Objective thoracoscopic criteria in differentiation between benign and malignant pleural effusions

Mohamed A Ellayeh[1,2,5], Eihab O Bedawi[1,2], Radhika Banka[1,2], Anand Sundaralingam[1,2], Vineeth George[1,2], Nikolaos I Kanellakis[1,4], Robert J Hallifax[1,2], Heba W Abdelwahab[5], Nasef A Rezk[5], Asem A Hewidy[5], Raed E Ali[5], John M Wrightson[1,2], Najib M Rahman[1,2,3].

[1] University of Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK

[2] Oxford Centre for Respiratory Medicine, Oxford University Hospitals NHS Trust, Oxford, UK

[3] NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

[4] Laboratory of Pleural and Lung Cancer Translational Research, Nuffield Department of Medicine, University of Oxford

[5] Department of Chest Medicine, Mansoura University, Mansoura, Egypt

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Corresponding Author:

Mohamed A Ellayeh, University of Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK

OX3 7LL

Department of Chest Medicine, Mansoura University, Mansoura, Egypt

Email: M_ellayeh@mans.edu.eg; Phone: +44(0)7415975531

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MPE – malignant pleural effusion

ICS - intercostal spaces

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- differentiation

Introduction

Pleural effusion is the most frequent pleural disorder with more than a million cases seen in the USA every year (1). Most malignant pleural effusions are secondary to metastases to the pleura from other sites, most commonly lung and breast, which together account for 50% to 65% of all MPE (2). Differentiation between benign and malignant pleural effusions is a key step in the management of pleural effusion(3). Thoracoscopy is considered the gold standard diagnostic modality for investigation of suspected pleural malignancy (4). The percentage of undiagnosed pleural effusions post thoracoscopy is approximately 10%, while this exceeds 30% post pleural fluid cytology and blind pleural biopsy (5).

Macroscopically, thoracoscopy demonstrates characteristics that are taught to be indicative of malignancy including nodules, large localized mass, hard pale pachypleuritis(6) and lymphangitis on either the visceral and/or parietal surfaces. However, in some cases only non-specific abnormalities are detected such as congestion and fibrinous pleurisy (7). Direct visualization of malignancy can inform the decision to proceed to concurrent thoracoscopic talc poudrage (8). Since Rapid On Site Evaluation (ROSE) is not readily available to most thoracoscopists, the operator needs to be confident in their visual assessment to aid targeted pleural biopsies and in order to proceed with pleurodesis(9). In a study of benign pleural effusion, inflammation was reported as the most abundant feature detected macroscopically(10). Thoracoscopy may aid in identifying the cause of benign effusion by direct visualization of features such as multiple micronodules in rheumatoid effusion (6) (11).

The precise mechanism whereby malignant cells originate and then spread within the pleura is unknown. It has been reported that the predominant site for pleural invasion is in the lower parts of the pleural surfaces, and that tumours tend to spread from lower to upper parts of the pleural surfaces and from the inner to the outer parts of the diaphragm(12). However, this postulated pattern of progression has never been the subject of thoracoscopic assessment. It is likely to have implications for the underlying biology of how malignancy spreads in the pleura and the meaning and significance of pleural tumour burden.

Scoring systems have been derived in the past to assess the likelihood of malignancy, and the degree of malignant involvement at thoracoscopy. The first of these, developed in 1993, concluded that there was no association between thoracoscopic tumour burden and overall survival(13). A further study using this score reported a strong association between pleural adhesions and tumour burden, and the authors postulated that pleural inflammation was associated with tumour progression, in a similar manner analogous to markers of inflammation in pleural fluid (low pH, high LDH) (14). However, the thoracoscopic score did not use a precise evaluation of each pleural surface, assumed that the three chosen areas (diaphragm, viscera and costoparietal) were equally contributory.

A further study using the same scoring system demonstrated no association between tumour burden and overall survival(15). However, this study did not include benign pleural disease, abnormalities in the parietal pleura were not assessed according to location and abnormality assessors were not blind to histopathological diagnosis.

More precise objective criteria are therefore needed in modern thoracoscopy practice to permit accurate differentiation of benign from malignant disease, and to assess the site of abnormality. The present study therefore aimed to conduct an objective and detailed macroscopic assessment of the pleural surfaces through scoring of three types of abnormalities (nodules, lymphangitis and inflammation) on different areas of each pleural surface (costoparietal, visceral and diaphragmatic). We thereby aimed to identify the location of the predominant abnormalities on the pleural surfaces, and their association with final clinic-pathological diagnosis, comparing benign and malignant disease.

