPE. If physicians could predict malignancy with a high degree of accuracy during diagnostic thoracoscopy, it would in theory be possible to convert diagnostic thoracoscopies in patients with a high probability of malignancy into therapeutic thoracoscopies.

To date, several techniques have been studied to determine whether they can intraoperatively predict an MPE, including rapid onsite evaluation (ROSE) of touch preparations (touch preps) and direct visual assessment of the pleura at the time of thoracoscopy. There are limited data on the performance of ROSE of touch preps and visual assessment in predicting malignancy in patients with pleural effusion. ROSE has been assessed in only one published study, of 62 patients, and this study showed high diagnostic accuracy (14). A survey of 16 centers that performed up to 10 thoracoscopies per month showed that direct visual assessment correctly diagnosed malignant or benign disease in only 12 of 20 patients (59.3%; SD, 2.5%) (15).

In light of the paucity of data, we developed this study to determine the performance of ROSE of touch preps during thoracoscopy in predicting malignancy. Our secondary aim was to evaluate the performance of direct visual assessment of the pleura during thoracoscopy and prethoracoscopy computed tomography (CT) and positron emission tomography (PET) in predicting malignancy.

Methods

We performed a retrospective review of all patients aged 18 years or older who underwent medical thoracoscopy with ROSE of touch preps for undiagnosed pleural effusion from January 2005 through January 2015 at the University of Texas M.D. Anderson Cancer Center (Houston, TX). Institutional review board approval was obtained for this study (protocol number PA16-0448). To identify cases, we used the M.D. Anderson database to search for all cases with Current Procedural Terminology or International Classification of Diseases procedure codes for thoracoscopy. Clinical–pathologic factors, including medical history, were abstracted from the patient charts.

Specimen Processing and Procedure

For specimen processing, a frosted-tip slide was labeled with the patient's name and hospital number. Representative fragments of the biopsied tissue were placed on a Telfa pad (Medtronic, Minneapolis, MN), and the labeled slide was gently touched to the tissue. Representative fragments of the biopsied tissue were placed on the labeled slide and gently rolled. The slide was either immediately immersed in a Coplin jar containing modified Carnoy's solution for rapid Papanicolaou staining or air-dried for Diff-Quik staining. The biopsied tissue was placed in a prelabeled container of 10% buffered formalin for histopathologic processing.

All our procedures were performed with a rigid thoracoscopy integrated system, and all the specimens were interpreted by a cytotechnologist. All the visual assessment interpretations were performed by the interventional pulmonologist attending on service.

Definitions

All patients were assigned a final histopathologic diagnosis based on the final pathology report from the pleural biopsy specimens obtained during thoracoscopy. The final diagnostic categories were malignant, meaning a final diagnosis consistent with malignancy; and not malignant, for example, infectious disease established by microbiologic cultures in the appropriate clinical context (e.g., histoplasmosis and tuberculosis). Findings of nonspecific pleuritis were categorized as not malignant.

Results of ROSE of touch preps were classified as no tumor; atypical cells, defined as atypical cells but inadequate for a definitive diagnosis; or tumor present, defined as adequate tissue with tumor present.

Results of direct visual assessment were abstracted from the procedure notes and were classified as either no tumor studding or tumor studding.

Findings on CT and PET were classified according to the presence or absence of nodular or focal pleural thickening or irregular pleural thickening or abnormal fluorodeoxyglucose avidity as either abnormal pleura or normal pleura. All imaging had to be performed within the month before thoracoscopy. The data were abstracted from the radiology reports, which were completed before the thoracoscopy results were known.

All patients with a final histopathologic diagnosis of malignancy based on thoracoscopic pleural biopsy specimens were considered to have malignancy, and this diagnosis served as the reference standard of truth.

Study Outcomes

The primary outcome was the performance of ROSE of touch preps in diagnosing malignant pleural disease. Secondary outcomes were the performance of direct visual assessment and prethoracoscopy CT and PET in diagnosing malignant pleural disease.

