Ultrasound – Assisted
Transthoracic Diagnostic Techniques

by
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DECLARATION

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SUMMARY

Although transthoracic ultrasonography is a well established modality, it is still underutilised by chest physicians. The aim of this research project was to investigate the feasibility, diagnostic yield and safety of ultrasound(US)-assisted transthoracic biopsies performed by clinicians in various settings relevant to daily practice of respiratory medicine. We conducted four clinical trials which are summarised below:

1. In a prospective study on the feasibility of US-assisted transthoracic fine needle aspiration (TTFNA) of drowned lung secondary to a proximal mass lesion, a novel indication for US-assisted TTFNA was described. TTFNA passes >20mm from the visceral pleura had a sensitivity of 74.2% and were also more likely to contain malignant cells than more superficial passes. The surprisingly high yield and the fact that no serious complications were observed validated this approach, which may be an alternative to bronchoscopy.

2. In the largest single-centre study on US-assisted TTFNA with rapid on-site evaluation (ROSE) and cutting needle biopsy (CNB) in the setting of superior vena cava (SVC) syndrome ever reported, we were able to accurately diagnose 96% of all patients who presented with an associated mass lesion that abutted or infiltrated the chest wall. No pneumothoraces or major haemorrhage was caused. We also validated the single-session

approach, and were able to conclude that US-assisted TTFNA (with ROSE) is the initial investigation of choice in suspected bronchogenic carcinoma, whereas both TTFNA and CNB need to be performed in all other cases.

3. We continued to validate the novel single-session sequential approach in a study on anterosuperior mediastinal masses. US-assisted TTFNA with ROSE was performed on 45 consecutive patients, immediately followed by CNB where a provisional diagnosis of epithelial carcinoma or probable tuberculosis (TB) could not be established. An accurate cytological diagnosis was made in 73.3%, and was more likely to be diagnostic in epithelial carcinoma and TB than all other pathology (p<0.001). CNB yielded a diagnosis in 88.2%. Overall 93.3% of patients were diagnosed by the single-session approach. No pneumothorax or major haemorrhage was observed.

4. In a prospective study, we compared US-assisted Abrams and Tru-Cut needle biopsies with regard to their yield for pleural TB. Pleural biopsy specimens obtained with Abrams needles contained pleural tissue in 91.0% of cases and were diagnostic in 81.8%, whereas Tru-Cut needle biopsy specimens only contained pleural tissue in 78.7% (p=0.015) and were diagnostic in 65.2% (p=0.022).

In conclusion, we investigated the feasibility of US-assisted biopsies performed by respiratory physicians in various settings, and consistently found acceptable to very high diagnostic yields with minimal complications. Furthermore, we were able to validate a novel indication for US-assisted TTFNA (US-assisted TTFNA of drowned lung), validate the use of a single-session sequential approach (US-assisted TTFNA with ROSE followed by CNB where indicated) in at least two clinical settings (SVC syndrome and anterosuperior mediastinal masses) and we were able to show that US-assisted Abrams needle biopsy is superior to Tru-Cut needles biopsy when histological confirmation of TB pleuritis is required.

OPSOMMING

Alhoewel transtorakale ultrasonografie 'n gevestigde modaliteit is, word dit onderbenut deur pulmonoloë. Die doel van hierdie navorsingsprojek was om die praktiese uitvoerbaarheid, diagnostiese opbrengs en veiligheid van sonargerigte transtorakale biopsies uitgevoer deur klinici in verskeie situasies relevant tot die alledaagse praktyk te ontleed. Ons het vier kliniese proewe uitgevoer wat hieronder opgesom word:

1. In 'n prospektiewe studie oor die praktiese uitvoerbaarheid van sonargerigte transtorakale fyn naald aspirasie (TTFNA) van areas van obstruktiewe pneumonitis sekondêr tot proksimale massa letsels, is 'n nuwe indikasie vir sonargerigte TTFNA beskryf. TTFNA aspirasies wat >20mm van die visserale pleura geneem is, het 'n sensitiwiteit van 74.2% gehad en was meer geneig om maligne selle op te lewer as meer oppervlakkige aspirasies. Die verbasende hoë diagnostiese sensitiwiteit en afwesigheid van ernstige komplikasies het die praktiese waarde van hierdie benadering bevestig.

2. In die grootste studie nog oor sonargerigte TTFNA met spoedige in-teater evalusies (SITE) en sny-naald biopsie (SNB) in die teenwoordigheid van superior vena cava (SVC) sindroom, kon ons 96% van pasiënte wat presenteer het met 'n geassosieerde massa letsel wat die borskaswand

betrek, akkuraat diagnoseer. Geen pneumotoraks of major bloeding is waargeneem nie. Ons kon ook die praktiese uitvoerbaarheid van 'n enkel-sessie benadering bevestig en kon tot die gevolgtrekking kom dat sonargerigte TTFNA (met SITE) die aanvanklike ondersoek van keuse is waar bronguskarsinoom vermoed word, maar dat beide TTFNA en SNB noodsaaklik is in ander gevalle.

3. Ons het voortgegaan om die waarde van die nuwe enkel-sessie benadering te bevestig in 'n studie oor antero-superior mediastinale massas. Sonargerigte TTFNA met SITE is uitgevoer op 45 pasiënte en in gevalle waar 'n voorlopige diagnose van epiteliale karsinoom of waarskynlike tuberkulose (TB) nie bevestig kon word nie, is dit onmiddelik gevolg deur SNB. 'n Akkurate sitologiese diagnose is gemaak in 73.3% van gevalle en meer algemeen in epiteliale karsinoom en TB as ander patologie (p<001). SNB was diagnosties in 88.2%. In 93.3% kon 'n diagnose verkry word met die enkel-sessie benadering. Geen pneumotoraks of major bloeding is waargeneem nie.

4. In 'n prospektiewe studie is sonargerigte Abrams naald en Tru-Cut naald biopsies se opbrengs vir pleurale TB met mekaar vergelyk. Pleurale biopsie monsters wat met 'n Abrams naalde geneem is, het pleurale weefsel in 91.0% gevalle getoon en was diagnosties in 81.8%, vergeleke

met Tru-Cut naalde wat slegs in 87.7% pleurale weefsel opgelewer het (p=0.015) en wat net in in 65.2% diagnosties was (p=0.022).

Opsommend het ons die praktiese uitvoerbaarheid van sonargerigte biopsies uitgevoer deur pulmonoloë in veskeie kliniese situasies nagevors, en het deurlopend aanvaarbare tot hoë diagnostiese opbrengste gevind met minimale komplikasies. Verder kon ons 'n nuwe indikasie vir sonargerigte TTFNA beskryf en evalueer (sonargerigte TTFNA van obstruktiewe pneumonitis); 'n enkel-sessie sekwensiële benadering se waarde bevestig (sonargerigte TTFNA met SITE, gevolg deur SNB waar aangedui) in ten minste twee kliniese situasies (SVC sindroom en anterosuperior mediastinale massas); en was dit moontlik om te bewys dat UK-geleide Abrams naald biopsies superior tot Tru-cut naald biopsies is in die histologiese bevestiging van TB pleuritis.

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DEDICATION

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ABBREVIATIONS

ADA	Adenosine deaminase
AIDS	Acquired Immune Deficiency Syndrome
CNB	Cutting needle biopsy
CT	Computed tomography (scan)
FNA	Fine needle aspiration
HIV	Human immunodeficiency virus
NSCLC	Non-small cell lung cancer
PTB	Pulmonary tuberculosis
ROSE	Rapid on-site evaluation (of cytological specimens)
SCLC	Small cell lung cancer
SD	Standard deviation
SVC	Superior vena cava
TB	Tuberculosis
TTFNA	Transthoracic fine needle aspiration
US	Ultrasound

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Chapter 1

INTRODUCTION

Transthoracic ultrasonography (US) is a well established modality in the evaluation of respiratory disorders, but is still not utilised to its full potential by chest physicians, both in the developed and developing world [1-7]. Transthoracic US has many advantages that make it an ideal investigation in a health care system with limited resources, the most significant being its cost in terms of acquisition, maintenance and consumables. Furthermore it is mobile, utilises no radiation and has a short examination time [1-5]. Moreover, US-assisted biopsy can be performed by a single clinician with no sedation and minimal monitoring, even potentially outside of theatre [1-3].

Transthoracic Ultrasound: Technical Aspects

Basic transthoracic US can be performed by means of the most basic entry-level two-dimensional ultrasound equipment [1,2]. A low frequency curvilinear probe (range: 2. 5 MHz) is essential, whereas a high frequency linear probe (range: 5. 10 MHz) is a useful addition [1,2]. Higher frequency gives better resolution closer to the probe, but at the cost of lower depth penetration. A lower frequency probe with its curvilinear shape is ideal for covering a large area and is therefore suitable for initial screening of superficial and deeper structures, while the high frequency probe with a linear shape is used for refined assessment of an

abnormal chest wall or pleural area [1,2]. A comprehensive review of the technical aspects of transthoracic ultrasonography is presented in Chapter 2.

Diagnostic Transthoracic Ultrasonography

Transthoracic US is frequently utilised for the qualitative and quantitative description of pleural effusions and the assessment of pleural thickening, pleural tumours and chest wall abnormalities [1-8]. Furthermore, US can visualise parenchymal pathology (tumours, consolidations and other processes) provided they abut the pleura [1-7]. More advanced applications include the detection of pneumothoraces and pulmonary emboli [1,2]. A comprehensive review of the practical application of diagnostic transthoracic US is presented in Chapter 2.

