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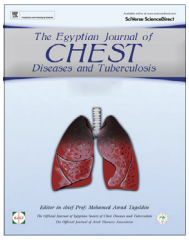

ORIGINAL ARTICLE

Diagnostic value of ultrasound guided biopsy in patients with malignant pleural effusion

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KEYWORDS

Ultrasound guided biopsy;
Malignant pleural effusion;
Thoracoscopy;
Tru-cut needle;
Pleural thickening

Abstract *Aim of work:* To study the diagnostic value of ultrasound guided biopsy in patients with malignant pleural effusion.

Patients and methods: This study involved 40 patients with malignant pleural effusion of indeterminate aetiology. All patients had a contrast CT chest performed and were divided into 3 Groups according to their radiologic appearance: GROUP 1: 10 patients having pleural effusion only. GROUP 2: 15 patients having pleural effusion and pleural thickening. GROUP 3: 15 patients having pleural effusion and pleural mass lesions. All 3 groups of patients underwent ultrasound examination in the Radiology department. In patients of Groups 2 and 3, ultrasound fluid aspiration and ultrasound guided core biopsy of the pleura were attempted. Patients of all 3 Groups performed Medical thoracoscopy in the interventional pulmonology unit.

Results: In Group 1 patients, US guided biopsy was contraindicated and could not be performed due to absence of pleural thickness, nodulation or masses. Thoracoscopy was performed in them all with a sensitivity reaching 90%. In Group 2, a malignant aetiology was reached in 5/10 cases whom had adequate tissue retrieval (sensitivity 50%). In Group 3, 12/15 patients were diagnosed by US guided biopsy (sensitivity 80%). The mean sensitivity of US guided biopsy in both Groups was 65%. Thoracoscopy was then performed successfully in all of patients in Groups 2 and 3 with a diagnostic sensitivity of 100% each. The mean diagnostic sensitivity of thoracoscopy for all 3 Groups was 96.7%.

Conclusion: The US guided pleural biopsy with a Tru-cut needle is simple, safe and well tolerated. It is especially useful for patients with pleural tumour, thickened pleura, small amounts of pleural effusion or loculated pleural effusion.

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Introduction

The CXR remains the initial examination of choice in the investigation of pleural disease and in assessing disease progress. Other radiological modalities such as ultrasound (US), CT, magnetic resonance imaging (MRI) and positron emission

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tomography (PET) can be used in the evaluation of abnormalities detected by CXR or to guide interventional procedures [1].

Computed tomography is the best means of further assessing pleural thickening seen on the CXR. Features of contrast-enhanced CT scanning that favor malignant disease rather than benign disease are nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening greater than 1 cm, and circumferential pleural thickening [1]. Circumferential pleural thickening has been shown to be less specific for malignancy in the presence of a pleural effusion [2].

A CT scan should be performed before drainage of the effusion to dryness as pleural abnormalities surrounded by fluid will be more easily seen. CT is superior to CXR in the differentiation of pleural from parenchymal disease. The detection of pleural nodules within an effusion is indicative of malignancy, whereas homogeneously echogenic effusions are most commonly the result of a haemorrhagic effusion or an empyema. CT is better than US for the evaluation of pleural thickening [3].

Ultrasound is most frequently used to evaluate or guide aspiration and drain insertion in patients with suspected pleural effusions seen on CXR. The intercostal spaces are used as sonographic windows [4]. A small footprint probe (either linear or phased array) allows the easiest intercostal access and probe selection is a balance between spatial resolution and penetration. A 7.5-MHz probe provides excellent spatial resolution of the pleural surfaces but might not provide sufficient penetration in larger patients or in large effusions. A 3.5–5.0-MHz sector transducer provides a good balance and can also be used to guide intervention [5,6].