Statistical Analysis

Descriptive statistics were used to summarize the patients' demographic and clinical characteristics. We used means and standard deviation to describe continuous variables distributed normally, medians to describe nonnormally distributed data, and frequencies to describe categorical data. Categorical data were compared using Fisher's exact test and the χ^2 test. The Kruskal–Wallis test was used to describe nonparametrically distributed data. Likelihood ratios (LRs) were calculated by dividing the probability of a result in patients with the disease by the probability of the same result in patients without the disease. For tests that had only two possible results, we also calculated sensitivity and specificity. We calculated positive predictive value (PPV) and negative predictive value (NPV) for all patients and for patients in prespecified

subgroups of interest. Pretest odds were calculated according to the following formula: pretest probability/(1 − pretest probability). Posttest odds were calculated according to the following formula: pretest odds × likelihood ratio, and posttest probability was calculated according to the following formula: posttest odds/(1 + posttest odds).

P values less than 0.05 were considered significant. All tests were two-sided. All statistical analyses were performed with STATA software (version 13; StataCorp LP, College Station, TX).

Results

Forty-four patients had ROSE of touch preps during thoracoscopy during the study period. All patients had good visualization of the pleura, defined as lung collapse that allowed visualization of the entire parietal pleura, diaphragm, and lung. One or two biopsy samples were taken for ROSE. A median of 10 biopsies were performed per patient (range, 7–12). Of these 44 patients, 26 (59%) had malignancy diagnosed on final histopathologic examination of pleural biopsy specimens. All patients with negative biopsy results on the final histopathology were monitored for a mean of 23.04 ± 11 months. None were diagnosed with malignant pleural disease during this time. Patient characteristics are summarized in Table 1. Patients with MPE tended to be older ($P = 0.021$), but we found no association between MPE and sex, race, or type of cancer.

Final malignancy diagnoses were as follows: nine adenocarcinomas of lung (primary), seven mesotheliomas, three adenocarcinomas of breast (primary), two squamous carcinomas, two high serous carcinomas, one sarcomatoid carcinoma, one thymic carcinoma, and one diffuse large B-cell lymphoma.

Table 1. Patient characteristics by final histopathologic diagnosis

Characteristic*	Malignancy (*n* = 26)	No Malignancy (*n* = 18)	*P* Value
Age (yr), median (IQR, 25th–75th percentile)	72.2 (62.2–51.5)	65.7 (56.2–71.5)	0.021†
Sex, n (%)			
Female	12 (46)	7 (39)	
Male	14 (54)	11 (61)	0.760
Race/ethnicity, n (%)			
White	19 (73)	13 (72)	
Nonwhite	7 (26)	5 (27)	1.000
History of active malignancy, n (%)			
No	10 (38)	6 (33)	
Yes	16 (62)	12 (67)	0.761
Cancer diagnosis before MT, n (%)			
Hematologic malignancy	1 (4)	0 (0)	
Lung cancer	7 (27)	5 (28)	
Solid nonlung cancer	8 (31)	7 (39)	
No malignancy	10 (38%)	6 (33)	0.956
Chemotherapy within 30 d of procedure, n (%)			
No	24 (92)	15 (83)	
Yes	2 (8)	3 (17)	0.386
Radiation within 30 d of procedure, n (%)			
No	26 (100)	18 (100)	
Yes	0 (0)	0 (0)	
Pleural abnormalities present on imaging, n (%)			
No	7 (27)	17 (94)	
Yes	19 (73)	1 (6)	0.000
Tumor deposits present on visual assessment, n (%)			
No	5 (19)	14 (78)	
Yes	21 (81)	4 (22)	0.000
ROSE touch prep result, n (%)			
Malignancy	20 (77)	7 (39)	
Atypical cells	5 (19)	5 (28)	
No malignancy	1 (4)	6 (33)	0.013

Definition of abbreviations: IQR = interquartile range; MT = medical thoracoscopy; ROSE = rapid onsite evaluation.
*Continuous variable reported as IQR.
†Kruskal–Wallis test.