Methods

Study design

This was a retrospective descriptive study of all patients who underwent medical thoracoscopy for undiagnosed exudative pleural effusions and in whom the cytological analysis was inconclusive, at the Oxford Pleural Unit from 2015 to 2017.

Primary objective: The primary objective was to assess the diagnostic value of defined thoracoscopically visible pleural abnormalities for benign and malignant pathologies.

Secondary objective: The secondary objective was to identify the locations of the pleural surfaces on which predominant abnormalities occur.

Patient data were collected from clinical records and included demographics (age and gender), smoking status, asbestos exposure history, side of effusion, size of effusion (estimated by calculating the number of intercostal spaces (ICS) using ultrasound from costophrenic angle (small-1 ICS, medium 2–3 ICS, large 4 ICS)(16), co-morbidities, histopathological diagnosis, and hospital stay (calculated from the day of thoracoscopy till discharge).

For clinical governance and audit purposes, all medical thoracoscopies in Oxford are routinely video recorded and stored.

Thoracoscopic video methodology:

Thoracoscopic videos were assessed using a predefined protocol and a score of pleural involvement obtained on the parameters below prior to review of histopathological diagnosis and the clinical record. Video assessment was blind to diagnosis, pathology, and clinical data. Medical thoracoscopy (rigid, one or two port as indicated) was performed using the standard approach(17).

For each thoracoscopic video, assessment proceeded from identification of the diaphragmatic pleura (the most dependant surface) followed by the visceral pleura overlying the lung, and the costoparietal pleura which was divided into lateral, anterior, and posterior surfaces. (Figure 1)

Initially, all surfaces were included in the video analysis. At a planned interim review after 10 cases, the ability to visualise all surfaces was assessed. This analysis demonstrated that the anterior costoparietal and mediastinal pleura surfaces (below the lung) were not routinely assessed / recorded by the thoracoscopist. Therefore, these areas were removed from further case assessment.

The final video assessment in all cases was therefore conducted in the following areas:

1. Costoparietal surface at 6 levels (apical lateral, middle lateral, inferior lateral, apical posterior, middle posterior, and inferior posterior surface), in which the apical area corresponds to the first 3 ribs, middle area corresponds to the 4^{th} to 6^{th} ribs and the inferior area corresponds to the 7^{th} to 10^{th} ribs.
2. Visceral pleural involvement (any abnormality seen on any lung surface)
3. Diaphragm pleural involvement (any abnormality seen on any diaphragm surface)

Pleural abnormalities in each of the above areas (total number of areas = 8) were scored according to the presence or absence of nodules, lymphangitis, and inflammation (see Figure 1):

- Nodules were defined as white-yellow soft protrusions of the pleura, which could be sessile, polypoid, or grapelike.
- Pleural lymphangitis was defined as an irregular, non-raised reticular formation on the pleural surface.
- Inflammation was defined as the presence of erythema (resembling simple inflammation) or diffuse homogenous white-grey opacity (resembling pleural thickening) (17).(Figure 1)

A pleural adhesion score was recorded, with the degree of pleural adhesion defined as follows:

1. No adhesions – a free pleural space with complete separation of the lung and parietal surface

2. Less than 3 adhesions: <3 localized and well demarcated lesions (fibrinous or collagenous) between the visceral and parietal pleura allowing normal or near normal thoracoscopic examination.
3. Extensive adhesions: > or = 3 adhesions anywhere in the pleural space, or diffuse adhesions between the lung and parietal pleura that hindered adequate pleural visual inspection.

A score on the basis of the entire thoracoscopic appearance was derived as follows:

- Each finding on each surface was assigned a score of 0 (not present) or 1 (present).
- The score was applied to each finding separately (lymphangitis, nodules, and inflammation) giving a minimum score of 0 for each finding, and a maximum score of 8.
- Surfaces which were not visualised were recorded as unseen (not 0).
- All scores were summated to provide a "total pleural score" of between 0 and 24.

Diagnostic Classification

Patients were classified as having malignant pleural disease based on positive histopathological diagnosis. Benign classification required biopsies demonstrating no evidence of malignancy and a period of at least 2 years clinical follow up, in which time there was no clinical / radiological evidence of the development of malignant disease.

