Biopsy Techniques for the Diagnosis of Mesothelioma

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Abstract The incidence of mesothelioma continues to increase in the Western world and is likely to do so until 2011–2015. It commonly presents with breathlessness secondary to a pleural effusion, and whilst guidelines still advise thoracocentesis as the first line investigation, the sensitivity of this is low and a tissue diagnosis is usually required. Abrams needle biopsy also has a low diagnostic yield and high complication rate and is not recommended in guidelines on the investigation of mesothelioma. Computed tomography–guided biopsy or thoracoscopy both have a comparable sensitivity and low complication rates. Local anaesthetic thoracoscopy is increasingly used by respiratory physicians and has a comparable diagnostic sensitivity to Video-Assisted Thoracoscopic Surgery (VATS) without the need for a general anaesthetic. The requirement for prophylactic radiotherapy after pleural procedures in cases of mesothelioma is contentious, as the results from early trials suggesting it reduces tract seeding have been disputed by more recent trials.

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4.1 Introduction

The incidence of mesothelioma continues to increase; it has a poor prognosis and definitive diagnosis is often difficult to obtain [56]. In Europe, 5,000 people die annually from mesothelioma [47] and in Britain the incidence is projected to peak in 2011–2015 at 1,950–2,450 deaths per year [29]. The prognosis is poor with a study in the USA [52] showing a 1-year survival of 64% from onset of symptoms and median survival of 10 months. A British study [61] found a median survival of 14 months from the onset of symptoms.

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4.2 Clinical Presentation

The most common clinical presentation for patients is progressive dyspnoea and/or chest wall pain [17]. Dyspnoea at presentation is usually caused by a pleural effusion but as the disease progresses this can be caused by pleural restriction. At presentation 90% patients have a pleural effusion with 10% patients having little or no fluid [30]. The effusion is usually unilateral (95%). The chest wall pain is usually caused by significant chest wall invasion. Other symptoms include a dry cough, weight loss, fever, fatigue or night sweats. The patient may also present after abnormalities are found on a routine chest radiograph [2] or present with minimal non-specific symptoms with the diagnosis only becoming apparent with time.

A detailed occupational history is important, although sometimes difficult because of the time that has elapsed since the exposure. Common prior occupational exposures include laggers, pipefitters, plumbers, heavy construction or shipbuilding industry workers and those working aboard ships, especially in the boiler room.

4.3 Investigation of Pleural Effusion

Mesothelioma may be suspected on presentation because of the history, including exposure and symptoms, and abnormalities on the chest radiograph. If a pleural effusion is present then the initial investigations should be a diagnostic/therapeutic pleural aspiration and contrast-enhanced computed tomography (CT) [62]. The contrast allows differentiation between thickened pleura, pleural effusion and underlying collapsed or aerated lung, allowing a detailed look at the pleura including whether the pleural thickening is irregular, circumferential and involves the mediastinal border. It also aids decisions regarding the next, most appropriate, investigation. Pleural aspiration is a simple investigation that can be performed, under ultrasound guidance, in clinic at the initial review and should be sent for cytology with immunocytochemistry if appropriate [2].

4.3.1 Cytology

The diagnostic sensitivity of pleural cytology with malignancy has been reported at about 60% [24, 43]; however, the reported sensitivity for mesothelioma has been reported as much lower than this at 20–32% [32, 51]. This number included those that were suspicious but not diagnostic for mesothelioma. If only the positive results were included and the suspicious results excluded, the sensitivity decreased to 16%. However, it is worth noting that if cytology is positive then the median time to diagnosis is reduced. In one study, this time was reduced from an average of 12 to 4 weeks. It often proves difficult to differentiate between reactive mesothelial cells secondary to an inflammatory response and malignant cells; therefore, pleural tissue is often required to confirm the diagnosis. Immunocytochemistry can help to differentiate between mesothelioma and adenocarcinoma [23]. Sending a second sample if the first was negative has been shown to increase the yield for malignancy by a further 27% [24]; however, in the case of mesothelioma it is unlikely to be this successful and likely to delay diagnosis further. Repeated thoracocentesis has also been shown to increase the number of pleural loculations [16] which could have an impact on later investigations such as thoracoscopy.