Performance of ROSE of Touch Preps

Patients with a final histopathologic diagnosis of malignancy were more likely than patients without malignancy to have malignancy demonstrated on ROSE of touch preps ($P = 0.01$; Table 1). LRs for each category of ROSE test result are shown in Table 2. Only the finding of "no malignancy" was statistically significant, with an LR of 0.11 (95% confidence interval [CI], 0.01–0.93). The area under the receiver operating characteristic curve (AUC) was 0.57 (95% CI, 0.40–0.75).

Performance of Direct Visual Assessment

Patients with a final histopathologic diagnosis of malignancy were more likely than patients without malignancy to have tumor deposits identified on direct visual assessment ($P < 0.001$; Table 1). Direct visual assessment had a sensitivity of 81% (95% CI, 0.60–0.93), specificity of 79% (95% CI, 0.52–0.93), PPV of 84% (95% CI, 0.64–0.95), and NPV of 74% (95% CI, 0.48–0.90). *See* Table 2 for LRs. The AUC was 0.79 (95% CI, 0.66–0.92).

Performance of Prethoracoscopy CT

All patients underwent CT before thoracoscopy. In the diagnosis of malignancy, prethoracoscopy CT had a sensitivity of 73% (95% CI, 0.62–0.88), specificity of 94% (95% CI, 0.72–0.99), PPV of 95% (95% CI, 0.75–0.99), and NPV of 71% (95% CI, 0.48–0.91). The AUC was 0.83 (95% CI, 0.73–0.94). The LRs for each category of CT results are provided in Table 2.

Performance of Prethoracoscopy PET

Thirty-five patients (79%) underwent PET before thoracoscopy. In the diagnosis of malignancy, prethoracoscopy PET had a sensitivity of 78% (95% CI, 0.56–0.92), specificity of 92% (95 CI, 0.62–0.99), PPV of 95% (95% CI, 0.74–0.99), and NPV of 69% (95% CI, 0.41–0.89). The AUC was 0.85 (95% CI, 0.73–0.96). The LRs for each category of PET results are provided in Table 2.

Table 2. Likelihood ratios of final histopathologic results: malignancy absent and malignancy present

Assessment	Malignancy Absent (*n* = 18)	Malignancy Present (*n* = 26)	Likelihood Ratio (95% CI)
Visual assessment			
Tumor studding	4	21	3.63 (1.32–9.99)
No tumor studding	14	5	0.24 (0.09–0.64)
ROSE test			
Malignancy	7	20	1.97 (0.90–4.34)
Atypical cells	5	5	0.69 (0.21–2.27)
No malignancy	6	1	0.11 (0.01–0.93)
CT imaging			
Abnormal pleura	1	19	13.15 (1.93–89.63)
Normal pleura	17	7	0.28 (0.15–0.54)
PET imaging*			
Abnormal pleura	1	18	9.39 (1.42–62)
Normal pleura	11	5	0.24 (0.11–0.52)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; PET = positron emission tomography; ROSE = rapid onsite evaluation.
*Thirty-five patients with PET available.

All patients with negative biopsy results on final histopathology were monitored for a mean of 23.04 ± 11 months, and none were diagnosed with malignant pleural disease during this time.

Discussion

In this study, we found that ROSE of touch preps during thoracoscopy and direct visual examination of the pleura during thoracoscopy were only modestly informative regarding the probability of a final histopathologic diagnosis of malignancy. Visual assessment and ROSE were more accurate if the findings were negative rather than positive. In contrast, abnormal pleura on CT or PET was associated with a high positive LR, which significantly increased the posttest probability of malignancy. Normal pleura on CT or PET was only modestly informative. With respect to the AUC statistic, the ability of PET and CT to discriminate between those with and without malignancy was good. ROSE had a smaller AUC than visual assessment and, hence, the worse performance in discriminating between patients with and without malignancy.

