

Clinical Application, Performance, and Common Pitfalls of Ultrasound-guided Pleural Biopsy: Our Local Experience

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ABSTRACT

Objectives: To investigate the diagnostic performance of ultrasound-guided pleural biopsy, and discuss its clinical applications, limitations, and pitfalls.

Methods: Clinical notes, pathological and microbiological reports, ultrasound and other imaging studies of 111 patients who underwent ultrasound-guided pleural biopsy from 1 January to 31 December 2014 were reviewed. The technique of the procedures was reviewed and correlated with the pathological yield of the specimens; any minor or major complications were identified. The application and usefulness of the biopsies in directing patient management were studied in view of the final patient outcome, which was determined by clinical and radiological follow-up of patients (range, 1-30 months).

Results: A total of 127 biopsies were performed (left: 64, right: 63) in 111 patients (59 male and 52 female). The mean age of patients was 69 (range, 23-101) years. Overall 89% (n = 113) of biopsies were performed with an 18G Temno needle, with a mean number of 1.4 cores; 75% (n = 83) of biopsies yielded a histologically conclusive specimen. When combined with the results of pleural aspirate cytology (n = 21) and microbiological assessment of both the pleural biopsy and pleural aspirate (n = 11), which were all obtained at the same procedure, a definitive diagnosis was made in up to 90% of cases (n = 115). The final diagnosis of these patients included primary lung carcinoma (n = 23, majority adenocarcinoma), tuberculosis (n = 18), pleural metastases (n = 10), lymphoma (n = 1), chylothorax (n = 1), pyogenic infection (n = 6), undifferentiated inflammation (n = 20), and 'no significant abnormality / pathology detected' (n = 28). A minority of cases remained inconclusive (7%) and the diagnosis was made upon further clinical assessment, including bronchoscopy (bronchoalveolar lavage) [n = 1] and fine-needle aspiration of cervical lymph node (n = 2). For those with a diagnosis made by pleural aspirate cytology or culture, the provision of a pleural biopsy allowed further molecular tests (e.g. tuberculosis-polymerase chain reaction, tumour marker staining, or immunohistochemical tests / mutation detection) to be made to guide further patient management. Major complications (3.9%) included pneumothorax and hydropneumothorax requiring chest drain insertion (n = 3), transfusion (n = 1), and localised infection (n = 1).

Conclusion: Ultrasound-guided pleural biopsy is a safe and useful procedure to help diagnose the aetiology of pleural effusions, in particular to obtain histological diagnoses for suspected tuberculosis and tumours, and to provide tissue for immunohistochemical testing in confirmed malignant conditions. Combination with pleural aspirate analysis and microbiological assessment is suggested to maximise its utility.

Key Words: Lung neoplasms; Pleural effusion

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中文摘要

超聲引導下胸膜活檢的臨床應用、效用和常見的缺點：經驗分享

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目的：探討超聲引導下胸膜活檢的診斷表現，並研究其臨床應用、效用和常見的缺點。

方法：回顧2014年1月1日至12月31日期間共111例接受超聲引導下胸膜活檢的臨床紀錄、病理及微生物報告、超聲和其他影像學報告。回顧這項技術，並與樣本的病理學結果比較是否有任何相關，亦找出是否有任何輕微或嚴重的併發症。按病人的最終結果，並使用其臨床和放射學為期1-30個月隨訪的資料，來界定活檢對於治理病人的應用和用途。