Ultrasound-Assisted Interventions

Principles and Basis Applications

As a guide to diagnostic procedures, US not only potentially increases the diagnostic yield, but also minimises risk compared to blind procedures [1-8]. It is therefore ideal for image-guided chest wall, pleural, peripheral pulmonary and mediastinal interventions, including diagnostic thoracentesis and biopsy [1-8]. Real-time US guidance of needle aspiration and/or needle biopsy may be performed with the aid of commercially available reusable probes. Most experienced physicians, however, prefer and utilise the "freehand" technique. After appropriate patient positioning, the intended site of needle insertion is sonographically identified and marked, while the direction, depth of interest and

safety range for the procedure are determined [1,2]. The procedure is then performed (not under real-time guidance), while the patient is requested not to change position in order to avoid a positional shift of the area of interest relative to the skin mark.

Transthoracic US assistance improves the success rate of pleural aspirations [9-11]. The success rate of US-guided thoracentesis can be as high as 97% [11]. US detects pleural fluid septations with greater sensitivity than computed tomography (CT) and also minimises the risk of visceral puncture [10]. Moreover, the risk of pneumothorax following aspirations is reduced, independent of the size of the effusion [12].

US is also ideal for identifying the optimal site for safe and effective intercostal drainage (ICD). The current British Thoracic Society pleural disease guideline states that US-guidance is strongly recommended for all drainage of pleural fluid [11]. This is particularly relevant in patients with loculated parapneumonic effusions, where thickened parietal pleura, adhesions or loculations often complicate insertion. Depending on operator experience, US may also guide further decisions regarding the need for intrapleural fibrinolytics, thoracoscopy or for surgical intervention in addition to tube drainage and antibiotics [13].

A recent survey carried out in the United Kingdom highlighted the dangers of blind pleural procedures: 67 of 101 trusts reported at least one serious

complication from ICD. In all, 47 cases of serious lung or chest wall injuries with 8 deaths and 6 cases of ICD placement on the wrong side were described [14].

Closed Pleural Biopsies

Closed pleural biopsy needles were introduced forty years after Jacobaeus established thoracoscopy. Within a decade various needles were described, including the Abrams (guillotine), Cope (hook) and Vim-Silverman (puncture) needles [15-18]. Of these devices, the Abrams needle was consistently shown to have a superior yield and became the most widely used instrument [15,19]. Cutting needle biopsy (CNB) was a relatively recent addition: In 1989 Macleod described the use of blind Tru-cut needle biopsy as an alternative to Abrams needles in patients who present with large pleural effusions [20].

A significant fall in the incidence of tuberculosis (TB) in most of the developed world over the last 50 years led to an equally significant reduction in operator experience amongst respiratory physicians, to the point where even relatively experienced pulmonologists have become reluctant to utilise blind closed pleural biopsy even in settings where reported diagnostic yields are relatively high [11]. Unaided (blind) closed pleural biopsy has a relatively modest diagnostic yield, particularly for pleural malignancy. The diagnostic yield of blind Abrams needle biopsies is less than 60% for pleural malignancy [21]. Tuberculous pleuritis leads to more homogenous pleural involvement, and unaided closed biopsies are therefore more likely to be diagnostic for pleural tuberculosis. Published results

vary, but the reported diagnostic yields are generally in the order of 80% [22-26]. Kirsch and co-workers even reported a yield of 87%, provided at least six specimens are harvested [27].

Recent studies have suggested that image-guidance may significantly increase the yield while also decreasing the risk for complications [28-30]. In fact, Qureshi et al. were able to identify 73% of malignant effusions on appearance alone [28]. They found that pleural thickening >10mm, pleural nodularity and diaphragmatic thickening >7mm were highly suggestive of malignant disease. Chang previously found that the diagnostic yield of US-guided Tru-cut pleural biopsy to be as high as 87% for all pleural pathologies (77% for malignancies) [29]. For malignant mesothelioma, Diacon showed that this figure may be as high as 100% [30].

Transthoracic Fine Needle Aspiration and Needle Biopsy of Solid Tumours
Peripheral lung, pleural based and mediastinal masses are detectable by US provided that chest wall contact is present [1,2]. These tumours most frequently appear hypoechoic with posterior acoustic enhancement and are ideally suited for transthoracic US-assisted biopsy, as no aerated lung needs to be transversed with the biopsy device [1-4]. US-assisted transthoracic fine needle aspiration (TTFNA) has the added advantage that it may be performed outside of theatre, which may be an important practical consideration in patients with advanced disease. TTFNA is generally performed under local anaesthesia with a 22-gauge injection-type or spinal needle [1,2]. CNB follow the same principles as TTFNA,

but the devices are more invasive and carry the higher risk of vascular or visceral trauma [2]. US has the added advantage that it may be used to screen for a pneumothorax following transthoracic biopsy, albeit a rare complication [1,2]. In fact, one study found US to be superior to chest radiographs in diagnosing pneumothoraces [31].

Diacon and co-workers found that US-assisted CNB had a sensitivity of 85.5% for lung tumours abutting the chest wall and a 100% for mesothelioma [30]. They observed a pneumothorax rate of 4%, and concluded that US-assisted CNB was safe in the hands of pulmonologists. In a subsequent study the same investigators found that US-assisted TTFNA with rapid on-site evaluation (ROSE) by a cytopathologist of tumours abutting the chest wall had a diagnostic yield of 82%. CNB was shown to be diagnostic in 76%, whereas CNB and TTFNA had a combined yield of 89% [32]. Both US-guided CNB and FNA had a low complication rate, with pneumothoraces observed in 4 and 1.3% respectively [32]. Subanalyses of their data showed that US-guided TTFNA was significantly superior to CNB in confirming a diagnosis of bronchogenic carcinoma (95% vs. 81%, $p = 0.006$), whereas CNB was superior in cases of non-carcinomatous tumours and non-malignant lesions. Schubert et al. reported similar findings [33]. Both investigators concluded that CNB may be reserved for cases where cytology is non-contributory and a diagnosis other than lung cancer is suspected.

In a landmark study from the late 1980s, Saito and co-workers were able to diagnose 31 of 45 mediastinal masses by means of US-guided needle biopsies [34]. In total, 13 of 15 patients with malignancies had diagnostic biopsies. Yang et al. subsequently found Tru-Cut needles to have a diagnostic yield of 88.9% for mediastinal tumours [35]. Yang also pioneered the supraclavicular approach for US-guided biopsies of superior mediastinal tumours [36], when they obtained diagnostic biopsies from 12 of 15 patients. Sawhney et al. reported the highest sensitivity: they were able to diagnose all 25 patients with mediastinal masses by means of US-guided Tru-cut needle biopsy [37]. Samad and co-workers reported a more modest yield of 80.5% [38]. Comparable findings were subsequently reported by Anderson, Ikezoe and Tikkakoshi [39-41]. Studies that included more than 40 patients reported a 1-6% complication rate from CNB, with pneumothoraces, haemothoraces and haemoptysis the most common serious complications [34-36,38-40].

Other Ultrasound-Assisted Interventions

The indications for US-assisted transthoracic TTFNA and CNB are not limited to solid tumours. Yang and co-workers, for example, reported a diagnostic yield as high as 93% with US-assisted biopsies of pulmonary consolidation of unknown aetiology [42]. This procedure is potentially useful in the immunocompromised patient, given the extensive differential diagnosis. Yang was also able to sonographically demonstrate abscess cavities in 94% of 35 patients with radiologically confirmed lung abscesses, and was able to obtain pathogens by means of aspirates in 90% [43].

Central Theme and Aims of Research Project

The central theme of this PhD research project was to investigate the feasibility, diagnostic yield and safety of US-assisted transthoracic biopsies performed by clinicians in various settings relevant to the daily practice of respiratory physicians. The ultimate aim was not only to broaden the potential indications for US-assisted transthoracic biopsies by investigating novel indications, but also to compare various biopsy devices and to validate a novel, single-session sequential approach of US-assisted transthoracic fine needle aspiration (TTFNA) with rapid on-site evaluation (ROSE) followed by cutting needle biopsy (CNB) in various settings. The central hypothesis was that US-assisted transthoracic diagnostic techniques in the hands of chest physicians would be safe and have a diagnostic yield comparable to more invasive investigations (generally perceived to be the gold standards). Four separate studies were conceptualised and designed in order to address the aims and central hypothesis of this research project.

Study Specific Aims & Objectives

Study 1 – US-assisted biopsy in a novel clinical setting: US-assisted TTFNA of drowned lung

The parenchyma of normal aerated lungs is not discernable by means of US [1-5]. Proximal lung tumours are therefore not considered amenable to US-assisted transthoracic FNA or CNB. Proximal lung tumours may, however, cause varying

degrees of pulmonary collapse (resorptive atelectasis) and postobstructive pneumonitis. %Drowned lung+ is a radiological term often used to describe these areas which are considered to represent accumulated secretions, and typified on chest CT by enhanced pulmonary vasculature contrasted against surrounding pulmonary consolidation [44,45]. Provided the consolidation extends to the chest wall, fluid filled airways are detectable on US as fluid bronchograms, which are dynamic anechoic tubular structures within consolidated lung that fluctuate with respiration [1,2,46].

The diagnostic yield for malignancy of US-assisted TTFNA harvested from areas of areas of drowned lung secondary to proximal tumours is not known. Moreover, endobronchial inspection and sampling by means of flexible bronchoscopy is generally considered the standard diagnostic approach in this scenario [47,48]. We therefore aimed to explore the feasibility of US-assisted TTFNA as an alternative to bronchoscopy in this setting by prospectively investigating its diagnostic yield and safety. This aim is addressed in Chapter 3.