Statistical analysis:

The collected data was anonymized, processed, and analyzed using SPSS (Version 18) for windows. Qualitative variables are presented as number and percent and Chi-squared tests used for comparison of proportions. Non-parametric variables were analysed using the Mann Whitney U test. A p-value of ≤ 0.05 was considered statistically significant.

Results

Baseline data

A total of 96 patients were included. The final diagnosis was benign in 51 patients (53%) and malignant in 45 (47%). Median age in the benign group was 71 years (IQR 63 to 82), while median age in the malignant group was 73 years (IQR 68.5 to 81).

There was a significant difference between benign and malignant groups regarding respiratory and cardiac pre-existing diseases: in the benign group, 25 patients (49%) and 26 patients (51%) had respiratory and cardiac disease respectively, which was higher in comparison to the malignant group (6 patients (13%) and 10 patients (22%), p <0.001 and 0.004 respectively). Most patients in the malignant group had large effusions (28 (62%)), while most in the benign group had moderate effusions (24 (47%)). There was a significant difference between groups regarding protein and LDH (mean protein 39 g/L (SD 8) in the benign group, 45 g/L (SD 8) in the malignant group, unpaired t-test, mean difference = 6.3, 95% CI for the difference 3 to 10, p <0.001).The mean LDH was 346 IU/L (SD 310) in the benign group and 673 IU/L (SD 1054) in the malignant group (unpaired t-test, mean difference 328, 95% CI for the difference 8 to 647, p=0.04) (**Table 1).**

Median survival in the benign group was higher at 721 days (IQR 286 to 1225) and 283 days (IQR 94 to 678) in the malignant group (Mann-Whitney, p=0.003). Median hospital stay in the benign group was zero days (IQR 0 to 1.25), and 2 days (IQR 0 to 4) in the malignant group (Mann-Whitney, p=0.002).

In the malignant group, the predominant malignancy type was mesothelioma followed by metastatic tumors from the lung and breast. **(Table 1).** Survival was variable according to underlying malignancy. Metastatic lung cancer had a median survival of 94 days (IQR 31 to 277), metastatic tumors other than lung had median survival of 468 days (IQR 227 to 910, Mann-Whitney, p=0.023), median survival in mesothelioma was 298 days (IQR 105 to 723).

Distribution of Disease

Involvement of the pleural surfaces

In the benign group, abnormalities were seen in the costoparietal pleura most commonly (42/51, 82.4%) followed by the visceral (25/51, 49%) and diaphragmatic pleura (17/51, 33.3%). In the malignant group, abnormalities were seen most commonly in the costoparietal pleura in 44/45 (97.8%) followed by the diaphragmatic (24/45, 53.3%) and visceral pleura (21/45, 46.7%) **(Table 2).**

Costoparietal pleural involvement

In the benign group, inflammation was seen most commonly in the middle lateral and inferior lateral areas (60% and 57.8% respectively). Lymphangitis was frequently observed in the inferior posterior area (52.2%).

In the malignant group, the surfaces most frequently affected with nodular change were the middle lateral (67.4%) and inferior lateral (66.7%) areas. Inflammation was almost equally distributed in all parts of the costoparietal pleura. Lymphangitis was frequent in both the middle lateral and inferior lateral areas (51.2% and 50% respectively), (**Table 3).**

Pleural adhesions

Pleural adhesions were absent in 16 cases in the benign group (31.4%), less than 3 adhesions were seen in 24 cases (47.1%) and extensive adhesions present in 11 cases (21.6%). In the malignant group, pleural adhesions were absent in 21 cases (46.7%), less than 3 adhesions were seen in 16 cases (35.6%) and adhesions were extensive in 8 cases (17.8%). (**Table 4)**

Macroscopic appearance association with final diagnosis

By involved pleural surface

Regarding the costoparietal pleura, there were significantly more patients with nodules in the malignant group than the benign group (OR 10, 95% CI 4 to 25). However, nodules were seen in 24% of benign patients on the costoparietal pleura. There were significantly more patients with inflammation in the benign group than the malignant group (OR 0.4, 95% CI 0.2 to 1). The presence of costoparietal pleural lymphangitis was similar in both groups (OR 1.1, 95% CI 0.5 to 2.5, χ^2, p value= 0.82). The presence of plaques on the costoparietal pleura was not different between groups (OR 0.85, 95% CI 0.3 to 2, χ^2, p value= 0.73)

The visceral pleura was involved with nodular change more frequently in the malignant group than the benign group (OR 5, 95% CI 1.5 to 18). There were significantly more patients with inflammation in the benign group compared with the malignant group (OR 0.4, 95% CI 0.2 to 1). The frequency of lymphangitis on the visceral pleura was similar in both groups (OR 1.2, CI 0.4 to 4, χ^2, p value= 0.71).