Normal pleura are seen as an echogenic stripe comprising both parietal and visceral pleura. During normal respiration, there is a shimmering of inhomogeneities, described as 'lung sliding', at the pleural stripe. There is also a 'comet tail' appearance of reverberation of the US wave distal to the pleura. In the presence of a pneumothorax, there is loss of the 'lung sliding' and 'comet tail' signs [7,8]. Focal pleural masses associated with an effusion are easily seen and biopsied under US guidance [9,10].

Thoracocentesis is diagnostic in 60% of patients with malignant carcinomatous effusions, but in less than 30% of patients with effusions secondary to mesothelioma [11]. If aspiration cytology is negative, biopsy of associated pleural thickening is required for tissue diagnosis [12]. Malignant pleural thickening tends to predominate close to the midline and diaphragm, areas best avoided when performing an Abrams biopsy. However, it is possible to take biopsy specimens safely from these anatomical regions under radiological imaging. Image-guided cutting-needle pleural biopsy has been shown to have a higher diagnostic yield than unguided biopsies. Diagnostic rates of 70% have been achieved with US-guided cutting-needle biopsy, and a sensitivity of 83% and a specificity of 100% have been reported for CT-guided cutting-needle biopsy [13].

Thoracoscopy is the investigation of choice in exudative pleural effusions where a diagnostic pleural aspiration is inconclusive and malignancy is suspected [14]. Medical thoracoscopy allows for the direct inspection of the pleura and biopsies taken under direct vision, has a diagnostic yield superior to that of blind closed pleural biopsy and thoracocentesis. The diagnostic yield is in the order of 91–95% for malignant disease and can be as high as 100% for pleural TB [14–17].

Aim of work

To study the diagnostic value of Ultrasound guided biopsy in patients with malignant pleural effusion.

Patients and methods

This study was conducted over a two year period from June 2010 till June 2012 in Radiology and Chest departments, Kasr Al Aini faculty of medicine, Cairo university hospital.

The study involved 40 patients, 32 males and 8 females, suffering from Malignant Pleural effusion whom underwent diagnostic thoracocentesis that revealed indeterminate malignant aetiology.

All patients had a contrast CT chest performed and were divided into 3 Groups according to their radiologic appearance:

Group 1: 10 patients having pleural effusion only.
Group 2: 15 patients having pleural effusion and pleural thickening.
Group 3: 15 patients having pleural effusion and pleural mass lesions.

All 3 Groups of patients underwent ultrasound examination in the Radiology department. Patients were placed in sitting position and initial Ultrasound scanning of the pleura was performed using 3–5 MHz curvilinear and 7–10 linear phased array probes (Logic P 6 pro –GE health care) to assess the amount of pleural collection, pleural thickness and any focal thickening or frank masses.

In Group 1 patients, ultrasound guided biopsy was not indicated due to absence of CT or ultrasound evidence of pleural involvement so only fine needle aspiration (FNA) of fluid was performed using a 22 gauge spinal needle in order to relieve symptoms. In patients of Groups 2 and 3, ultrasound fluid aspiration and ultrasound guided core biopsy of the pleura were attempted. The free handed biopsy technique was performed using 18 gauge, semi automatic Tru-cut needle (Medikalite Tibbi Malzeme Ticareti, Turkey).

The biopsy specimens were in the form of 2–3 cylinders of tissue 1.8 cm in length each. The amount of tissue generally sufficed to provide routine hematoxylin-eosin stains on a set of three levels, with Alcian blue/periodic acid-Schiff staining. Spare sections for immunostaining were cut at the same time.

A panel of antibodies (cytokeratin cocktail, epithelial membrane antigen [EMA], carcinoembryonic antigen, and Ber EP4, with the additional use of cytokeratin 5/6 and thrombomodulin) was applied for distinguishing metastatic carcinoma from mesothelioma and reactive mesothelial proliferation.