結果：替111名病人（59男和52女）進行了127次活檢（左胸膜64例，右胸膜63例），病人平均年齡69歲（介乎23-101歲）。89%（113例）活檢使用18G Temno針進行，平均每例穿刺1.4次。75%（83例）得到決定性的病理樣本。同一個程序下得到的胸膜抽吸的細胞學結果（21例）和胸膜活檢及胸膜抽吸的微生物評估結果（11例）結合時，90%（115例）得出明確的診斷。最終診斷為原發性肺癌（23例，多為腺癌）、肺結核（18例）、胸膜轉移（10例）、淋巴瘤（1例）、乳糜胸（1例）、化膿性感染（6例）、未定性的炎症（20例）和「無顯著異常」（28例）。有少數病例（7%）的結果未能得出定論，須作進一步的臨床評估，包括支氣管鏡（支氣管肺泡灌洗）1例，頸部淋巴結的細針穿刺2例。至於那些按胸腔穿刺細胞學檢查或培養做出診斷的病例，胸膜活檢標本容許進一步的分子測試（如肺結核聚合酶鏈反應、腫瘤標誌物染色或免疫組化測試 / 突變檢測）來進一步決定治理病人的方法。主要併發症（3.9%）包括氣胸和需胸腔引流的液氣胸（3例）、輸血（1例）和局部感染（1例）。

結論：超聲引導下胸膜活檢是一種安全有用的程序，它有助診斷胸腔積液，尤其是對於疑似結核和腫瘤的病例可以達至病理學診斷，以及確診為惡性腫瘤的病例可以提供組織作免疫檢測。建議結合胸膜穿刺物分析和微生物評估使超聲引導下胸膜活檢發揮最大效用。

INTRODUCTION

Transthoracic ultrasound has long been adopted by radiologists and respiratory physicians as an adjunct to guide closed pleural biopsy, which is often performed together with thoracentesis as one single procedure. Practice varies among different units, however, and the most efficient approach remains uncertain. In this retrospective review, we studied the utility and safety of ultrasound-guided pleural biopsy in the management of undiagnosed pleural effusion.

METHODS

All patients who underwent ultrasound-guided pleural biopsy in the Department of Radiology in a local acute hospital in Hong Kong from 1 January to 31 December 2014 were identified from the electronic Patient Record. Clinical notes, pathological and microbiological reports, ultrasound and other imaging studies related to or performed around the time of the biopsy procedure were

retrospectively reviewed.

All procedures were performed by radiologists, either by FRCR-qualified fellows or by residents supervised by FHKAM-qualified fellows, with 7 to 20 years of experience in interventional radiology.

Patients with significant bleeding risk (e.g. international normalised ratio >1.5 or platelet count <50 x 10⁹/l) were excluded from the procedure. Nonetheless, in exceptional cases and following consensus of the referring team and the operating radiologists, biopsies would be performed in selected patients if platelet concentrate or fresh frozen plasma (at least 6 units) were given just prior to the procedure.

Biopsy Technique

All patients were referred with a prior chest radiograph showing either pleural effusion or pleural mass on

at least one side of the chest. Informed consent was obtained from all patients before the procedure. The region of interest was examined with an ATL 3000 ultrasound unit (Philips Medical Systems, Bothell [WA], USA) using a 2-5 MHz curvilinear probe. Patients with conditions deemed suitable for biopsy (e.g. mass, pleural thickening, or significant pleural effusion with a safe window away from the heart or diaphragm) then underwent skin preparation using an aseptic technique. The exact location for skin incision and needle entry was selected by a combination of manual palpation of the chest wall and sonographic guidance, and was usually aimed at the upper margin of the ribs to avoid injury to the subcostal neurovascular bundles. Local anaesthesia (2-5 ml 2% lignocaine) was injected subcutaneously prior to the skin incision. Pleural biopsy was then performed using a Tru-cut needle under ultrasound guidance and a freehand technique. The specimens were placed in formalin and sent for histology; and if necessary for microbiology work-up in a small amount of normal saline in sterile bottle.

If pleural effusion was present, even if small, ultrasound-guided placement of a 7-Fr pigtail pleural drain was performed immediately following the pleural biopsy using a 18G diamond needle and Seldinger technique using guidewire and 7-Fr dilator. All pleural aspirates were sent for cytology and microbiology work-up.