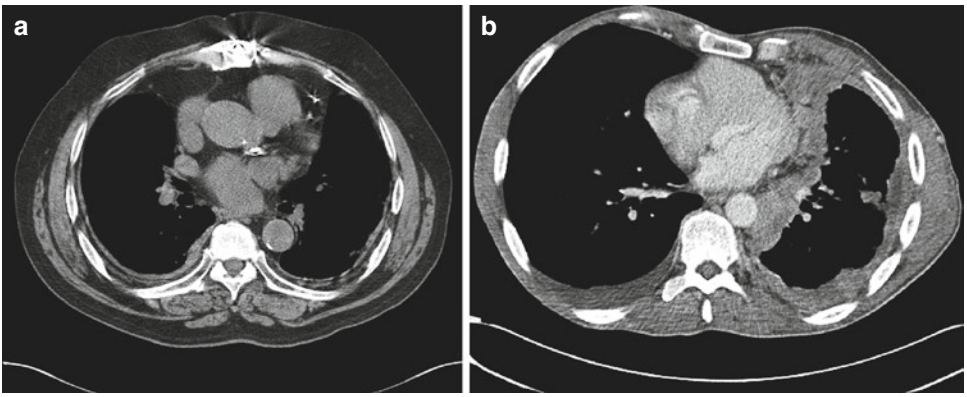

Fig. 4.1 (**a**, **b**) Benign and malignant pleural thickening on CT scan

The European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) guidelines on the management of mesothelioma state that it is not recommended to make a diagnosis of mesothelioma based on cytology alone because of the high risk of diagnostic error.

4.4 Investigation of Pleural Thickening with No Effusion

Benign causes of pleural thickening commonly include previous pleural infection or haemothorax and benign asbestos-related pleural thickening. When seen at the lung apices it is generally due to prior infection from tuberculosis or fungi [17]. It is uncommon for asbestos to cause apical pleural thickening.

CT changes suggesting malignancy as opposed to benign pleural thickening are (1) circumferential thickening, (2) nodular pleural thickening, (3) parietal pleural thickening >1 cm and (4) mediastinal pleural involvement [35]. Whilst these changes were specific (100%, 94%, 94% and 88%, respectively), they were not overly sensitive (41%, 51%, 36% and 56%, respectively), and did not allow differentiation of mesothelioma from other cancers. If there is evidence suggesting malignancy, these patients will require a pleural biopsy. The thoracic CT scan is helpful in deciding which method would be most suitable (Fig. 4.1a, b).

4.5 Percutaneous Pleural Biopsy Techniques

4.5.1 Abrams Needle

The use of a blind closed needle biopsy (BCNB) was first described by Abrams in 1958 [3]. It provided an alternative to an open pleural biopsy, which requires a general anaesthetic [7]. Compared to other pleural biopsy techniques it

is inexpensive and can be carried out under local anaesthetic. Chakrabarti et al. found no difference in the diagnostic sensitivity between respiratory registrars and their more junior counterparts [13]. Although low yields were reported when diagnosing mesothelioma, it was hoped that this might be improved with the advent of improved histopathological tests [7].