All patients returned to the ward immediately after the procedure and on a separate day, patients of all 3 Groups performed Medical thoracoscopy in the interventional pulmonology unit. Under general anaesthesia and using a single port of entry the pleural space was entered, all amounts of pleural fluid aspirated and all surfaces of the parietal and visceral pleura visualized. Biopsies were taken from the lesions under direct vision and sent for histopathologic examination using

the same staining techniques used before for the ultrasound guided biopsy specimens.

An intercostal chest tube was introduced into the pleural space and patients were followed up, sometimes for several days, until the amount of draining fluid was less than 100 ml per day before the tube was removed.

Results

40 patients were involved in this study, 22 males and 18 females. Their ages ranged between 35 and 68 years (mean 58 years) (see Figs. 1–9).

In Group 1 (10 patients) U/S biopsy was not performed, however thoracoscopy was done for all patients showing the following results:

In Group 2 patients (15 patients), U/S guided biopsy was performed successfully in 10 of them with adequate tissue retrieval while in 5 patients there was inadequate tissue retrieval. 5 out of the 10 patients in which adequate tissue was retrieved, showed a specific malignant aetiology (sensitivity 50%) as can be seen in Table 2. Thoracoscopy and biopsy was then performed in the 15 patients with correct diagnosis in all of them (sensitivity 100%).

In all of patients in Group 3 (15 patients), U/S guided biopsy was performed successfully with adequate tissue retrieval. A pathological diagnosis was reached in 12 patients with a sensitivity of 80%.

Thoracoscopy was also performed in all of these patients with a diagnosis reached in all of them (sensitivity 100%). Table 3 shows the results of thoracoscopy compared to U/S guided biopsy.

Discussion

Recent studies have proposed that image guidance during performance of closed pleural biopsy may significantly increase the yield while decreasing the risk for complications when compared to blind technique. Both transthoracic US and CT scanning have been utilized. Modern mobile US units are cheap and available in practically all secondary and tertiary, as well as many primary health-care facilities, even in the developing world [18–22].

Our study shows that in patients with Malignant pleural effusion (MPE) and CT evidence of pleural pathology (thickening, nodules or masses), US guided closed pleural biopsy can obtain adequate tissue for diagnosis with a mean diagnostic sensitivity of 65%. The diagnostic yield is much higher in those patients with less effusion size and larger mass lesions. Thoracoscopy achieves higher mean diagnostic sensitivity of 96.7% in all cases of malignant pleural effusion even in Group 1 patients with no CT evidence of pleural pathology.

In our study, patients with MPE were divided into 3 Groups according to CT appearance of the pleura. Other than

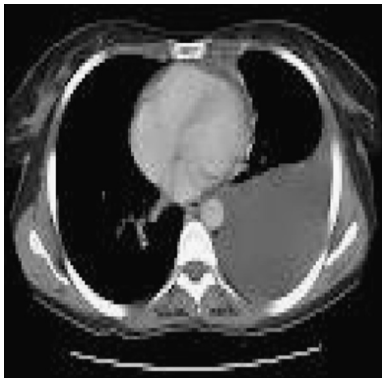

Figure 1 CT showing moderate to massive pleural effusion with no evident pleural thickening or masses.

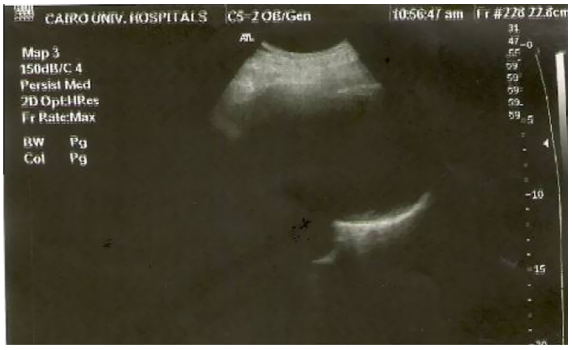

Figure 2 Ultrasound image of the pleural effusion with no evidence of thickening or masses.