The choice of biopsy needle was recorded and correlated with the pathological results of the specimens, where the pathology and / or microbiology report of the specimens were reviewed and the yield was calculated. A positive yield was defined as having a pathologically conclusive specimen that could guide further patient management. The pathological diagnoses of the biopsy were also correlated with the final diagnoses and outcome of the patients as determined by clinico-radiological follow-up (at 1-30 months).

The minor and major complications related to the procedures were recorded according to the definition from quality improvement guidelines issued from the Society of Interventional Radiology Standards of Practice Committee.¹ Minor complications were defined as those requiring no therapy, or nominal therapy including overnight admission for observation, and have no consequence. Major complications were defined as those requiring major therapy, unplanned increase in level of care, hospitalisation of >48 hours, permanent

adverse sequelae, or death. Complications that occurred immediately after the procedure or delayed presentations were both included.

Statistical Analysis

The diagnostic yield, sensitivity, specificity, accuracy, and positive and negative predictive values of pleural biopsy sent for histology alone and combined assessment (of biopsy histology, pleural aspirate cytology, and microbiology) were calculated.

RESULTS

A total of 127 biopsies were performed (64 on the left side and 63 on the right side) in 111 patients (59 male and 52 female patients). The mean age of the patients was 69 years (range, 23-101 years). Overall, 16 patients had repeated biopsy, including 12 patients in whom repeated biopsy was on the same side (for once), and four patients who had biopsy taken on both sides, of whom three had separate procedures while one had biopsies taken from both sides at the same time.

Indications for Biopsy

In 122 (96%) cases, the patients were referred for management of pleural effusion, i.e. with a clinical suspicion of parapneumonic effusion, tuberculosis (TB), malignancy (secondary more than primary), or transudative effusion related to fluid overload. On review of these ultrasound procedural reports, the severity of pleural effusion was graded as massive amount (n = 24, 19%), moderate amount (n = 56, 44%), or small amount (n = 23, 18%); in 19 (15%) reports the effusion was not graded. 'Non-target biopsy' was performed for all patients within this group, i.e. random selection of pleura for biopsy under ultrasound guidance, and all these patients, except one, had pleural fluid aspiration and pigtail catheter insertion performed immediately after the biopsy.

Pleural effusion was not present at the time of the biopsy in five (3.9%) patients. These included two (1.6%) patients with pleural mass and three (2.4%) with pleural thickening, which was suspicious of malignancy. Only ultrasound-guided 'target biopsy' of the region of interest was performed in these cases.

Choice of Needles

Of the biopsies, 89% (n = 113) were performed with an 18G Temno needle, with a mean number of 1.4 cores. One biopsy (0.8%) used a larger-size Temno needle (16G), while three (2.4%) used a smaller-size Temno

needle (20G). Eight (6.3%) biopsies used coaxial system (17G) with Temno needle (18G). One used an 18G Franseen needle. In one (0.8%) biopsy procedure, the choice of needle was not documented.

Yield and Diagnostic Performance

Specimen Sent for Histology Alone

Of the biopsies sent for histological examination alone, 83 (75%) yielded a pathologically conclusive specimen. The accuracy in diagnosing TB and malignancy (primary or metastases) was 71%. It had a low sensitivity (54%) but high specificity (98%). The positive predictive value was 97% and negative predictive value was 67%.

Performance of ‘Non-target’ Versus ‘Target’ Biopsy

For the 122 cases referred for work-up of pleural effusion, where random ‘non-target’ biopsy of the pleura was performed, six were rendered “quantity insufficient for diagnosis” (QI). For the remaining 116 cases, it achieved a sensitivity of 53%, specificity of 100%, and accuracy of 76%. For the five cases of ‘target’ biopsy of pleural mass or thickening, two were QI and the other three were able to yield accurate diagnosis of pleural metastases. The number of cases was too small for subgroup analysis, however.