Abrams needle biopsy has been shown to increase the yield in diagnosing malignancy over cytology by 7–27% [43, 48]. There have been two recent reviews of BCNB. In one, of 75 patients with a pleural effusion who underwent BCNB, 46 patients were ultimately diagnosed with malignancy. The initial Abrams biopsy was diagnostic in 20 of the 46 patients diagnosed with malignancy (43%). In those diagnosed with mesothelioma the Abrams biopsy was diagnostic in 4 of 13 cases (31%) [13]. In another review of 119 patients ultimately diagnosed with mesothelioma who underwent BCNB, a definitive diagnosis was made in 44 (46%) whilst the result was suspicious in 20 (21%) [37]. The results in an earlier trial were higher, with five of seven (71%) patients with mesothelioma being diagnosed with an Abrams needle biopsy [7]. A recent trial attempted to increase the sensitivity of an Abrams needle biopsy by determining the entry site with the use of a contemporaneous thoracic CT and measuring the distance between entry and target site two dimensionally on the CT [39]. The sensitivity for diagnosing mesothelioma was 80%. Other attempts have been made to increase the sensitivity by methods such as pleural brushings [6], but diagnostic yields are no greater than 50%. The only randomised controlled trial directly comparing CT-guided cutting needle to blind Abrams biopsy [36] looked at 50 consecutive patients. It showed a significantly increased sensitivity with a CT-guided cutting needle (87%) compared to the Abrams biopsy (47%) in the diagnosis of malignancy and the results were similar when looking at mesothelioma.

Complications of Abrams biopsy include site pain (1–15%), pneumothorax (3–15%), vasovagal reaction (1–5%), haemothorax (<2%), site haematoma (<1%), transient fever (<1%) and very rarely death secondary to haemorrhage.

4.5.2 Radiologically Guided Percutaneous Pleural Biopsy

Pleural thickening, whether benign or malignant, is frequently not uniform, and image-guided biopsy facilitates selection of the most appropriate biopsy site. It also enables safe biopsies in the absence of a pleural effusion. Percutaneous pleural biopsy has been described with both transthoracic ultrasound (US) and CT as image guidance modalities.

US has been used increasingly by respiratory physicians to assess pleural effusions as it has become clear that it increases the success of pleural aspiration and reduces complications [25, 33] and is now recommended in the 2010 BTS pleural disease guidelines for all pleural procedures performed on the ward [62]. US allows real-time images of the biopsy, is readily available and has no radiation risk to the patient. In one review of US-guided cutting needle biopsy versus Abrams needle biopsy, 49 patients underwent pleural biopsy, 25 with an US-guided Tru-Cut needle and 24 with an Abrams needle [14]. In the subgroup diagnosed with mesothelioma, the sensitivity was higher with a US-guided Tru-cut needle with a trend towards statistical significance. Another study looked at the sensitivity and safety of using an US-guided Tru-Cut needle in the diagnosis of pleurally based abnormalities >20 mm in the absence of a pleural effusion (those with effusions underwent aspiration +/− thoracoscopy) [20]. Ninety-one patients underwent biopsies by either a respiratory physician or a registrar under supervision. Of these, 10 had mesothelioma and all were diagnosed on the first biopsy. Helio et al. found

similar sensitivities for diagnosing mesothelioma with a US-guided cutting needle [28]. Of 52 patients diagnosed with mesothelioma, 40 (77%) were diagnosed after their first biopsy attempt.

CT-guided biopsy permits access to areas not easily accessible to ultrasound such as pleural lesions near or behind ribs or along the paravertebral surfaces [50]. Higher sensitivities have been reported with CT than with US-guided biopsies although there have been no trials directly comparing them [49]. Metintas et al. looked at 30 patients with mesothelioma who underwent CT-guided closed needle biopsy. This was diagnostic in 25 (83.3%) [41]. Adams et al. reviewed 21 cases of mesothelioma that had received an image-guided biopsy in their work up (6 US and 15 CT) [5]. Their diagnostic sensitivity was 86%. It is also worth noting that of these, four patients had a pleural thickness of less than 5 mm and all of these biopsies were successful.

Cutting needle biopsy has been shown to be more sensitive than fine needle aspiration in the diagnosis of malignancy and the difference is even more marked with mesothelioma [4, 5] with a sensitivity of 93 versus 50% in favour of using a cutting needle. The overall sensitivity can be increased with a combination of both techniques.

Complications occur in less than 5% patients using image-guided pleural biopsy techniques [50] and include pneumothorax, intrapleural bleeding, subcutaneous haematoma and damage to the diaphragm and abdominal viscera.