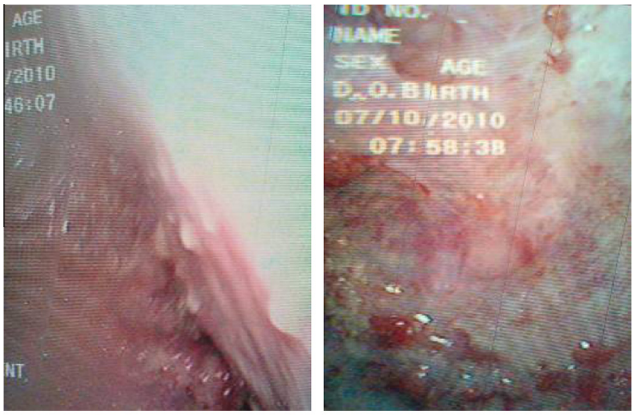

Figure 3 Thoracoscopic images of the patient showing tiny nodules scattered along the diaphragmatic pleura (a) and parietal pleura (b).

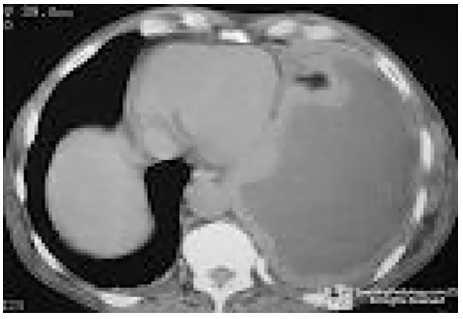

Figure 4 CT showing massive effusion and circumferential pleural thickening.

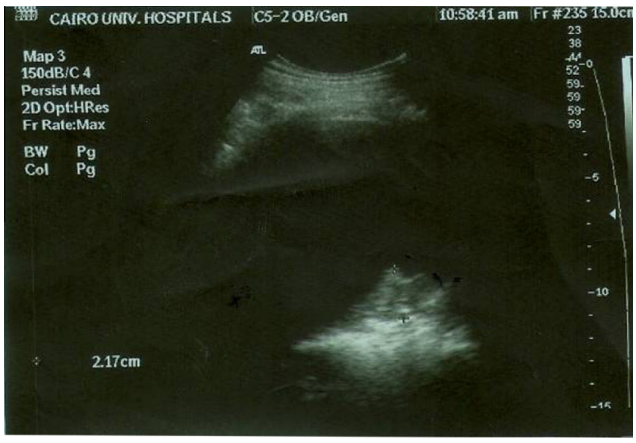

Figure 5 Ultrasound image showing pleural effusion in addition to pleural thickening with nodularity.

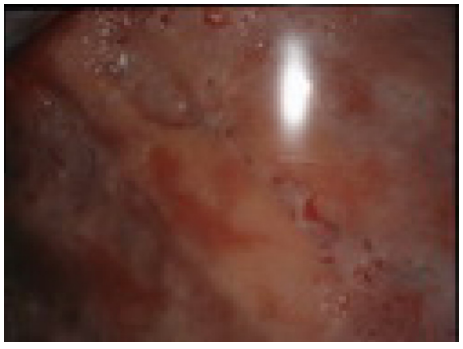

Figure 6 Thoracoscopic image showing diffuse parietal pleural thickening with few pleural nodules.

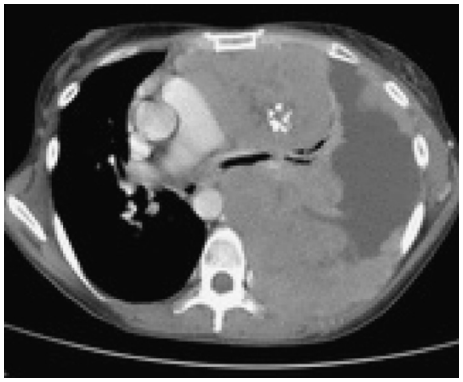

Figure 7 CT showing pleural effusion + mass lesions.

radiologic evidence of effusion in all Groups, Group 1 patients had a smooth pleural appearance on CT whilst patients in Groups 2 and 3 had pleural abnormalities ranging from thickening to nodular or mass lesions respectively. In a recent study, Qureshi et al. were able to identify 73% of malignant effusions on US appearance alone.[23] They found that pleural thickening >10 mm, pleural nodularity and diaphragmatic thickening >7 mm were highly suggestive of malignant disease.