Combined Assessment of Pleural Biopsy (Histology With or Without Microbiology) and Pleural Aspirate (Cytology and Microbiology)

When combined with additional results of pleural aspirate cytology (n=21) and microbiological assessment of both the pleural biopsy and pleural aspirate (n=11), where all were obtained at the same procedure, a definitive diagnosis was made in up to 90% of cases (n=115). The overall accuracy in diagnosing TB and malignancy (primary or metastases) was 91%. It had high sensitivity (92%) and specificity (98%). The positive predictive value was 98% and negative predictive value was 92%.

The final diagnosis of these patients, confirmed on combined assessment, included primary lung carcinoma (n=23, majority adenocarcinoma; Figure 1), TB (n=18; Figure 2), pleural metastases (n=10), lymphoma (n=1), chylothorax (n=1), pyogenic infection (n=6), undifferentiated inflammation (n=20), and ‘no significant abnormality / pathology detected’ (n=28). Of note, only 13 (57%) of the 23 patients with primary lung carcinoma and 12 (67%) of 18 patients with TB were diagnosed by pleural biopsy histology alone. On

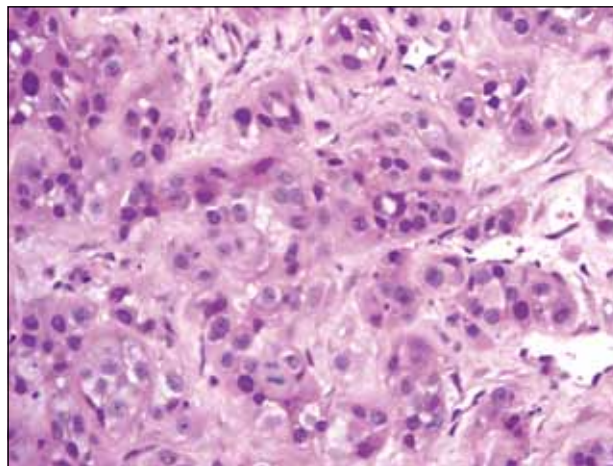


Figure 1. Pathological specimen of a pleural biopsy showing adenocarcinoma of the lung (H&E; original magnification: x 400).

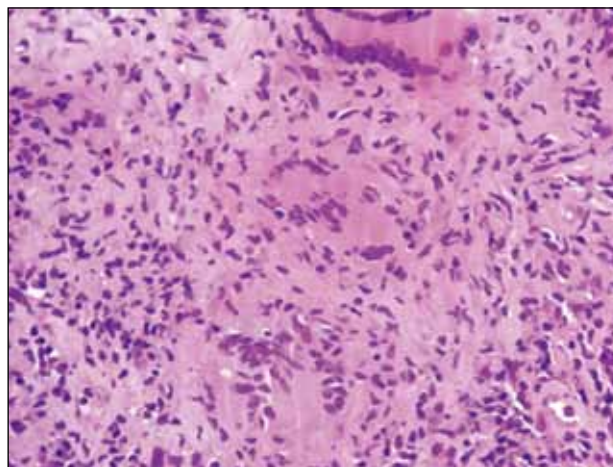


Figure 2. Pathological specimen of pleural biopsy showing tuberculous pleuritis with caseous granuloma (H&E; original magnification: x 400).

the contrary, 9 (90%) out of 10 patients with metastases were diagnosed by pleural biopsy histology.

A minority of cases remained inconclusive (7%; Figure 3) and the diagnosis was made upon further clinical assessment, including bronchoscopy (bronchoalveolar lavage) [n=1] and fine-needle aspiration of cervical lymph node (n=2).