One study of 85 image-guided biopsies showed their rate of new pneumothoraces was 11% but only 4.7% patients had a new pneumothorax visible on chest radiograph [8]. Of these patients two already had a chest drain in situ and six had had a drain inserted as part of the procedure for drainage of pleural fluid. Therefore, no patient required insertion of a chest drain solely for drainage of a biopsy-induced pneumothorax. 7.5% CT-guided biopsies were associated with significant bleeding but all remained haemodynamically stable.

4.5.3 Positron Emission Tomography (PET) CT

PET scans are increasingly being used in the evaluation of patients with mesothelioma [58]. F-fluoro-2-deoxy-D-glucose (FDG)–PET has been shown to accurately differentiate benign pleural disease from mesothelioma. In one study of 98 patients with 63 pleural malignancies, FDG-PET had a sensitivity for detecting malignancy of 96.8% and a specificity of 88.5% and appeared to confirm malignant pleural disease that cannot be identified at CT [21]. Neither of the two malignancies that did not show FDG were mesothelioma.

Another study of nine patients with mesothelioma [45] showed that all the primary tumours were FDG positive.

Although no trials have looked at PET-CT being used to increase the diagnostic yield of CT-guided biopsies, there may be a role for this in the future, particularly in those patients who clinically appear to have mesothelioma but have already had negative biopsies and are not suitable for thoracoscopic/surgical biopsies.

4.6 Thoracoscopy

Thoracoscopy was first described in 1910 [31]. It provides a means of diagnosis for effusions of unknown cause and is particularly important in the diagnosis and management of malignant pleural mesothelioma [2]. It is now recommended by the European Respiratory Society and the European Society of Thoracic Surgeons [56] and the British Thoracic Society [63] early in the diagnostic pathway of patients with a symptomatic exudative pleural effusion

of unknown cause. Thoracoscopy can be performed by surgeons under general anaesthetic – Video-Assisted Thoracoscopic Surgery (VATS) but increasingly is being performed by physicians under local anaesthetic – Local Anaesthetic Thoracoscopy (LAT). In the UK the number of centres offering LAT has increased from 11 in 1999 to 37 in 2009 [63].

Thoracoscopy allows direct visual assessment of the pleura and subsequent biopsy of the abnormal areas as well the option of a therapeutic talc poudrage at the same time. Success rates for pleurodesis via thoracoscopy are generally very good and can be as high as 86% [38] at 1 month.

4.6.1 Local Anaesthetic Thoracoscopy

This allows direct visualisation of the pleura and the option of a therapeutic procedure without the need for a general anaesthetic. This is an important advantage over VATS as many patients requiring thoracoscopy have comorbidities and a reduced performance status leading to significant risk from a general anaesthetic. It should, however, be noted that across Europe many physicians carrying out thoracoscopy choose to perform this in the presence of an anaesthetist (and often a GA). Boutin et al. reviewed 188 cases of mesothelioma that had undergone thoracoscopy [10]. 185/188 (98.4%) were diagnosed after thoracoscopy with a 100% specificity. These results have been mirrored in a number of recent studies [9, 22, 38, 42, 54, 57, 59] with the sensitivity for the diagnosis of mesothelioma ranging from 88% to 100% with a specificity of 100% (see Table 4.1).

The thoracoscope can be flexible, semirigid or rigid. One study comparing the use of rigid with flexible thoracoscope [18] looked at 30 consecutive patients with pleural effusion of unknown cause. The first 10 underwent rigid thoracoscopy whilst the following 20 underwent thoracoscopy with both rigid and flexible thoracoscope. Of those with a final diagnosis of mesothelioma 13/15 (87%) were diagnosed at thoracoscopy. Three biopsies were more informative with the flexible thoracoscope whilst eight were more informative with the rigid thoracoscope. Two biopsies from the flexible thoracoscope were upgraded from reactive pleurisy to mesothelioma by the rigid thoracoscope biopsies. Overall, it was felt that the rigid instrument was superior because it was easier to manipulate and obtain larger biopsies. Munavvar et al. [42] trialled the use of a semirigid thoracoscope, hoping to combine the advantages of the flexible and rigid instruments. They correctly diagnosed 15/15 patients with mesothelioma and did not appear to experience the difficulties previously described with the flexible thoracoscope.