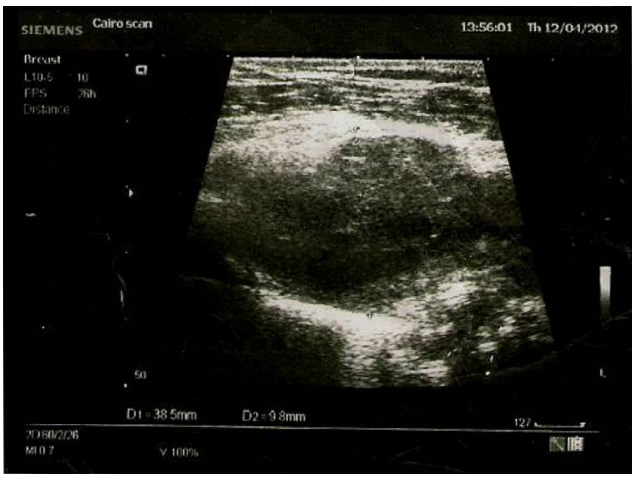

Figure 8 Ultrasound images showing mass lesions affecting the pleura in addition to minimal effusion.

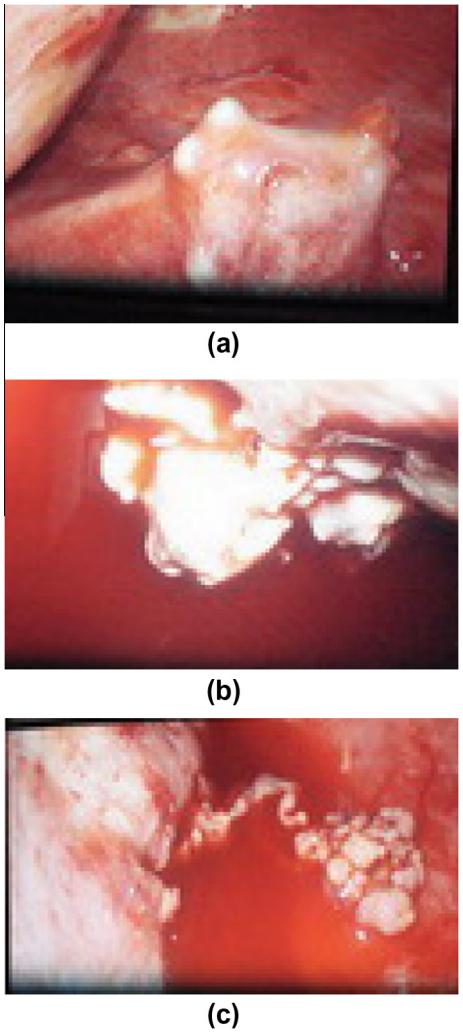

Figure 9 Thoracoscopic images of the patient showing malignant effusion and numerous pleural masses covering the visceral pleura (a), parietal pleura (b) and costophrenic recess (c).

Table 1 Results of thoracoscopic biopsies in Group 1.

Pathology	No. of patients
Mesothelioma	Total = 3 patients
Epithelial	2
Sarcomatous	0
Mixed (biphasic)	1
Metastatic adenocarcinoma	Total = 5 patients
Lung cancer	3
Ovarian cancer	0
G IT Cancer(stomach/colon)	1
Breast cancer	1
Non hodgkin lymphoma	1 patient
Non specific inflammation	1 patient
Total patients	10 patients
Sensitivity	9/10 patients = 90%

CT, ultrasound and thoracoscopic findings of a patient in Group 1 (pleural effusion only).