Complications and Adverse Events

Major complications (3.9%) included pneumothorax and hydropneumothorax requiring chest drain insertion (n=3), transfusion (n=1), and localised infection (n=1). Minor complications included pneumothorax not requiring chest drain insertion (n=3, 2.4%). One

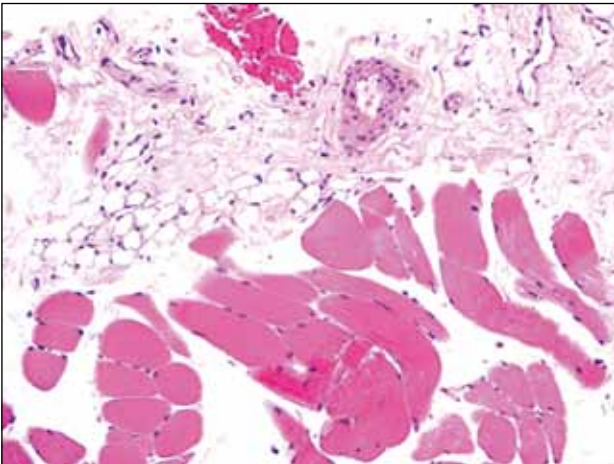


Figure 3. Pathological specimen of a pleural biopsy of quantity insufficient for diagnosis. Only scanty skeletal muscle and fibroadipose tissue is present. No mesothelial cells are evident to suggest pleural tissue (H&E; original magnification: x 200).

patient had a cardiac arrest in the waiting area within 15 minutes of the procedure being performed and was successfully resuscitated, but was noted to have poor baseline cardiopulmonary status that was likely challenged by the agitation during the biopsy procedure. There was no procedure-related death or long-term sequelae identified.

DISCUSSION

Pleural effusion is a common problem encountered in daily medical practice. With TB being endemic in our locality, lung carcinomas being the top killer among all malignancies, and pleural metastases a common final destination in metastatic disease, clinicians often need early cytology and histological diagnosis to help guide patient triage and offer prompt treatment. Thoracocentesis alone has been reported in previous studies to be insufficient for making a diagnosis, especially in malignant conditions where the yield varies greatly among different types of tumours and relies heavily on the experience of the cytopathologist.² For instance, adenocarcinoma has a higher cytological detection rate than squamous cell carcinoma.³ Pleural biopsy therefore serves an important role in making definitive diagnosis of pleural diseases, and also often provides tissue for additional histochemical tests to aid further patient management.

Interventional radiologists have since then taken up a more important role in frontline patient management. Nonetheless, the most efficient, risk-free, and cost-

effective approach to pleural effusion is yet to be determined.²

Yield and Diagnostic Performance

In our cohort, pleural biopsy alone had only a 75% yield for a pathologically conclusive specimen. This is consistent with the figures reported in previous cohorts (ranging from 54% to 76.5%).⁴

Regarding its use to diagnose TB and malignancy, despite having very high specificity (98%) and positive predictive value (97%) that is comparable with the literature, the sensitivity, negative predictive value, and accuracy remained average (54%, 67%, and 71%, respectively). Our sensitivity was lower than the reported figures from literature (70%-94%).³

By combining the histology examination of pleural biopsy with pleural aspirate cytology and microbiology of both the pleural biopsy and aspirate, there is significant improvement in the yield (90%) and diagnostic performance, with accuracy, sensitivity and negative predictive value all reaching over 90%. The specificity and positive predictive value remain comparable with specimen histology alone (both 98%).

Of note, only two-thirds of the cases of TB and around half the cases of primary lung malignancy were diagnosed by histology of the specimen alone. Most cases of pleural metastases, on the contrary, were diagnosed by specimen histology rather than pleural aspirate cytology. It has also been reported that inferior biopsy sites closer to the diaphragm are more likely to elicit positive biopsy samples as metastases are more likely to be found there.⁵

It was also noted that some diagnoses were only depicted on pleural aspirate assessment (including chylothorax, empyema, or definitive infections in parapneumonic effusions). Therefore we believe that sending an extrapleural specimen for culture and sending pleural aspirates for assessment serve an important role in maximising the utility of the procedure.