Diaphragmatic pleural lymphangitis was more commonly observed in the malignant group than the benign group (OR 3.8, 95% CI 1 to 16). Diaphragmatic nodular change was observed more frequently in the malignant group than the benign group (OR 10, 95% CI 2.6 to 40) **(Table 5).** The frequency of plaques on the diaphragmatic pleura was not different between groups (OR 0.83, 95% CI 0.2 to 3, χ^2, p value= 0.78)

By macroscopic abnormality

Nodular change was seen more frequently in all six areas of the costoparietal pleura in the malignant group in comparison to the benign group.

Detection of nodules in only one out of the six areas of the costoparietal pleura without any other nodularity of the visceral or diaphragmatic surfaces was seen more frequently in the benign group (8(80%)) in comparison to the malignant group (3(10%)). However, finding of nodules on more than one area of the six areas of the costoparietal pleura without any other (visceral or diaphragmatic) involvement was seen more frequently in the malignant group (27(90%)) in comparison to the benign group (2(20%)). (OR 36, 95% CI 5 to 254, χ^2, $p<0.001$).

Inflammation was significantly more frequent in five of six costoparietal pleural areas in the benign group in comparison to the malignant group. However, apical posterior inflammation was demonstrated 1.5 times more frequently in the malignant group than the benign group.

Lymphangitic change was detected more in the malignant group in the apical lateral and the apical posterior areas than the benign group. However, lymphangitis was detected more in the benign group than the malignant group in the inferior posterior area (**Table 3).**

Costoparietal plaques were detected in 7 (31.8%) of the mesothelioma group, and in 9 (32%) of the benign group who were exposed to asbestos (OR 0.98, 95% CI 0.3 to 3, χ^2, p value= 0.98)

Discussion

To our knowledge, this is the first study to critically assess the differentiation of benign and malignant thoracoscopic patterns by direct visualization. In contrast to previous studies, our score was objective as we used a methodology where the assessor was blind to the imaging, clinical records and final histopathological diagnosis. In addition, meticulous assessment of the whole pleural cavity was performed by dividing the costoparietal pleura into six areas for better identification of the predominant areas with abnormalities.

Primary objective:

Comparing benign and malignant cases, there was a significant difference in the frequency of nodules in the parietal, visceral and diaphragmatic pleura. In the benign group, although inflammation was the predominant finding, nodules were present in 24%, 8% and 8% of cases in the parietal, visceral and diaphragmatic surfaces respectively. This contradicts previous literature which suggests that the presence of nodules is pathognomonic of malignant disease (7). Nodules have been described in benign diseases such as tuberculosis (sago pattern) (18) and rarely rheumatoid nodules have been described (19). There are benign lesions that mimic a localized nodule such as thoracic splenosis, pleural endometriosis, thoracolithiasis, foreign bodies, pleural plaques, and pleural pseudotumor (20). While there was no significant difference between benign and malignant cases with regard to the frequency and distribution of lymphangitis, inflammation on the costoparietal pleura, which was seen significantly more frequently in the benign group. Pleural plaques were detected with similar frequency in benign cases exposed to asbestos and cases of mesothelioma.

Our results are comparable to a previous study, in which the predominant macroscopic pattern during thoracoscopy was inflammatory in 40% of benign cases (10). The increased prevalence of inflammation in malignant cases may be attributable to the process of formation of malignant effusion, which develops due to angiogenic pathways and increased vascular permeability (21). Many cytokines which are considered inflammatory, including Vascular endothelial growth factor 3 (VEGF3), Interleukin-8 (IL-8), and Angiogenin (AGN) have been detected in high levels in malignant effusions (22).

Pleural nodules were less frequently seen in the malignant group in our study compared to a previous study, but pleural inflammation and lymphangitis were more commonly seen. This may be attributed to exclusion of mesothelioma in their study, whereas, mesothelioma was present in 48% of our cases (15). Pleural nodule frequency in malignant cases in our study was less than that seen in another study, in which nodules were reported in 36%, as they also included more patients with metastatic pleural disease (60%) (23). Our results are comparable to one study, in which thoracoscopic findings of 342 patients with malignant pleural effusion included pleural nodules in 243 patient (71.1%) and hyperemia in 159 patients (46.5%). However, this study included total pleural involvement and did not divide pleural inspections into surfaces (24).