In Group 1 patients, US guided biopsy was contraindicated and could not be performed due to absence of pleural thickness, nodulation or masses. Thoracoscopy was however performed in them all with a sensitivity reaching 90%. 3/10 pts had mesothelioma, 5/10 had metastatic adenocarcinoma, 1 patient had non Hodgkin lymphoma and in 1 patient the biopsy results were non-specific (Table 1). Other studies also showed that Thoracoscopy has a 90% to 100% sensitivity for MPE [24,25]. In some patients, studding of pleural surfaces with tumor can be subtle, or coexisting benign lesions could misdirect biopsy sampling. For such patients, techniques that cause metastases to fluoresce can guide biopsy sampling [26,27].

In Group 2 patients with CT evidence of pleural thickening, US guided biopsy was performed retrieving adequate tissue in 10/15 cases (66.7%) whilst in Group 3 patients with mass lesions of the pleura, adequate tissue was obtained in 15/15 patients (100%). Various studies have shown that adequate tissue is obtained in 71% to 91% of closed-needle biopsy specimens [28,29].

In Group 2, a malignant aetiology was reached in 5/10 cases whom had adequate tissue retrieval (sensitivity 50%). In Group 3, 12/15 patients were diagnosed by US guided biopsy (sensitivity 80%). The mean sensitivity of US guided biopsy in both Groups was 65%. Again, the malignant aetiology was mostly Mesothelioma *(Epithelial subtype more frequently in Group 2, Sarcomatous subtype more frequently in Group 3)* or Metastatic adenocarcinoma *(more frequently due to primary lung and breast carcinoma, in both Groups)* (Tables 2 and 3). The higher diagnositic sensitivity in Group 3 agrees with various studies that showed that image-assisted biopsy is more likely to be diagnostic in the presence of pleural thickening >10 mm, pleural nodularity, pleural based mass lesions of >20 cm and solid pleural tumours [23,30–32]. Thoracoscopy was then performed successfully in all of our patients in Groups 2 and 3 with a diagnostic sensitivity of 100%.

Chang [9] previously found the diagnostic yield of US-guided Tru-cut pleural biopsy to be 70% for pleural neoplasia irrespective of pleural thickening or nodularity. In a study by Koegelenberg et al. [33] the respective yield for both US-assisted Abrams or Tru-cut needle types for pleural malignancies was comparable and relatively high being diagnostic in approximately 83.3% of cases. Diacon et al. [30] reported an 86% sensitivity and a 100% specificity with transthoracic ultrasonography-guided biopsy when they used a 14-gauge cutting needle for pleura-based lesions 20 mm or greater in diameter.

In the Helio study [34] which aimed to assess the clinical use of ultrasonographically (US) guided core-needle biopsy, performed with a one-hand automatic sampling technique, in the diagnosis of malignant pleural mesothelioma (MPM), a sensitivity of 77%, specificity of 88%, accuracy of 80%, positive predictive value of 100%, and negative predictive value of 57% were found. This differed from the results regarding diagnosis of mesothelioma in Group 2 patients of our study (with CT evidence of pleural thickening only) where US guided biopsy had a sensitivity of 3/8 (37.5%) (Table 2). In Group 3 patients, however, results regarding diagnosis of mesothelioma were similar, with US guided biopsy sensitivity increasing to 7/10 patients (70%) (Table 3) due to the presence of evident nodules and mass lesions on CT examination making the

Table 2 Results of U/S guided and thoracoscopic biopsies in Group 2.