Choice of Needles

Blind 'closed needle' biopsy of the pleura with an Abrams or Cope needle has been popular among physicians since the 1950s.³ The increasingly adopted alternative, the Tru-cut needle, was first described by McLeod et al in 1989.⁶ Its small calibre has been

thought to reduce the risk of complications, especially in patients with computed tomography–proven pleural thickening or malignancy. Only a few small-scale studies have been performed on non-selected patients with pleural effusion alone, however. As for assessment of suspected TB pleuritis, current evidence still favours Abrams needle as one study found an overall yield of 81.8% for Abrams needle compared with 65% for Tru-cut needle.⁷

Most of the biopsies performed in our unit were performed with an 18G Temno needle, which is smaller than the needles used by Koegelenberg et al² in their recently published prospective study of a similar nature (14G). Nonetheless, the use of a larger cutting needle (14G vs. 18G) has been shown to be of no diagnostic benefit.^{8,9} Only one of our cases adopted the use of a 18G Franseen needle, which yielded insufficient material for diagnosis. Therefore, its use is not advised; it has not been described in the literature and is probably of questionable utility.

The average number of cores obtained by our cohort was 1.4, which is less than the practice reported by other centres (average, 3 cores). This might explain our relatively low yield; as in previous studies, a supradiaphragmatic biopsy site with at least six biopsy samples was shown to be useful for increasing yield.¹⁰ The use of a Coaxial system for obtaining multiple cores of specimens has not been described, although in our cohort the few cases adopting its use all yielded satisfactory results.

Special Care in Tissue Handling

One potential cause of false-negative cultures of pleural biopsy would be a suboptimal sequence in specimen sending. It is always preferable for the very first core obtained to be sent for microbiology in a sterile bottle, flushed out only with sterile normal saline when adherent to the biopsy trocar. The second core can then be sent for histology, often with the trocar inevitably soaked in the bottle of formalin during flushing of the specimen. The order of specimen sending should not be reversed as formalin has a sterilising effect and may result in false-negative culture results.¹¹ In addition and as mentioned previously, taking more cores of specimen should increase the chance of getting a positive yield and minimise sampling errors. One should nonetheless balance the risk of injury to intercostal vessels, pneumothorax, or visceral injury. Figures 4 and 5 show the special care in handling tissues.

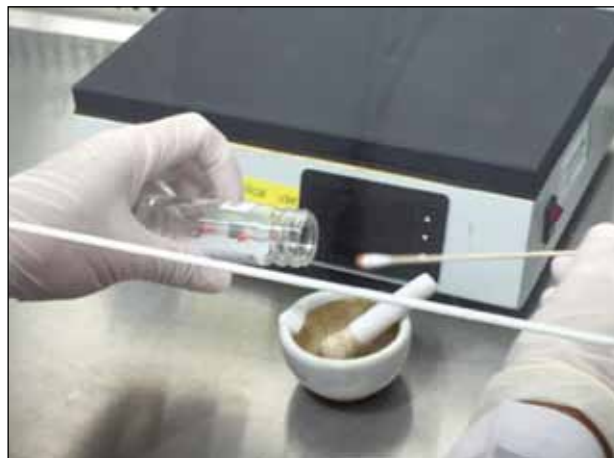


Figure 4. Processing of pleural biopsy specimens in the microbiology laboratory. The tissue is grinded into paste with a mortar and pestle, diluted with sterile normal saline, in a negative-pressure suite as shown. The mixture is then split, to be spread on agar plates for routine microscopy or sent to a negative-pressure tuberculous laboratory for special culture (see Figure 5).



Figure 5. Media for tuberculous culture. L-J medium (right) is the routine medium used, checked for colonies weekly. MGIT-medium (left) is a special broth with enrichment, which is monitored hourly and can help pick up culture-positive cases earlier, usually within 14 days. Both medium are kept in a negative-pressure environment at 35°C. Negative cultures are defined as absence of colony after 6 weeks (MGIT medium) to 8 weeks (L-J medium).

Application of Additional Tests

For those with a diagnosis made by pleural aspirate cytology or culture, the provision of a pleural biopsy specimen allowed further molecular tests (e.g. TB-polymerase chain reaction [TB-PCR], tumour marker

staining, or immunohistochemical tests / mutation detection) to be carried out to guide further patient management. One should note that TB-PCR currently is validated for testing respiratory secretions only, and its use on pleural biopsy specimen is solely for general guidance (i.e. 'off-label use').¹² A positive result strongly supports the diagnosis of tuberculous infection, but a negative result does not exclude the diagnosis.