Our findings for visual assessment of malignancy are similar to those reported by Hallifax and colleagues (15) with respect to sensitivity but superior with respect to specificity. Those authors used thoracoscopic video clips to evaluate whether physicians could differentiate malignant from benign pleural disease by visual assessment. They reported that the sensitivity of visual assessment in diagnosing malignancy was 82%, and the specificity was 51% (15). However, our findings for visual assessment of malignancy contrast with those reported by Porfyridis and colleagues, who evaluated the ability of the thoracoscopist to visually predict malignancy in 61 patients (14). In that study, the thoracoscopists' impressions were recorded as malignant, indeterminate, or benign. The authors found that visual assessment had a sensitivity of 100% but a specificity of 46% (14). A potential reason for the differences between our findings and those of Porfyridis and colleagues is that these other authors reclassified patients with indeterminate appearance of the pleura (17 of 62 patients) as having malignancy. Reanalyzing the data from Porfyridis and colleagues without reclassifying the indeterminate lesions as malignant resulted in LRs of 4.65 (95% CI, 2.53–9.20) for malignancy, 0.31 (95% CI, 0.10–0.99) for indeterminate findings, and 0 (95% CI, 0.00–0.73) for benign. Another reason for differences may be that there is selection bias in our study as ROSE was performed in only a selected group of patients, and perhaps those were the patients more difficult to diagnose. Florid inflammation was one of the most common causes of false positive visual inspection findings.

In the same paper by Porfyridis and colleagues, the authors concluded that ROSE of touch preps during thoracoscopy was highly accurate in predicting malignancy. On ROSE, samples were reported as malignant, suggestive of malignancy, negative for malignancy, or inadequate. The authors reported the sensitivity as 79%; specificity, 94%; diagnostic accuracy, 88%; PPV, 90%; and NPV, 87% (14). However, similar to the findings on visual assessment, findings on ROSE of touch preps were collapsed into two categories: diagnostic for malignancy and not diagnostic for malignancy. Collapsing a range of test results into positive and negative categories can result in a loss of information that translates into decreased discriminatory function.

LRs are an effective way to describe how informative a particular test result is, especially when there are more than two possible test results. LRs are defined as the probability that someone with the disease of interest will have a given test result, divided by the probability that someone without the disease will have the same test result. LRs of 1 are noninformative, and those with high values (typically about 4 to 5) or low values (0.2) are informative.

However, the clinical implications of our findings depend not only on the LR but also on the pretest probability of disease (16). For example, if malignancy is suspected and ROSE of touch preps during thoracoscopy shows malignancy, the decision whether to perform pleurodesis may not be straightforward. If the pretest probability of malignancy for that patient was 59% (the prevalence of malignancy in our study), the posttest probability of malignancy would be 74%. In other words, the ROSE results increase the probability of malignancy but do not definitively confirm it. In contrast, with the same pretest probability of malignancy (59%) but no malignancy on ROSE of touch preps, the posttest probability of malignancy would be only 14%. In other words, the ROSE results substantially decrease the probability of malignancy but do not definitively rule it out. A finding of atypical cells would be uninformative, with a posttest probability of malignancy of 50%. Therefore, findings of atypical cells on ROSE are not informative (Figure 1A).

Furthermore, for the same pretest probability of malignancy (59%), visual assessment showing tumor deposits would increase the posttest probability of malignancy to 84%, whereas visual assessment showing no tumor deposits