Most centres require at least some pleural fluid to be able to perform thoracoscopy. One centre found approximately 10% of pleural effusions too small for a standard thoracoscope and therefore trialed a smaller instrument [59]. They used a minilaparoscope, which was 3.3 mm rather than the standard 7 mm. They were able to they were able to use this on small, loculated effusions inaccessible to the larger instrument, but no figures were given. They felt that the histological samples were comparable although the samples were smaller with the 3.3mm instrument, only 8F drains could be used, the procedure was 20% longer and conversion to conventional thoracoscopy was sometimes used.

Autofluorescence has also been used to try and improve diagnostic yield by correct identification of the abnormal area to biopsy and to aid with staging by helping to delineate the tumour margins [15]. Preliminary results from 24 patients showed that in all 16 cases of pleural malignancy (seven of whom had mesothelioma) the colour of the affected area changed from white/pink to red, giving a sensitivity of 100%. However, in 2/8 cases of chronic pleurits, there was a similar colour change giving a specificity of 75%.

Alternative forceps has also been used to try and increase the yield. Sasada et al. [55] have used an insulated-tip diathermic knife and

Table 4.1 Results from local anaesthetic thoracoscopy reported since 2000

Trial	Number of thoracoscopies for undiagnosed pleural effusion	Number of patients where biopsies possible	Diagnostic yield %[a]	Number diagnosed with malignancy/ total with malignancy (sensitivity)	Number with mesothelioma	Number diagnosed with mesothelioma
Tassi et al. [59]	30	30	93.4	12/13 (92.3%)	5	5 (100%)
Medford et al.[b] [38]	125	117	90.4	57/60 (95%)	30	29 (96.6%)
Fletcher et al. [22]	50	47	90	37/42 (88.1%)	35	31 (88.6%)
Munavvar et al.[b] [42]	57	54	86.0	32/37 (86.5%)	15	15 (100%)
Blanc et al. [9]	149	142	93.3	77/85 (90.6%)	48	42 (87.5%)
Simpson et al. [57]	89	89	95.5	69/73 (94.5%)	25	24 (96%)
Sakuraba et al. [54]	138	138	97.1	25/27 (92.6%)	10	10 (100%)

[a]Diagnostic yield includes patients where biopsy attempts were unsuccessful
[b]Data not available on patients where biopsies not taken therefore not included when calculating sensitivity for diagnosing malignancy or mesothelioma

compared this to standard flexible forceps in 20 cases. There overall diagnostic yield was low using the standard forceps at 60% and this was increased to 85% with the use of the diathermic knife. Combined, they achieved a sensitivity of 100%. It is worth noting, however, that the diagnosis of mesothelioma was only reached in 3/6 patients using the diathermic knife and in all 6 with the standard forceps.

The main reason for failure or 'non-diagnosis' with LAT was inability to visualise the presence of all the pleural space or significant adhesions, making further investigation too difficult or unsafe. Major complications following thoracoscopy are rare. The BTS guidelines for thoracoscopy reviewed 47 trials that reported complications [63]. Death occurred in 16/4,736 cases (0.34%) but was reduced to 0/2,421 when only studies involving diagnostic thoracoscopy were included. A major contribution to the mortality (9/16 deaths) occurred in a trial of talc poudrage in the USA where ungraded talc particles were used. Major complications (empyema, haemorrhage, port site tumour growth, bronchopleural fistula, post-operative pneumothorax or air leak and pneumonia) were reported in 1.8% cases whilst minor complications (subcutaneous emphysema, minor haemorrhage, operative skin site infection, hypotension during procedure, raised temperature and atrial fibrillation) were reported in 7.3% cases.