Studies 2 and 3 – The single-session approach: US-assisted TTFNA with ROSE followed by CNB (where indicated) in two novel clinical settings
US-assisted TTFNA and CNB in the setting of chest wall, pleural and pulmonary malignancies abutting the chest wall have a very high diagnostic yield and are safe, even in the hands of non-radiologists [30,32,48]. TTFNA with ROSE and CNB have been shown to be complementary techniques for intrathoracic mass

lesions [30,32,33]. The former has a significantly higher sensitivity for bronchogenic carcinoma, but the latter remains superior in non-carcinomatous tumours and in benign lesions [30,32,33]. Ultrasound and the addition of ROSE therefore potentially allow for a single-session approach, with US-assisted TTFNA followed by CNB limited to those cases where diagnostically useful material cannot be confirmed [30,32,33]. Although this single-session approach has been validated in pulmonary and pleural mass lesions [30,32,33], its applicability to other clinical settings remains unknown. We therefore aimed to assess the diagnostic yield and safety of the single-session sequential approach in two novel settings: superior vena cava syndrome and anterosuperior mediastinal masses. These aims are addressed in Chapter 4.

Study 4 – US-assisted pleural biopsy: A direct comparison of the diagnostic yield of Abrams and Tru-cut needle biopsies for pleural tuberculosis

Although a presumptive diagnosis of pleural tuberculosis (TB) can be made based on elevated levels of adenosine deaminase (ADA) and interferon-gamma in pleural fluid, actual histological and/or microbiological confirmation of TB pleuritis remains the gold standard [22,49]. Pleural tissue can be harvested either by means of closed biopsy, thoracoscopy or open surgical biopsy [22,49]. Access to thoracoscopy and open surgical biopsy is limited in many parts of the world where closed biopsies remain the preferred initial investigation [22].

In a small prospective study, Chang and co-workers found a superior diagnostic yield for pleural TB with US-assisted Tru-cut compared to traditional Abrams needle biopsies [29]. In that study, which was performed in an area with moderate TB prevalence, only two of ten Abrams needle biopsies in cases of pleural TB were diagnostic. As most authors have reported diagnostic sensitivities in the order of 50-85% for Abrams needle biopsies [22,49,50], uncertainty remained as to which closed pleural biopsy techniques was superior for the confirmation of pleural TB.

The aim of this prospective study was to compare US-assisted Abrams needle biopsies to US-assisted Tru-cut needle biopsies with regards to their diagnostic yield for pleural TB. This aim is addressed in Chapter 5.

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Chapter 2

COMPREHENSIVE LITERATURE REVIEW

> **Koegelenberg CFN, Bolliger CT, Diacon AH. Pleural Ultrasound; in Light RW, Lee YC (eds). Textbook of Pleural Disease. 2nd Edn. London, Hodder & Stoughton, 2008, pp 275-283**

> **Koegelenberg CFN, Diacon AH, Bolliger CT. Transthoracic Ultrasound of the Chest Wall, Pleura, and the Peripheral Lung; in Bollger, CT, Herth FJF, Mayo PH, Miyazama T, Beamis JF (eds). Progress in Respiratory Research. Clinical Chest Ultrasound. Basel, Karger, 2009, vol 37, pp 22-33**

21

Radiology: pleural ultrasound

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INTRODUCTION

Although the introduction of diagnostic sonography of the abdomen dates back to the late 1940s, ultrasonography of the thorax lagged behind by many decades. The inability of ultrasound (US) to penetrate aerated tissue has diverted chest physicians from recognizing its excellent ability to visualize the chest wall, pleura and pathology of lung abutting the pleura. The major advantages of thoracic US include its dynamic properties, low cost, lack of radiation, mobility and short examination time.[1–6] It is also well suited for use in intensive care units, where suboptimal conditions for radiography make the diagnosis of clinically significant thoracic abnormalities difficult.[3] Furthermore, US of the chest is increasingly being used to guide interventional procedures, such as thoracentesis, biopsies of the chest wall, pleura or abutting lung and the placement of intercostal drains. The indications for pleural and chest wall US are summarized in Table 21.1. The main aim of this chapter is to demystify ultrasonography for the chest physician by reviewing the basic principles and techniques from the perspective of the non-radiologist.

AN APPROACH TO THORACIC ULTRASONOGRAPHY

Technical principles

'Ultrasounds' are acoustic waves with a frequency above human hearing. Most US scanners operate in the frequency range of 2–15 megahertz (MHz). A very basic understanding of how the US scanner employs these ultra-

Table 21.1   The indications for pleural and chest wall ultrasound[a]

Indications
1   To detect a pleural effusion and guide thoracentesis and drainage, especially in small or loculated effusions
2   To differentiate a subpulmonary effusion from a subphrenic fluid accumulation and diaphragm paralysis in radiographically elevated hemidiaphragms
3   To localize pleural tumors, pleural thickening and lung tumors that abut the pleural surface and to guide needle aspiration and/or biopsies thereof
4   To assist the evaluation of patients with pleuritic chest pain
5   To clarify the nature of unknown pleural densities
6   To recognize pneumothorax, especially for emergency situations, or when radiographic equipment is unavailable
7   To localize pleural fluid prior to a thoracoscopy
8   To evaluate empyema and a parapneumonic pleural effusion in order to detect loculations and septae, and to guide aspiration with or without tube drainage

[a]Adapted with permission from: Tsai TH, Yang PC. Ultrasound in the diagnosis and management of pleural disease. *Curr Opin Pulm Med* 2003; **9**: 282–90.

sounds to generate an image is paramount in order to comprehend its uses and limitations.

The US unit produces sound by means of a piezoelectric transducer encased in a handheld probe that is attached to the processing unit with an electric cable. This

sound is focused in the transducer and is efficiently transmitted into the thorax. Ultrasound waves are propagated in liquid media (e.g. pleural effusions) or in tissues with a high water content (e.g. muscle, liver, consolidated lung or tumors), but are reflected off interfaces between dissimilar densities (e.g. gas or bone). If the US encounters gas (e.g. normal aerated lungs or a pneumothorax) or solids (e.g. ribs), the density difference is so great that most of the acoustic energy is reflected. This phenomenon is known as acoustical impedance and explains why structures deeper than the visceral pleura are invisible by means of ultrasonography in the non-diseased state.

The reflected part of the sound waves is detected as an echo. The time delay between emitted US and the received echo is used to calculate the depth of the structure causing the reflection. Furthermore, the greater the difference between acoustic impedances, the larger the echo will be. The transducer captures sound waves returning to the probe and converts these echoes into electrical pulses, which are ultimately processed and transformed into a digital image. The intensity and distribution of the pixels appearing on the screen is determined by three characteristics of the echo, namely (1) its direction, (2) its intensity and (3) the time elapsed from emission to capture. Images may contain 'hyperechoic' or white areas caused by high-amplitude echoes and 'hypoechoic' or dark areas from low-amplitude echoes.

The ultrasound unit

Adequate pleural and chest wall ultrasonography can be performed by means of the most basic, entry-level, two-dimensional black-and-white US equipment. Doppler and color flow echo are not required for routine pleural examination. For documentation of still images, a basic thermal printer is sufficient. Most modern scanners also allow for the transferral of images to data storage devices and can capture dynamic information in video format, which is preferable.

The US scanner is adorned by a confusing array of controls and options. It is imperative that the occasional sonographer familiarizes themself with the scanner and its most important function keys. It is helpful to differentiate between settings to optimize the machine for thoracic US in general, and controls for fine tuning the scanning for the individual case. For occasional thoracic scanning, basic settings programmed for abdominal sonography will suffice. However, if a machine is to be used mainly for thoracic US, we recommend calling upon an expert to assist with the basic setting up of the machine, which includes contrast and brightness of the monitor as well as default settings of depth and gain when using different probes.

Thoracic US is best performed with two transducers. A 3.7 MHz (range: 2–5 MHz) curvilinear probe is compulsory, and an 8 MHz (range: 5–10 MHz) linear probe is a very helpful addition. As a rule, higher frequency gives better resolution closer to the probe, but at the cost of lower penetration. A lower frequency probe (e.g. 3.5 MHz) with curvilinear shape for covering a large area is therefore suitable for initial screening of superficial and deeper structures, while the high frequency probe (e.g. 8 MHz) with a linear shape is used for refined assessment of an abnormal chest wall or pleural area.

The three most important controls on a standard keyboard are 'depth', 'gain' and 'freeze'. The depth function is a digital zoom that defines what portion of the scanned image is displayed on the monitor at what magnification. The scale is displayed on a vertical axis. Obese subjects or patients with a large effusion or intrathoracic tumors may require a depth setting of up to 12 cm. High frequency scanning is performed at a maximum depth of around 3–4 cm. The gain is, in essence, a measure for the amplification of the echoes and determines the brightness of the image. The freeze function allows for the capturing of still images, and to perform measurements with the appropriate keys and the trackball. Only experienced users should change advanced parameters, such as the frequency of a particular probe.

Patient positioning

The optimal patient position for scanning is a paramount but under-appreciated aspect. Sonographic access to the chest can be achieved via the abdomen, intercostal spaces or the upper thoracic aperture (supraclavicular fossa). It is important to review a patient's chest radiograph and computed tomography (CT) scan prior to performing a chest US examination. This will not only identify the area of interest, but will also guide the positioning of the patient. The posterior chest is best scanned with the patient in the sitting position using a bedside table as an armrest (Figure 21.1a,b), whereas the lateral and anterior chest wall can be examined with the patient in either the lateral decubitus or even supine position (Figure 21.1c). Maximum visualization of the lung and pleura is achieved by examining along the intercostal spaces. Raising the arm above the patient's head increases the intercostal space distance and facilitates scanning in erect or recumbent positions. A patient can fold the arms across the chest in order to displace the scapulae when surveying the upper posterior thorax. Superior sulcus pathology can be visualized apically with the patient in the supine or sitting position.