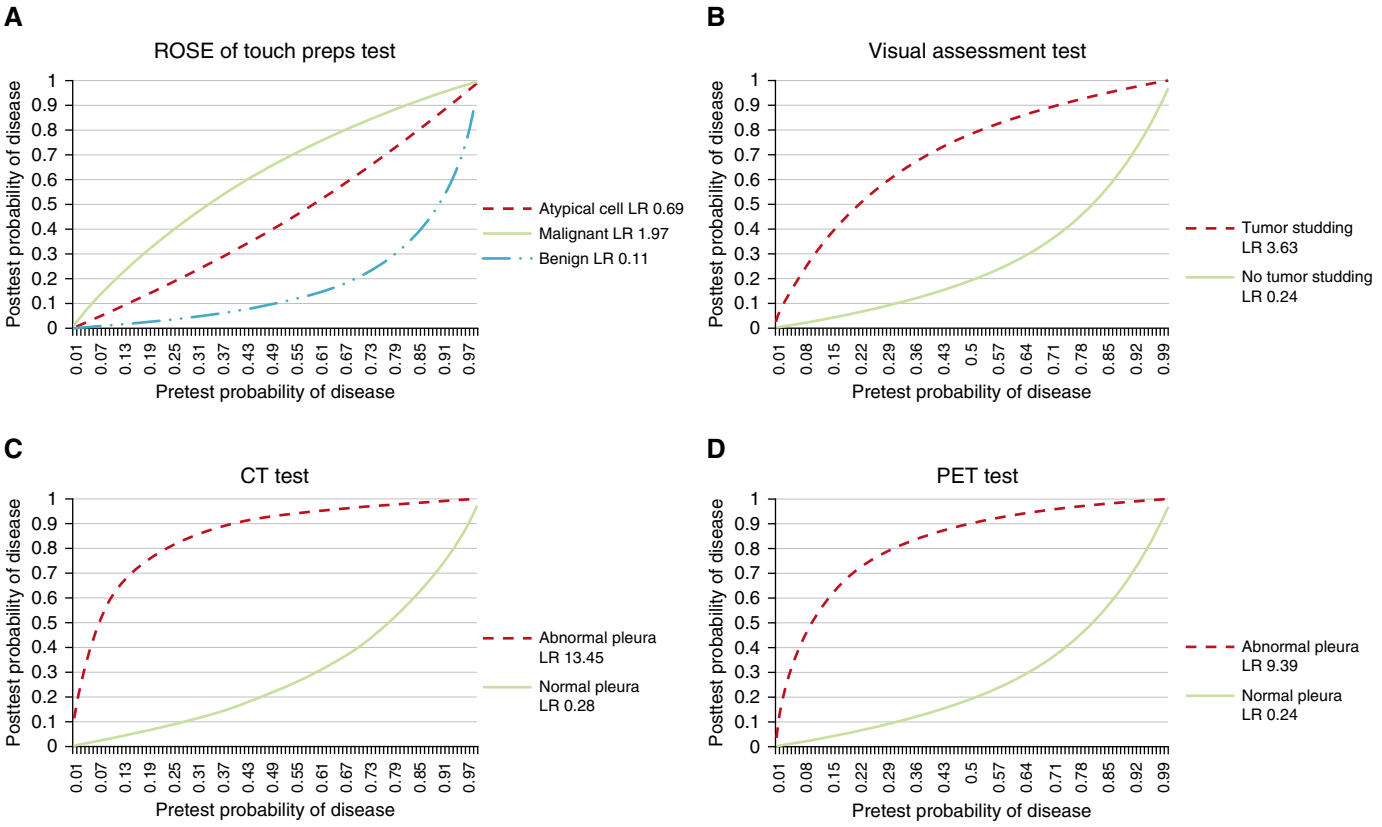

Figure 1. Pretest and posttest probabilities of malignancy calculated using the likelihood ratio method for findings on (*A*) rapid onsite evaluation of touch preparations; (*B*) visual assessment of the pleura; (*C*) computed tomography; and (*D*) positron emission tomography. CT = computed tomography; LR = likelihood ratio; PET = positron emission tomography; ROSE = rapid onsite evaluation.

would decrease the posttest probability of malignancy to 27%. Therefore, a positive or negative finding during direct visualization leads to a moderate increase or decrease in the likelihood of malignancy but cannot rule it in or out when the pretest probability is intermediate (Figure 1B). In visual assessment, for the PPV to be close to 95%, the prevalence of disease must be greater than 80%, whereas for the NPV to be close to 95%, the prevalence of disease must be less than 20%; everything else is intermediate. This has important implications for clinical practice, as many physicians performing thoracoscopy may feel confident in making the diagnosis based on visual assessment only, which would result in some patients inappropriately receiving pleurodesis.