4.6.2 Video-Assisted Thoracoscopic Surgery

VATS usually requires general anaesthesia and the placement of a dual lumen tube. VATS is therefore more expensive and time consuming than LAT [53]. There have been no trials directly comparing it to LAT; however, the diagnostic efficacy of the two methods appears comparable. Harris et al. performed VATS on 182 patients [27]. Of the 98 patients with malignancy 29

(30%) had mesothelioma. Their diagnostic sensitivity for malignancy was 95% with a specificity of 100% though they did not state what malignancies the 5 false negatives were. Grossebner et al. reported on 25 patients referred with suspected mesothelioma [26]. Of these 23 had mesothelioma and all were diagnosed from VATS biopsy.

Comparing complications and length of stay in hospital is difficult because more extensive procedures are often carried out in the VATS groups and there are no recent trials looking purely at diagnosis with or without pleurodesis. Studies looking at complications from VATS often include patients with conditions such as empyema that require the extensive breaking down of adhesions, which is more difficult with LAT. However, complications do seem higher with VATS; de Groot et al. reported that nine (26%) of their patients had a major complication [19] whilst Harris et al. reported one death (due to pulmonary laceration), major complications in 15% (haemorrhage, prolonged air leak, empyema, pneumonia, wound infection, congestive cardiac failure, entering peritoneum, biopsy pneumothorax, myocardial infarction, post operative seizure) and minor complications in 8% (subcutaneous emphysema, fever, hypotension, intercostal neuritis) [27]. However, Viskum et al. reported no deaths in their series of 566 examinations with air embolism and cardiac dysrhythmias occurring in less than 1% [60].

4.7 Open Biopsy

Prior to thoracoscopy, this was the next stage in the diagnostic pathway if closed needle biopsy failed. It is now required only if there is obliteration of the pleural space and CT-guided biopsy is not possible or has failed to reach a diagnosis [46].

Its main complication is intractable chest wall pain [7]. Of all the pleural biopsy techniques, this technique has the highest rate of tract seeding [34, 40].

4.8 Prophylactic Radiotherapy

Mesothelioma seeding along pleural intervention tracts is well recognised and present as subcutaneous nodules of varying size. O'Rourke et al. recorded the characteristics of 12 patients that had subcutaneous nodules [44]. 75% reported mild pain, 17% slight pain and 8.3% moderate pain with ulceration in 1 patient. A review of the literature on tract seeding of mesothelioma [34] found that this ranged from 0% to 48% with the risks highest after thoracotomy (24%) and thoracoscopy (9–16%) and lower for smaller incisions such as needle biopsy (0–22%). A recent study of 212 patients who did not receive prophylactic radiotherapy showed that there was an overall rate of tract seeding of 13.2% [40]. Seeding was more common after thoracotomy (25.8%) versus thoracoscopy and closed needle biopsy or CT-guided biopsy (11.0%). 157 patients received chemotherapy and 26 received multi-modal therapy which may explain why the recurrence rate was lower than the 40% reported by Boutin et al. [11] in the control arm of their trial of prophylactic radiotherapy. Boutin showed no tumour seedling in the intervention arm (21 Gy in three fractions) and this trial result led to national guidelines promoting the practise of giving prophylactic radiotherapy after pleural interventions in patients with mesothelioma [1, 2]. Recent trials, however, have failed to support its use. Bydder et al. randomised 43 patients (58 sites) to receive a single dose of radiotherapy (10 Gy) or no radiotherapy [12] whilst O'Rourke et al. recruited 61 patients (60 sites) to have three fractions of 7 Gy or no radiotherapy. Both studies showed no difference in tumour seeding between their control and treatment groups

(10% control vs 7% radiotherapy and 10% control vs 13% radiotherapy, respectively). Important differences between the trials were that all of the patients in Boutin's original trial underwent a thoracoscopy (with a large chest wall incision) whilst only 23–39% in the two more recent trials did. There was also a difference in the radiotherapy regime in Bydder trial. All of these trials are underpowered and there is therefore still the need for a definitive trial to inform practise.

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