Scanning

Once the patient is adequately positioned and the area of interest is identified, liberal application of gel is the final step before scanning. It is advisable to hold the probe like a pen for writing on paper, and not like chalk for writing on a blackboard (Figure 21.1b). Experienced sonographers keep their eyes on the screen while their hand moves the probe across the area of interest and provides the posi-
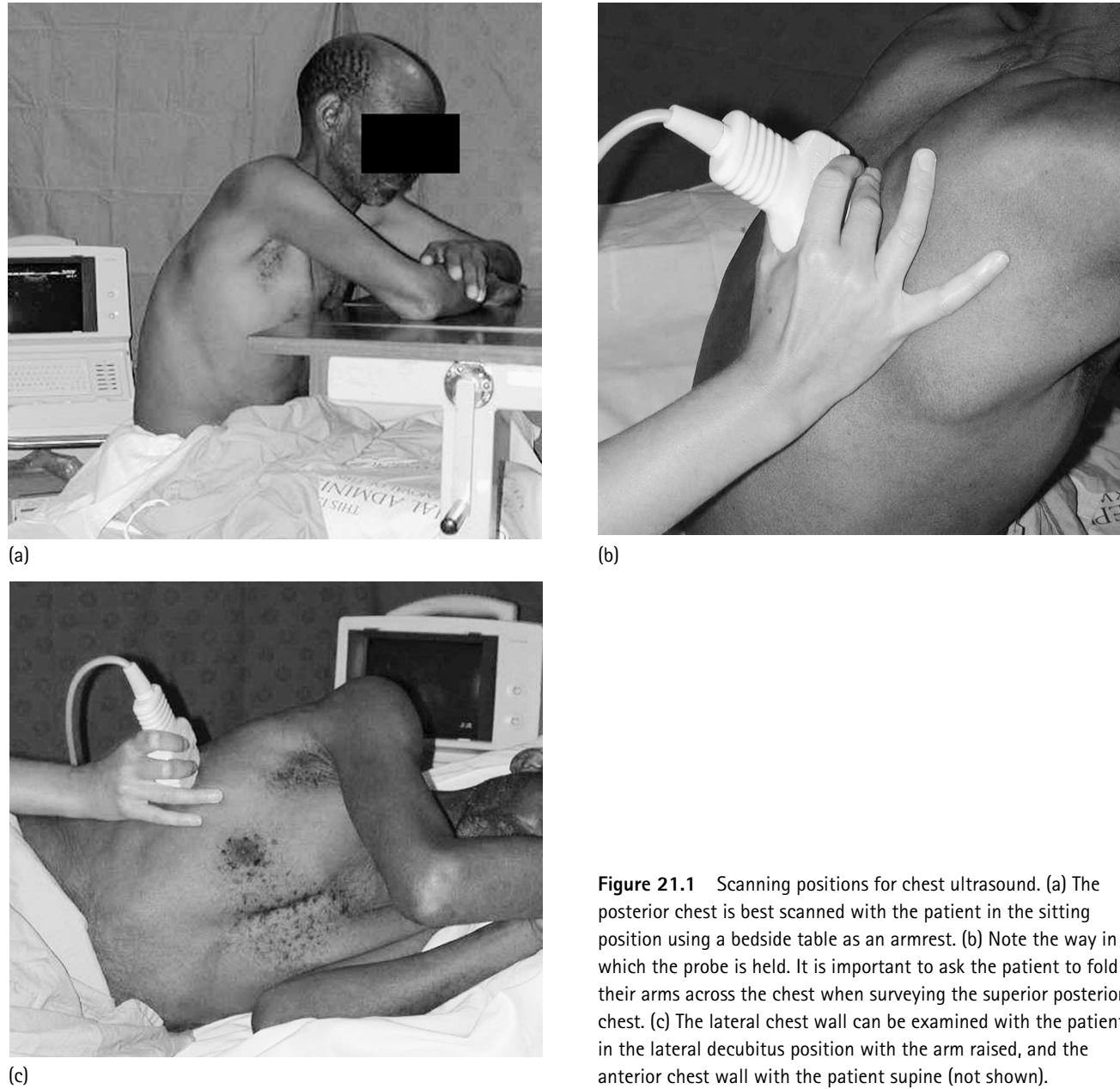
(a)

(b)

(c)

Figure 21.1   Scanning positions for chest ultrasound. (a) The posterior chest is best scanned with the patient in the sitting position using a bedside table as an armrest. (b) Note the way in which the probe is held. It is important to ask the patient to fold their arms across the chest when surveying the superior posterior chest. (c) The lateral chest wall can be examined with the patient in the lateral decubitus position with the arm raised, and the anterior chest wall with the patient supine (not shown).

tional information. The probe is moved slowly, preferably along intercostal spaces, which are oblique and not horizontal. Frequent pauses are needed for observing the spontaneous movement of structures with respiration. Unclear findings can be compared with the contralateral side.

DIAGNOSTIC THORACIC ULTRASONOGRAPHY

Normal chest wall and pleura

The initial surveillance of a normal chest with the low frequency probe will yield a series of echogenic layers of muscles and fascia planes (Figure 21.2a). The ribs appear as curvilinear structures on transverse scans, associated with posterior acoustic shadowing (Figure 21.2b). When the ribs are scanned along the longitudinal, the anterior cortex appears as a continuous echogenic line.

The visceral and parietal pleura can normally not be differentiated by means of a low-frequency probe, which instead displays one highly echogenic line representing the pleura and pleuropulmonary surface. With a high-resolution linear probe (e.g. 8 MHz), the visceral and parietal portions of the pleura can be seen as two distinct echogenic lines, with the latter seemingly thinner in appearance. The two layers can be seen to slide over each other with respiratory motion. The respiratory movement of the lung relative to the chest wall is visible with both probes and is called the 'lung sliding' sign. Its presence on real-time US is strong evidence against a pneumothorax.[7]

(a)

(b)

(c)
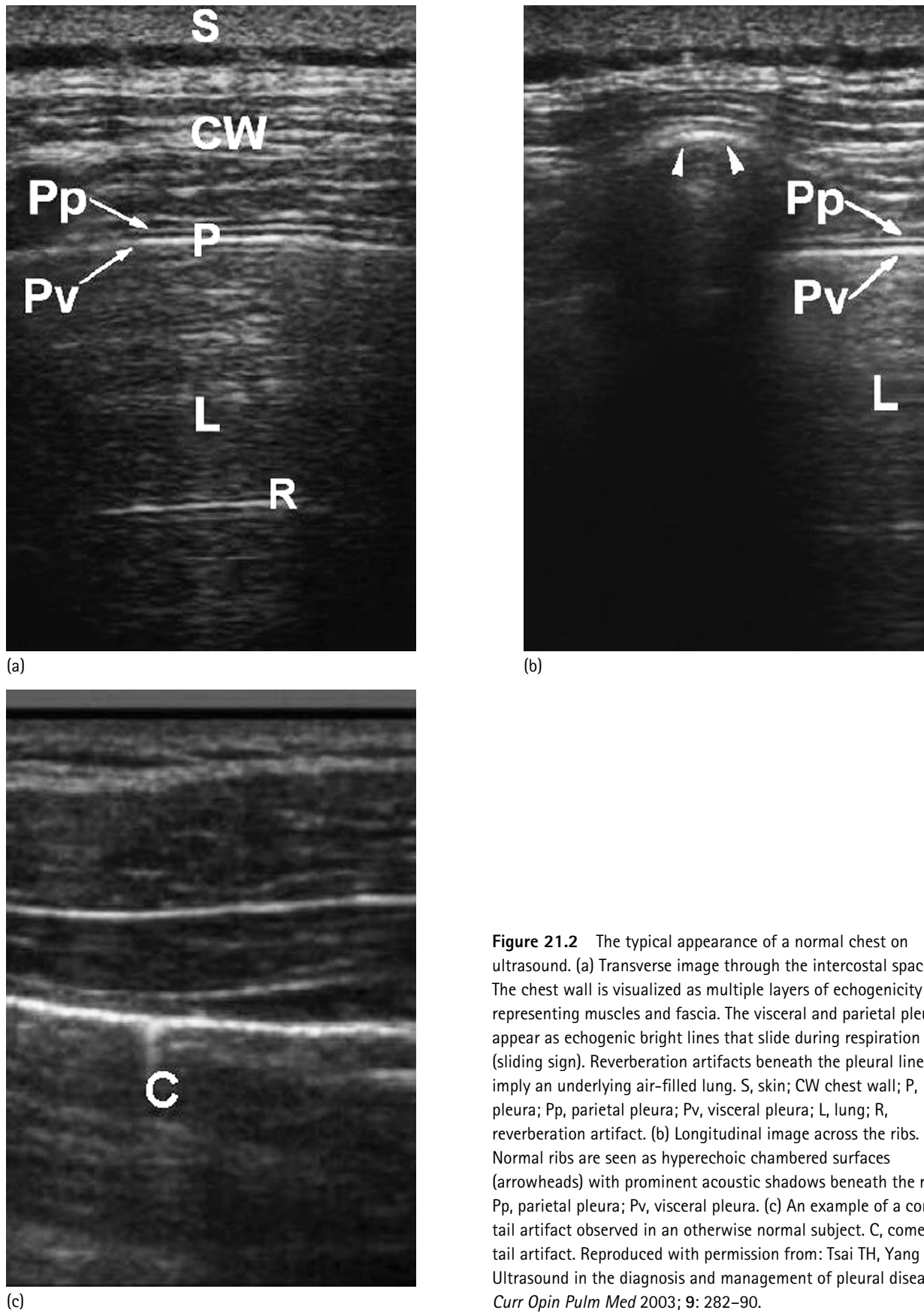
Figure 21.2   The typical appearance of a normal chest on ultrasound. (a) Transverse image through the intercostal space. The chest wall is visualized as multiple layers of echogenicity representing muscles and fascia. The visceral and parietal pleura appear as echogenic bright lines that slide during respiration (sliding sign). Reverberation artifacts beneath the pleural lines imply an underlying air-filled lung. S, skin; CW chest wall; P, pleura; Pp, parietal pleura; Pv, visceral pleura; L, lung; R, reverberation artifact. (b) Longitudinal image across the ribs. Normal ribs are seen as hyperechoic chambered surfaces (arrowheads) with prominent acoustic shadows beneath the ribs. Pp, parietal pleura; Pv, visceral pleura. (c) An example of a comet tail artifact observed in an otherwise normal subject. C, comet-tail artifact. Reproduced with permission from: Tsai TH, Yang PC. Ultrasound in the diagnosis and management of pleural disease. *Curr Opin Pulm Med* 2003; **9**: 282–90.