Another finding of interest in our study was the high sensitivity and specificity of PET and CT in predicting malignancy. Our findings were similar to those of Kim and colleagues, who previously reported that PET had a sensitivity and specificity of 87.5 and 88.0%, respectively, and CT had a sensitivity and specificity of 83.3 and 88.8%, respectively, in the diagnosis of MPE (17). Our findings are in contrast with those reported in the systematic review by Porcel and colleagues, in which PET-CT imaging had only moderate accuracy for discriminating malignant from benign pleural effusions but, as authors pointed out, a potential reason for the differences is the heterogeneous data that are prone to spectrum bias (18). Our patient population may be different as patients did receive care in a cancer institution with more than 60% of patients having an active malignancy at the time of thoracoscopy. Using the LRs identified in our study, for a pretest probability of malignancy of 59% and imaging showing abnormal pleura, the posttest probability of malignancy would be 95%, whereas for the same pretest probability of malignancy and imaging showing normal pleura, the posttest probability of malignancy would decrease to 30%. Therefore, a positive finding on PET and/or CT can be informative in predicting malignancy (Figure 1D).

When the pretest probability of malignancy is high, greater than 80%, then visual findings or malignancy on ROSE of touch preps may suffice for clinical decision making. However, for patients with an intermediate pretest probability of malignancy, visual findings or ROSE results may not be sufficient to rule in or rule out disease. It is therefore important to consider the relative potential for benefit and harm from pleurodesis (19). Treatment decisions should be made only after consideration of the pretest probability, all available data at the time of thoracoscopy, and benefits and harms of treatment.

Limitations

Limitations of this study include the small sample size, the retrospective design, and the fact that all cases came from a single institution. In addition, the posttest probabilities in our study were

contingent on the prior probabilities of disease; thus, our results may not be generalizable to other patient populations because of differing malignancy prevalence rates. The type of malignancy is also important; for example, it is more difficult to distinguish benign, reactive mesothelial cells from mesothelioma than it is to identify metastatic adenocarcinoma, using touch preps. In this study we had seven patients with a final diagnosis of mesothelioma, and five were diagnosed by touch prep; however, the sample size is too small to draw any conclusions. Also, our findings may have been influenced by selection bias, because ROSE was performed in only a minority of patients (44 of 199; 22%) who underwent thoracoscopy during the study period. If ROSE were used in all cases, its performance might be much better. Also, ROSE interpretation was done by rotating cytotechnologists and, because it is done rarely, the results may be limited by the experience with ROSE of the cytotechnologists involved.

Decision-making regarding definitive management of MPE at the time of thoracoscopy must include consideration of findings on prethoracoscopy imaging, visual assessment, and ROSE of touch preps to limit potentially harmful complications. Although definitive management of MPE is predicated by several assumptions, such as selection of patient for talc pleurodesis having a good intraprocedural test such as rapid on site determination of malignancy could not only guide therapeutic interventions such as talc pleurodesis or placement of an indwelling pleural catheter at the end of the procedure, but also guide further diagnostic interventions. For example, if the likelihood of pleural malignancy is deemed sufficiently low after visual inspection and negative ROSE result, staging endobronchial ultrasound could be performed in the same setting, rather than waiting for the final pathology result. Nevertheless, decision making should begin with estimation of the pretest probability of malignancy and weighing of the potential positive and negative consequences of various treatment strategies. Potential avenues for further research include the use of other technologies to improve prediction of malignancy during thoracoscopy.

Conclusions

A finding of no malignant cells on ROSE of touch preps during thoracoscopy lowers the likelihood of malignancy significantly whereas a finding of tumor studding on direct visual assessment during thoracoscopy only moderately increases the likelihood of malignancy. A positive finding on PET and or CT increases the likelihood of malignancy significantly in a moderate-risk patient group and can be used as an adjunct to predict malignancy before pleurodesis. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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