Pathology	No. of patients diagnosed by thoracoscopy	No. of patients diagnosed by U/S guided biopsy
Mesothelioma	Total = 8 pts	Total = 3 pts
Epithelial	4	1
Sarcomatous	2	2
Mixed (biphasic)	2	0
Metastatic adenocarcinoma	Total = 7 patients	Total = 2 patients
Lung cancer	3	1
Ovarian cancer	1	0
GIT cancer (stomach or colon)	1	1
Breast cancer	2	0
Non hodgkin lymphoma	0	0
Non specific inflammation	0	0
Total patients	15 patients	5 patients
Sensitivity	15/15 patients = 100%	5/10 patients = 50%

CT, ultrasound and Thoracoscopic findings of a patient in Group 2 (pleural effusion ± pleural thickening).

Table 3 Results of U/S guided and thoracoscopic biopsies in Group 3.

Pathology	No. of patients diagnosed by thoracoscopy	No. of patients diagnosed by U/S guided biopsy
Mesothelioma	Total = 10 pts	Total = 7 pts
Epithelial	3	3
Sarcomatous	4	4
Mixed (biphasic)	3	0
Metastatic adenocarcinoma	Total = 4 patients	Total = 4 patients
Lung cancer	2	2
Ovarian cancer	0	0
GIT cancer (stomach or colon)	0	0
Breast cancer	2	2
Non hodgkin lymphoma	1 patient	1 patient
Non specific inflammation	0	0
Total patients	15 patients	12 patients
Sensitivity	15/15 patients = 100%	12/15 patients = 80%

CT, ultrasound and Thoracoscopic findings of a patient in Group 3 (pleural effusion ± mass lesions).
Mean sensitivity of medical thoracoscopy for Groups 1–3 = 96.7%.
Mean sensitivity of U/S guided biopsy for Groups 2 and 3 = 65%.

biopsy procedure more rewarding. Diacon et al. [30] showed that for malignant mesothelioma extending at least 20 mm in any accessible dimension on US, the diagnostic yield of US guided Tru-cut biopsy may be as high as 100%.

Throughout our study, medical thoracoscopy was performed in all 3 Groups of patients with a mean diagnostic sensitivity of 96.7%. It was the only means of diagnosis (sensitivity 90%) in Group 1 patients whom had indeterminate malignant pleural effusion with no CT evidence of pleural thickening or masses thus preventing the use of US guided biopsy. In the other Groups (2 and 3), the diagnostic sensitivity of thoracoscopy reached 100%, thus ensuring exact aetiology determination in all of the cases of malignant effusion.

Another point worth mentioning is that for diagnosis of mesothelioma and classification of its subtype, a large pleural biopsy specimen is often necessary which can usually be obtained thoracoscopically. Immunohistochemical staining provides essential information in the diagnostic evaluation. Some specimens could require electron microscopy to differentiate mesotheliomas from adenocarcinomas or fibrous pleuritis. Mesothelioma subtype classification becomes important in centers that recommend aggressive trimodality therapy with extrapleural pneumonectomy for the epithelial but not the mixed or sarcomatoid subtypes [35].

Canto et al. [36] considered thoracoscopy to be an invasive study, not suitable for dense adhesions in the pleural space and usually calls for general anaesthesia. They found that with the use of US guidance, pleural biopsy with Tru-cut needle was done precisely and safely even in the presence of only small amount of loculated pleural effusion.

In conclusion, thoracoscopy has a superior diagnostic yield for pleural malignancy and is therefore considered by many to be the investigation of choice in exudative pleural effusions where a thoracocentesis was nondiagnostic and particularly when malignancy is suspected. Furthermore, it allows for the direct inspection of the pleura. Access to thoracoscopy is, however, limited in many parts of the world, as significant resources and expertise are required. Blind closed pleural biopsy has a modest yield. Recent studies suggest that image guidance improves the yield, particularly for malignancy. An US-guided second thoracocentesis combined with an US-guided pleural biopsy with a Tru-cut needle may therefore be an acceptable alternative to thoracoscopy. Cases that remain undiagnosed warrant thoracoscopy.

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