The 'curtain-sign' describes the variable obscuring of underlying structures by air containing tissue. In normal subjects, the curtain-sign is seen in the costophrenic angle. The upper abdominal organs are easily visible on expiration, but during inspiration the normal air-filled lung is moved downwards in front of the probe and temporarily obscures the sonographic window.

The parenchyma of normal aerated lungs is invisible by means of US. The large change in acoustic impedance at the pleura–lung interface causes horizontal artifacts that are seen as a series of echogenic parallel lines equidistant from one another below the pleura. These bright but formless lines are known as reverberation artifacts and diminish in intensity with increasing distance from the pleura (Figure 21.2a). Vertical 'comet-tail' artifacts (Figure 21.2c), caused by fluid-filled subpleural interlobular septae, can also be seen originating at the pleura–lung interface. The normal diaphragm is best seen through the lower intercostal spaces or via the liver or spleen. It is seen as an echogenic 1 mm thick line which contracts with inspiration.

Pleural effusions

SONOGRAPHIC DIAGNOSIS

The value of ultrasonography for detection and quantification of pleural effusions is uncontested. Ultrasound is particularly helpful in determining the nature of localized or diffuse pleural opacities, and is more sensitive than decubitus expiratory films in identifying minimal or loculated effusions.[8] Sonographically, a pleural effusion appears as an anechoic, homogeneous space between parietal and visceral pleura (Figure 21.3). This space may change in shape with respiration, and the atelectatic lung inside a large effusion may appear as a tongue-like structure within the effusion. In inflammatory effusions, adhesions between the two pleural surfaces may result in the absence of lung motion above the effusion. If an abnormal elevation of a hemidiaphragm is noted on the chest radiograph, subpulmonary effusion can be differentiated from a subphrenic fluid collection or diaphragm paralysis.[9]

DETERMINING THE NATURE OF A PLEURAL EFFUSION

The sonographic appearance of a pleural effusion depends on its nature, cause and chronicity. Four appearances are recognized based on the internal echogenicity: anechoic; complex but non-septated; complex and septated; and homogenously echogenic. Transudates are invariably anechoic, unseptated and free flowing, whereas complex, septated or echogenic effusions are usually exudates.[10,11] Malignant effusions are often anechoic. Nodular pleural thickening is apparent in the minority of malignant effusions, and echogenic swirling patterns have recently been linked to these effusions.[12] Inflammatory effusions are often associated with strands of echogenic material and septations which show more or less mobility with respiration and the cardiac cycle. The presence of septae has several implications. Chen et al.[13] demonstrated that patients with septated effusions needed longer chest tube drainage, longer hospital care and were more likely to require fibrinolytic therapy or surgery compared with those with unseptated effusions. Tu et al.[14] recently confirmed some of these findings in medical intensive care unit patients. Empyema may cause a strongly echogenic effusion that may be mistaken for a solid pleural lesion.

ESTIMATING THE VOLUME OF A PLEURAL EFFUSION BY ULTRASOUND

Several studies have shown reasonable correlation between the volume of an effusion estimated with planimetric measurements and its square dimensions.[15–17] Such geometric calculations are hampered by the uneven distribution of fluid in the presence of pleuropulmonary adhesions. We suggest the following practical way to classify the volume of an effusion: minimal, if the echo-free space is confined to the costophrenic angle; small, if the space is greater than the costophrenic angle but still within the range of the area covered with a 3.5 MHz curvilinear probe; moderate, if the space is greater than a one-probe range but within a two-probe range; and large, if the space is bigger than a two-probe range.

DIFFERENTIATION OF EFFUSION FROM PLEURAL THICKENING

To distinguish small effusions from anechoic pleural thickening can be challenging. Both may appear as anechoic on US. Nearly 20 percent of echo-free pleural lesions will not yield free fluid, whereas a significant percentage of complex-appearing lesions will do so. Mobility is a good sign for effusion. Marks et al.[18] found that if a lesion changed shape with respiratory excursion and if it contained movable strands or echo densities, the lesion was an effusion. If a color Doppler is available, the fluid color sign is the most sensitive and specific ultrasonographic evidence of a small effusion. The sign refers to the presence of a color signal within the fluid collection that is believed to arise from transmitted motion during respiratory or cardiac cycles. This sign has a sensitivity of 89.2 percent and specificity of 100 percent in detecting minimal fluid collections.[19]

Pleural thickening

Pleural thickening is defined as focal lesions arising from the visceral or parietal pleura that is greater than 3 mm in width with or without an irregular margin (Figure 21.4). It appears as broadening of the pleura and does not exhibit a fluid color sign or display movement relative to the chest wall. Pleural thickening most often appears hypoechoic,

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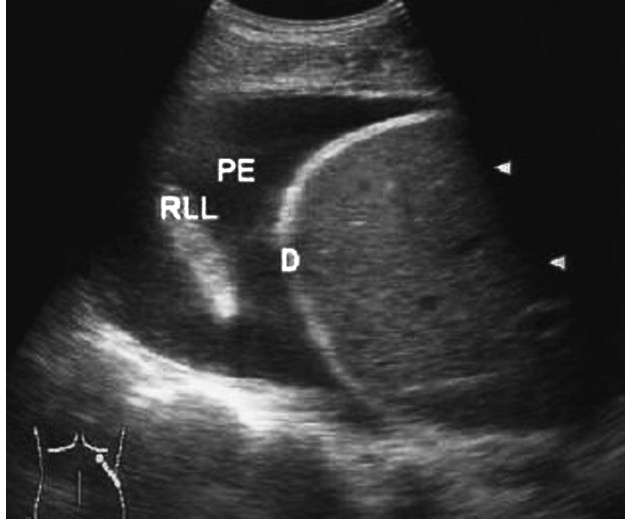
(a)
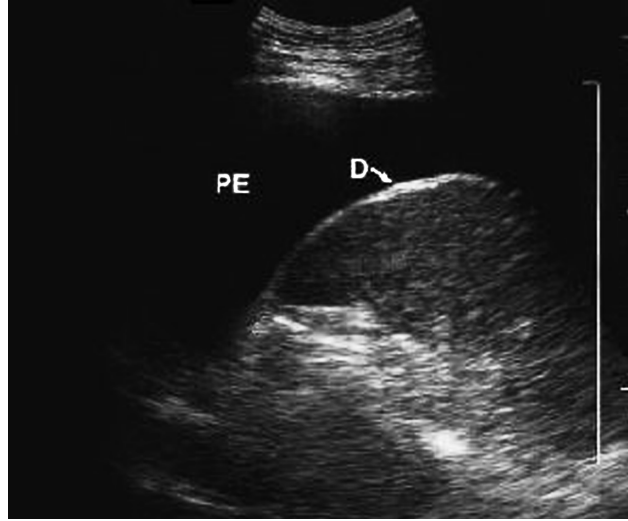
(b)

(c)

(d)

(e)

(f)

Figure 21.4 Pleural thickening: The arrows indicate sheetlike pleural thickening. Pp, parietal pleura; PE, pleural effusion. Reproduced with permission from: Tsai TH, Yang PC. Ultrasound in the diagnosis and management of pleural disease. *Curr Opin Pulm Med* 2003; **9**: 282–90.
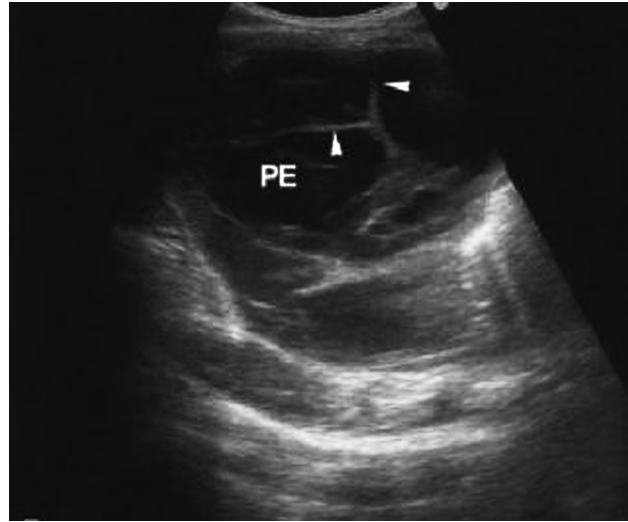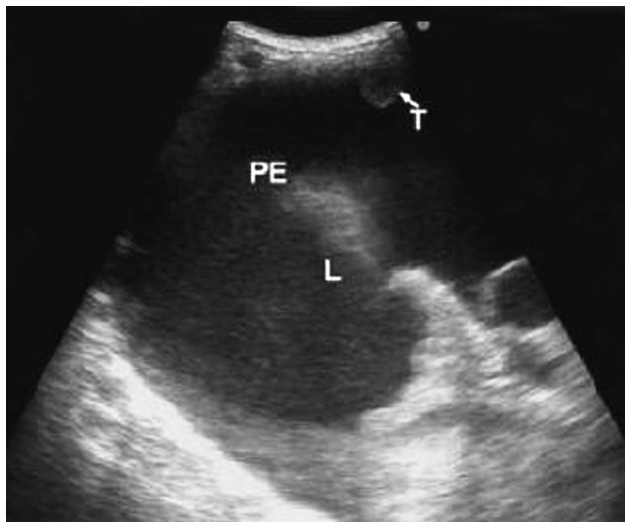