Complications

The most common complications include pneumothorax and bleeding.^{1,3} The rate also varies between 0% and 10%, although usually on the low side.³ In our cohort, patients at risk of bleeding were those with acute lupus flare up, nephrotic syndrome, or other coagulopathies. Two pneumothoraces were delayed diagnoses as the findings on the initial post-procedural chest radiograph were missed by the attending clinician, and the radiographs were not sent to radiologists for reporting. Careful patient selection, a low threshold for correction of bleeding diatheses before the procedure, and more routine requests of chest radiographs immediately after the biopsy by attending radiologists, are all possible measures to help reduce the risk of adverse outcomes.

Limitations of Study

This study had its limitations. First, it was a retrospective study, so data were incomplete: some reports did not document the choice of needle or grade the severity of pleural effusion. Second, this was a single-centre study, so the diagnostic yield of pleural techniques (e.g. cytology) may not be generalised. Third, as most of the cases (n=122) were 'non-target biopsy' of the pleura under ultrasound guidance, and only five cases were 'target biopsy' of specific region of interest, subgroup analysis comparing the performance of these two approaches was not feasible. Last, the effect of antibiotics (e.g. quinolones that are known to have anti-TB action) before biopsy and thoracentesis was not studied. Larger-scale prospective and randomised study may be helpful to further evaluate the performance of 'targeted biopsy' of pleural mass, the utility of pleural biopsy versus pleural aspirate analysis for assessment of effusion, or a combination of both.

Alternative Biopsy Method: a Discussion on Comparison and Contrast

Local anaesthetic thoracoscopy (LAT), a commonly used alternative method for pleural biopsy, involves insertion of a port under local anaesthesia into the pleural space,

with the patient lying in a lateral decubitus position. The pleural fluid is first removed by a suction catheter, and a camera is introduced to visualise and examine the pleura. Any abnormal pleural tissue can be biopsied and a chest drain then inserted to allow for re-expansion of the lung after the procedure. Similar to our ultrasound-guided biopsy procedure, LAT is also reported to have a high sensitivity for diagnosing malignant pleural disease (91%) and TB (up to 100%), and a low complication rate (major complication rate 1.8%).³

The potential advantage of this procedure over ultrasound-guided biopsy is that it offers a combined diagnostic and therapeutic procedure in one stop. It allows large-volume thoracentesis, direct visualisation, and hence more targeted biopsy (including assessment of the general appearance of the pleura, as compared with grey scale images on ultrasound), and if necessary talc poudrage to prevent recurrence of the effusion.³

LAT also has several disadvantages, however, and this explains why ultrasound-guided biopsy remains a relatively popular first-line procedure in our local institutes. LAT has to be performed in an operating theatre or procedure room with access to full hospital services if required. It can take from 30 minutes to several hours, as the procedure itself takes a relatively long learning curve and is heavily dependent on the operator's technique, and the demand for this is higher than that for the ultrasound-guided procedure. As the patient is required to lie in the decubitus position for a longer period of time, frail old patients or dyspnoeic patients may be deemed unfit for LAT. The risk for patients with bleeding tendency, despite correction before the procedure, would also be higher for LAT than for ultrasound-guided biopsy.³ To conclude, both procedures have their advantages and weak points, and hence they remain complementary in the management of pleural diseases.

CONCLUSION

Ultrasound-guided Tru-cut pleural biopsy is a safe and useful procedure to help diagnose the aetiology of pleural effusions, in particular, to obtain histological diagnosis for suspected TB or tumours, and to provide tissue for immunohistochemical testing in confirmed malignant conditions. Combination with pleural aspirate analysis and microbiological assessment is suggested to maximise its utility.

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