Secondary objective:

Regarding total pleural involvement, the costoparietal pleura was the most involved surface by nodules, inflammation and/or lymphangitis in both the benign and malignant groups which was similar to a previous study, in which parietal pleural invasion was found in 278 patients (97%) while visceral invasion was detected in 169 (58.9%). Parietal pleural involvement may be explained by the presence of several routes for tumor spread to the parietal pleura which are direct implantation, blood stream and lymphatics indicating that parietal pleural spread occurs before the other pleural surfaces (25).

In malignant patients, the most affected surfaces with nodules were the middle lateral (67.4%) and the inferior lateral (66.7%). These findings are comparable to a study which reported that tumor invasion tends to affect the lower portions of the pleural surfaces more than the upper portions. In addition, they found that 84% of the metastasis were detected in the lower portions (12). These findings could be explained by the predilection of the metastasis to grow in an upward direction (26). Inflammation was almost equally distributed in all parts of the costoparietal pleura, while, lymphangitis was frequent in both middle lateral and inferior lateral (51.2% and 50% respectively).

The absence of adhesions and the presence of only light adhesions in previous studies (14, 27) were comparable to our study, however, the difference between these studies and our study regarding the moderate to severe adhesions may be attributed to the difference in the grading system of adhesions and to the large number of mesothelioma cases in our study.

This study has the potential to impact clinical practice. We have described differential patterns of intrapleural involvement in malignant and benign disease. If prospectively validated, this may add confidence to clinician's decision to perform immediate pleurodesis at thoracoscopy without the need to wait for the results of the biopsy. Our study has allowed identification of the predominant areas with abnormalities which occur in benign and malignant disease. Such knowledge may be helpful in targeting biopsies. From our results, we hypothesize that the finding of nodules in more than one area of the costoparietal pleura is in favor of a malignant diagnosis. The detection of lymphangitis on the diaphragm and the apical area of both lateral and posterior costoparietal pleura is in favor of malignant diagnosis. In contrast, detection of nodules in only one area of the costoparietal pleura is in favor of a benign diagnosis and inflammation without nodular changes on the visceral pleura and the middle and inferior parts of the costoparietal pleura is in favor of a benign diagnosis.

The derived precise scoring system may be used in future validation studies to calculate tumor burden macroscopically, and thereby assess associations between tumor burden and clinical outcomes such as survival and pleurodesis success. The precise macroscopic pattern of spread may be of use in considering the evolution of intrapleural pathology.

This study has several limitations. The size of individual nodules could not be estimated accurately via the macroscopic view, and we did not subdivide the category of nodules when present on a single surface into single or multiple. The study included cases with moderate to extensive adhesions and trapped lung which made the assessment of some pleural surfaces difficult – however, this is a reflection of "real world" practice, and therefore the derived score is highly applicable. The views taken by the thoracoscopist were limited – in that the anterior costoparietal surface was not usually visualised in this study. The proportion of mesothelioma patients in this study is potentially higher than in other similar studies – we attribute this to the poor sensitivity of cytological examination in the diagnosis of, thus increasing the proportion of patients requiring thoracoscopic pleural biopsy with a final diagnosis of mesothelioma (28).

Conclusion

Benign and malignant pleural pathologies are associated with distinct macroscopic patterns at thoracoscopy, which appear to be different both in terms of total pleural involvement, and regional pleural change. Nodules are the predominant pattern seen in malignant pleural disease, with detection of nodules in more than one area of the costoparietal pleura strongly in favor of a malignant diagnosis. Inflammation appears to be the predominant pattern in benign pleural effusion, but nodules are present in up to 24% on the costoparietal pleura and detection of nodules in only one area of the costoparietal pleura is in favor of a benign diagnosis.

Statement of Ethics: not required. (as our study is an observational retrospective study)

Conflict of Interest Statement: None

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Author Contributions: MAE and NMR conceived and designed the study. MAE, EOB, RB, AS, VG and RJH collected the data. MAE and NMR wrote the first draft of the manuscript. MAE, EOB, RJH, NIK, HWA, NAR, AAH, REA, JMW and NMR performed the data analysis. All authors reviewed the draft and approved the final manuscript.

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