Figure 21.5 A pneumothorax. It should be appreciated that the most specific sign, namely the absence of the sliding sign (see text), can only observed in real time. Note the broadened pleural line, reverberation artifact and absence of comet-tail artifacts. Ppl, parietal pleura; Pn, pneumothorax; R, reverberation artifact.

but increased echogenicity with focal shadowing is sometimes observed and is indicative of calcification.

Pneumothorax and hydropneumothorax

Pneumothorax detection requires more skill and experience than the investigation of pleural fluid. A pneumothorax (Figure 21.5) can be diagnosed by means of the absence of normal lung sliding, exaggerated horizontal reverberation artifacts and the loss of comet-tail artifacts, provided that no diaphragmatic paralysis, prior pleurodesis, pleural adhesions or adult respiratory distress syndrome are present.[20–22] Chronic obstructive pulmonary disease (COPD) can mimic the sonographic sings of pneumothorax. This allows the exclusion, but not the confirmation of pneumothorax in such patients with US.[23] Despite these limitations, ultrasonography is particularly useful in intensive care units and in other situations where radiographic equipment is unavailable. Herth *et al*.[24] have recently shown that a pneumothorax following transbronchial biopsy can be reliably excluded with US (sensitivity 100 percent; specificity 83 percent). This is likely to reduce costs for chest radiographs, increase patient comfort and offers an excellent opportunity to acquire and practice pneumothorax detection.

Hydropneumothorax can also be identified with US by means of the visualization of air–fluid boundary.[25] The sliding sign above the air–fluid level will be absent. A mobile air–fluid level will generate a 'curtain sign' with respiration, because the air within the pleura obscures the underlying effusion during inspiration.

Figure 21.3 (opposite) (a) Pleural effusion is presented as an echo-free space between the visceral and parietal pleura. Compressive atelectasis of the lung may be seen in a large effusion. The effusion can be subclassified as anechoic (b), complex non-septated (c), complex septated (d), or homogenously echogenic (e). Note the movable echogenic spots within the complex non-septated effusion, and the floating strands and septa within the complex septated effusion (arrowheads). (f) Pleural effusion associated with pleural nodules or nodular thickenings is characteristic of malignant effusion. PE, pleural effusion; D, diaphragm; RLL, right lower lobe; L, lung; T, pleural tumor. Reproduced with permission from: Tsai TH, Yang PC. Ultrasound in the diagnosis and management of pleural disease. *Curr Opin Pulm Med* 2003; **9**: 282–90.

(a)

(b)

Figure 21.6   Pleural tumors: Two examples of the ultrasound appearance of pleural tumors, one with a large pleural effusion (a) and one without (b). Note the posterior echo enhancement. PE, pleural effusion; T, pleural tumor; Pp, parietal pleura; L, lung. Reproduced with permission from: Tsai TH, Yang PC. Ultrasound in the diagnosis and management of pleural disease. *Curr Opin Pulm Med* 2003; **9**: 282–90.
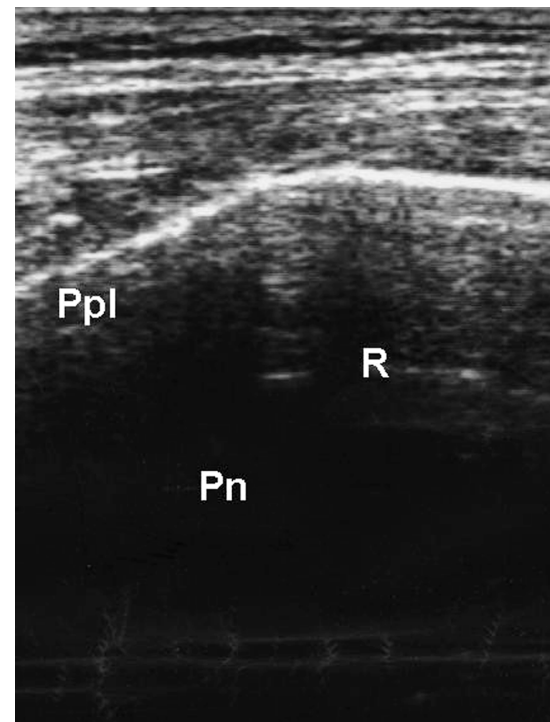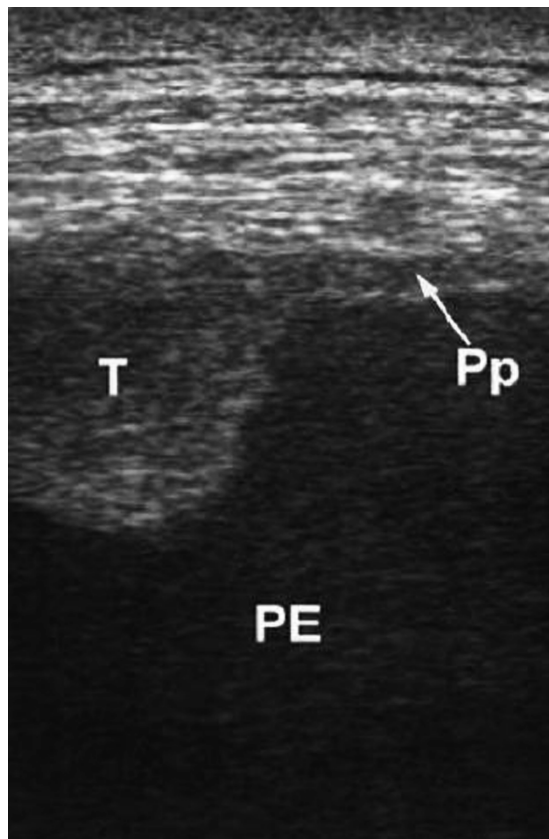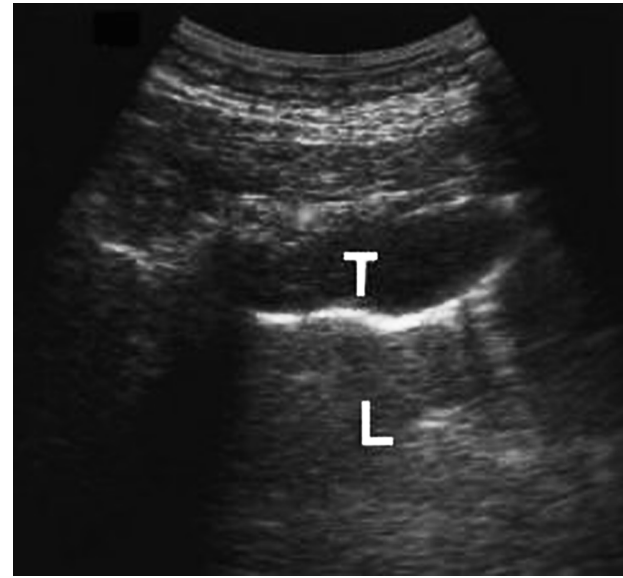
Pleural tumors

Benign pleural tumors appear on US as well-defined rounded masses of variable echogenicity on either the parietal or visceral pleura. Both metastatic pleural tumors and malignant mesothelioma appear as polypoid pleural nodules or irregular sheetlike pleural thickening,[26] often with large pleural effusions (Figure 21.6). Tumors with low echogenicity can exhibit posterior echo enhancement.

Lung tumors abutting or invading the pleura and chest wall

A peripheral lung tumor will be detectable by US provided that pleural contact is present (Figure 21.7). Visceral pleura or chest wall invasion has important implications for lung tumor staging (T2 or T3 staging, respectively). Although CT is routinely used for determining the extent of invasion, high-resolution real-time US scanning has been found to be superior to routine chest CT in evaluating tumor invasion of the pleura and chest wall.[27,28] When a tumor abutted to the chest wall is visualized with US, all layers of the chest wall, i.e. muscle, fascia, parietal pleura and visceral pleura, can be examined and the extent of tumor invasion can be accurately determined (Figure 21.8).
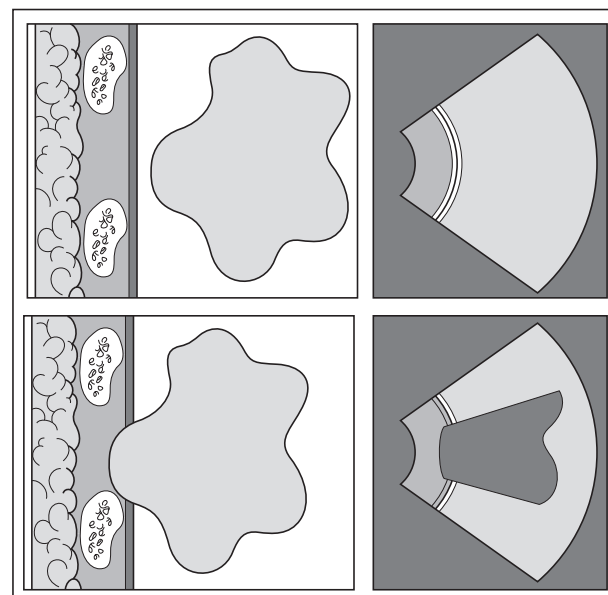
Figure 21.7   A peripheral lung lesion is shown schematically on the left without (top) and with (bottom) pleural contact. The corresponding sonar images recorded with a sector scanner are shown on the right. Only the lesion with pleural contact is visible on ultrasound. Note that the acoustic window is too narrow to demonstrate the whole circumference of the lesion, but it allows determination of its full depth. Reproduced with permission from: Diacon AH, Theron J, Bolliger CT. Transthoracic ultrasound for the pulmonologist. *Curr Opin Pulm Med* 2005; **11**: 307–12.

(a) (b)
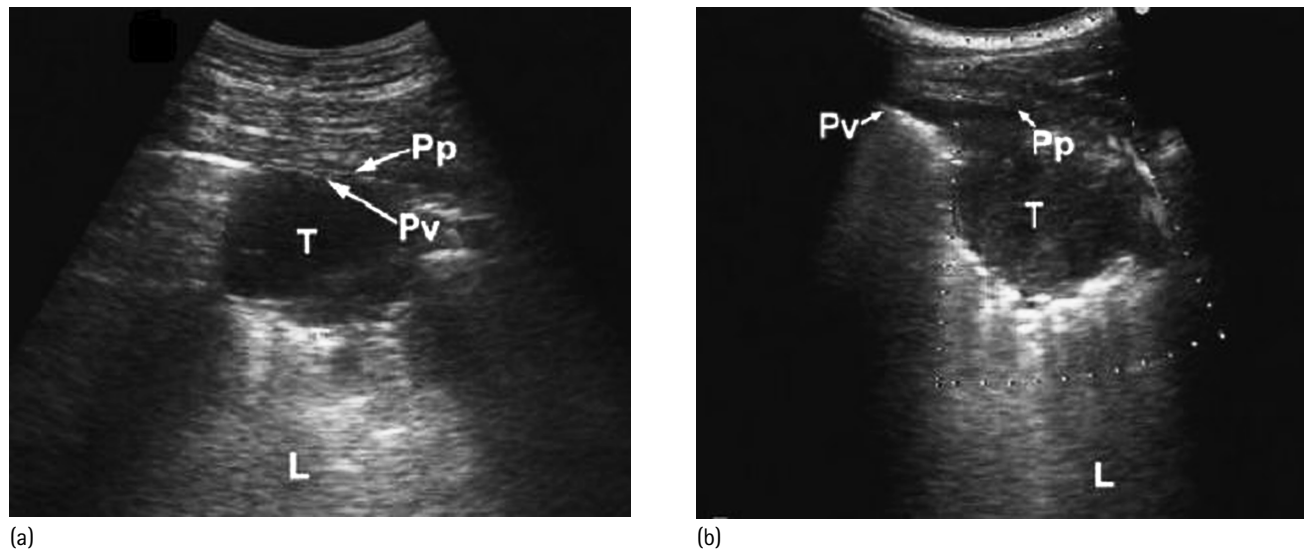
Figure 21.8   (a) An ultrasound (US) image showing a lung tumor with posterior echo enhancement. Note that both of the visceral and parietal pleural lines are intact. (b) This US shows tumor extension beyond the pleura. The visceral pleural line is interrupted, and the respiratory movement of the tumor is disturbed in real-time US. Invasion of the pleural cavity by the tumor is evident. L, lung; T, tumor; Pv, visceral pleural; Pp, parietal pleura. Reproduced with permission from: Diacon AH, Theron J, Bolliger CT. Transthoracic ultrasound for the pulmonologist. *Curr Opin Pulm Med* 2005; **11**: 307–12.

Chest wall pathology

Soft-tissue masses such as lipomas can readily be detected by high-frequency US. Supraclavicular and axillary lymph nodes with malignant infiltration appear bulky, rounded and hypoechoic.[29] Extracapsular spread is suggested by irregular borders. Sonography can detect bony metastases to the ribs, which appear as hypoechoic masses in place of the normal echogenicity of the rib with disruption of the cortical line. US is also reported to be more sensitive than radiography in the detection of rib fracture, which appears as a breach or displacement of the cortex of the rib with or without localized swelling or haematoma.

Diaphragmatic paralysis

The diaphragm is best visualized at the costophrenic angle or through the liver or spleen. Sonographic examination of a paralyzed diaphragm will yield paradoxical movement of the diaphragm with respiration.[30] This can be accentuated with forced inspiration ('sniff' test). Long-term paralysis causes muscle atrophy.[30]

## Diverse pulmonary pathology

Apart from solid tumors, numerous pathological processes can replace the air within lung tissue and thereby become detectable with US, provided that the pleura is abutted.

PNEUMONIA AND LUNG ABSCESSES

Pleural based pneumonic consolidation is detectable by means of US, although the extent of disease appears smaller on US than on chest radiographs. In the early phase of consolidation the lung appears diffusely echogenic, resembling the sonographic texture of the liver. Air bronchograms appear as echogenic branches. Fluid bronchograms are sometimes observed. They appear as anechoic tubular structures, representing fluid-filled airways, and are typically seen in bronchial obstruction. Their presence should alert the clinician to the possibility of a post-obstructive pneumonitis, secondary to a proximal tumor. Sonographically observed consolidation is not indicative of an infective etiology. Pulmonary infarction, hemorrhage and bronchoalveolar carcinoma are three examples of non-infective consolidation that is similar in appearance on US. US may guide transthoracic needle aspirations or biopsies of peripheral pulmonary infiltrates in cases with diagnostic uncertainty regarding the aetiology.[31]

A lung abscess abutting the pleura appears sonographically as a hypoechoic lesion with a well-defined or irregular wall (Figure 21.9). The centre of the abscess is most often anechoic, but may reveal internal echoes and septations. Abscesses with air fluid levels on chest radiograph are more inhomogeneous and will display the curtain sign.

PULMONARY EMBOLISM

Ultrasound can serve for the acute bedside assessment of patients presenting with possible pulmonary embolism.[32] Pulmonary infarction is recognized as a peripheral wedge-
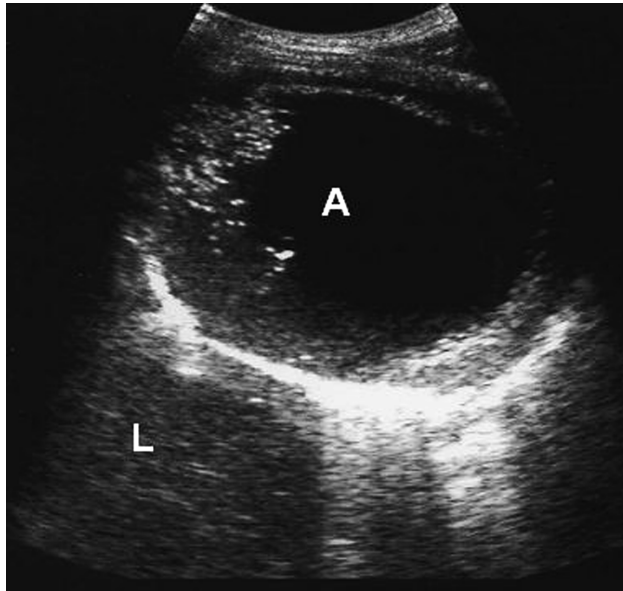
Figure 21.9   A peripheral lung abscess. Note the hypoechoic centre and irregular wall. A, abscess cavity; L, lung.

shaped consolidation, often accompanied by a pleural effusion. US is also useful to diagnose venous thrombosis as well as the sequelae of thromboembolic disease such as right ventricular overload and dilated hepatic veins. This indication of US is currently still reserved for experienced physicians with a keen interest in US, as pulmonary spiral CT angiography remains the investigation of choice.

PULMONARY EDEMA

In the setting of patients with acute dyspnea it has been reported that the presence of bilateral, widespread comet-tail artifacts is a reliable sign to differentiate patients with pulmonary edema from those with chronic obstructive airway disease in the intensive care unit (ICU).[33] Comet-tail artifacts were absent in 92 percent of patients with chronic obstructive airway disease.

ULTRASOUND–GUIDED INTERVENTIONS

Principles

Ultrasound is particularly well suited for assisting pleural and chest wall interventions, including diagnostic thoracentesis, closed tube drainage, chest wall and pleural biopsies and biopsies of lung tumors abutting or invading the pleura. The use of US for these procedures increases the success rate and minimizes risk compared with procedures carried out blindly.

With regard to needle biopsies, specific reusable probes for real-time US guidance of needle biopsies are commercially available. Many prefer the so-called 'freehand' tech-

nique for its simplicity. Following adequate patient positioning, the intended site of needle insertion is sonographically identified and marked, while the direction, the depth of interest and the safety range for the procedure are memorized. The patient must not change position in order to prevent a positional shift of the area of interest relative to the skin mark. It is occasionally even necessary to ask the patient to hold their breath for the duration of the aspiration. The practice of identifying a puncture site at a radiology department prior to transporting a patient elsewhere for thoracentesis should be discouraged, particularly in the case of small effusions, as both the fluid collection and the skin mark might shift considerably with minor changes in body position.

Thoracentesis

Sonography is superior to chest radiographs in detecting pleural effusions and identifying the optimal site for diagnostic thoracentesis.[34] The largest and most accessible area of fluid accumulation can be identified, and an aspiration can easily be performed by means of the 'freehand' technique. The success rate of US-guided thoracentesis can be as high as 97 percent.[35] US guided thoracentesis improves the diagnostic yield and decreases the risk of complications in all patients, but is particularly helpful when a safe procedure is mandatory, e.g. in patients with bleeding diathesis or the critically ill patient.

Closed tube drainage

Ultrasound is ideal for identifying the optimal site for effective and safe pleural drainage. This is particularly relevant in an ICU setting and in patients with loculated parapneumonic effusions and empyemas with septations. Depending on operator experience, US may also guide further decisions regarding the need for subsequent intrapleural fibrinolytics or for surgical intervention in addition to drainage and antibiotics.[36]

Effusions can also be accessed by means of an 18- or 16-gauge needle under direct (real-time) US visualization. This allows direct thoracentesis followed by an insertion of a guide wire, which is used to guide serial incremental dilatation of a tract and deployment of a pigtail small-bore catheter (8–14 F). These tubes are better tolerated than large bore (20–24 F) intercostal drains.[37]

Closed pleural biopsy in the presence of a pleural effusion

Sonography is an extremely useful guide for biopsies of the pleura. Focal pleural abnormalities (thickening or tumors) can be identified with US, and biopsy can be aimed at these areas of interest. The ability to estimate the size of an asso-

ciated effusion decreases the risk of visceral pleural lacerations, which is particularly relevant in cases with minimal pleural effusion.

Conventionally, closed pleural biopsies (e.g. with the Abrams needle) could only safely be performed in the presence of a sizeable pleural effusion or pneumothorax determined clinically or on chest radiography. However, US can demonstrate small fluid collections and facilitate the use of devices that were not primarily designed for fluid aspiration (e.g. Tru-cut needles). Numerous studies have concluded that US-guided Tru-cut needle biopsies have higher sensitivity and specificity in the diagnosis of pleural malignancy and tuberculosis than unaided Abrams needle biopsies.[38–41]

Transthoracic fine needle aspirations and needle biopsies of solid tumors

Ultrasound-guided fine needle aspiration or cutting biopsy performed under local anesthesia is safe and has a high diagnostic yield.[42] Chest wall and anterior mediastinal masses, pleural tumors or thickening, as well as peripheral lung tumors that either abut or invade the pleura or chest wall, are ideally suited for US-guided biopsy procedures. The risk of pneumothorax is low as no air-containing tissue needs to be transversed with the biopsy device. US-guided biopsies can be performed at the bedside, which offers advantages in distressed patients with advanced disease. The shortened procedure time is also particularly helpful in less cooperative patients.

Transthoracic fine needle aspirations (TTFNA) are performed under local anaesthesia, preferably with a 22-gauge injection-type or spinal needle. A recent prospective study found that TTFNA and closed needle biopsies corresponded well in the diagnosis of epithelial lung carcinoma and in the distinction of small cell and non-small cell lung cancer. TTFNA alone seems sufficient for the diagnosis of epithelial lung carcinoma, while closed needle biopsies have a higher yield in non-carcinomatous lesions and pleural tumors.[43]

Cutting needle biopsies follow the same principles as TTFNA, but such devices are more invasive and carry the risk of vascular trauma if the anatomical locations of subclavian, brachial, intercostal and mammarian arteries are not respected. Chang et al.[38] found that US-guided Tru-cut had a sensitivity of 61.5 percent and specificity of 100 percent. Tru-Cut biopsy is particularly helpful for diagnosing malignant mesothelioma without open surgical biopsy. A recent study of cutting needle biopsies under CT-guidance in diffuse pleural thickening showed a sensitivity and specificity for mesothelioma of 88 and 100 percent, respectively.[44] In a study employing US for tumors greater than 3 cm in diameter, the sensitivity and specificity for mesothelioma was 100 percent.[42]

Cytopathological support for rapid on-site evaluation (ROSE) of TTFNA smears is extremely helpful in deciding whether a histological specimen obtained via cutting needle biopsy is needed or not.[43] In the absence of ROSE, cutting biopsies should be performed in all cases where cytology is non-contributory and in cases where a diagnosis other than lung cancer is suspected. Conveniently, US is a good tool for exclusion of a pneumothorax post-aspiration or biopsy. If the lesion remains visible on US and is unchanged in location, shape and size, it implies that no free air is present between the sampled lesion and the visceral pleura, and that a clinically relevant pneumothorax is unlikely. US-guided biopsies are safe procedures, with an overall complication rate of only 1–2 percent.[42,43]

Aspiration and biopsy of diffuse pulmonary infiltrates, consolidations and lung abscesses

The indications for US-assisted TTFNA and biopsies are by no means limited to solid tumors. Yang et al.[31] found US-guided biopsy of pulmonary consolidation helpful in determining its cause, and reported a diagnostic yield of as high as 93 percent. This procedure is particularly useful in the immunocompromised patient, given the extensive differential diagnosis. The same author was able to sonographically demonstrate abscess cavities in 94 percent of 35 patients with radiologically confirmed lung abscesses.[45] By US, lung abscesses were depicted as hypoechoic lesions with irregular outer margins and an abscess cavity that was manifested as a hyperechoic ring. More than 90 percent of all aspirates of these abscesses yielded pathogens, whereas less than 10 percent of patients had positive blood cultures.

CONCLUSION

The usefulness of US for chest physicians is firmly established. Basic thoracic ultrasonography is an elegant and low-cost investigation that extends the physicians' diagnostic and interventional potential at the bedside in peripheral lung, pleural and chest wall disease. It has the potential to replace CT-guided fine needle aspirations or biopsies of all lesions involving the pleura and chest wall, as well as lung masses or consolidations abutting the pleura. Basic thoracic sonography is fairly simple and easy to learn. Academic institutions should strive to have a basic formal training program in ultrasonography in place in order to ensure that all aspiring chest physicians are familiar with chest ultrasonography.

ACKNOWLEDGEMENTS

KEY POINTS

- Thoracic ultrasonography can be performed by means of the most basic ultrasound equipment.
- In healthy individuals, ultrasound can visualize the chest wall, the diaphragm and the pleura, but not the lung parenchyma.
- The main domain of thoracic ultrasound is the investigation of chest wall abnormalities, pleural thickening and pleural tumors, and the qualitative and quantitative description of pleural effusions.
- Ultrasound can visualize lung tumors and other parenchymal pulmonary processes provided that they abut the pleura.
- Ultrasound is the ideal tool to assist with thoracentesis and drainage of effusions.
- Ultrasound-assisted fine needle aspiration and cutting needle biopsy of lesions arising from the chest wall, pleura and lung are safe and have a high yield in the hands of chest physicians.
- New applications of ultrasound include the diagnosis of pneumothorax and pulmonary embolism.

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● = Key primary paper

◆ = Major review article

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Transthoracic Ultrasound

Transthoracic Ultrasound for Chest Wall, Pleura, and the Peripheral Lung

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Abstract

Thoracic ultrasonography can be performed by means of the most basic ultrasound (US) equipment. In healthy individuals, US can visualize the chest wall, the diaphragm and the pleura but not the lung parenchyma. The main domain of thoracic US is the investigation of chest wall abnormalities, pleural thickening and pleural tumours, and the qualitative and quantitative description of pleural effusions. US can visualize lung tumours, pulmonary consolidations and other parenchymal pulmonary processes provided they abut the pleura. US is the ideal tool to assist with thoracentesis and drainage of effusions. US-assisted fine needle aspiration and cutting needle biopsy of lesions arising from the chest wall, pleura and peripheral lung are safe and have a high yield in the hands of chest physicians. US may also guide aspiration and biopsy of diffuse pulmonary infiltrates, consolidations and lung abscesses, provided the pleura is abutted. Advanced applications of transthoracic US include the diagnosis of a pneumothorax and pulmonary embolism.

Ultrasonography of the thorax remains an underutilized investigation. Although diagnostic sonography of the abdomen has been around for more than 60 years, its thoracic counterpart has lagged behind for many decades. The inability of ultrasound (US) to penetrate aerated tissue diverted clinicians from appreciating its excellent ability to visualize the chest wall, pleura and pathology of lung abutting the pleura [1]. The major advantages of thoracic US include its mobility, dynamic properties, low cost, lack of radiation, and short examination time [1–6]. Thoracic US is also increasingly being used to assist interventional procedures. The main aim of this chapter is to demystify ultrasonography for the clinician by reviewing the basic principles and recent advances from the perspective of the non-radiologist.

General Technical Aspects

Adequate thoracic ultrasonography can be performed by means of the most basic, entry-level, two-dimensional black-and-white US equipment. A low frequency probe (e.g. 3.5 MHz) with curvilinear shape for covering a large area is suitable for initial screening of superficial and deeper structures, while a high frequency probe (e.g. 8 MHz) with a linear shape is used for refined assessment of an abnormal chest wall or pleural area. Doppler and colour flow echo are not required for routine thoracic examination.

Optimal patient position for scanning is an underappreciated aspect. It is important to review a patient's chest radiograph and computed tomography (CT) scan prior to performing a thoracic US examination. This will not only identify the area of interest, but will also guide the positioning of the patient. The posterior chest is best scanned with the patient in the sitting position using a bedside table as an armrest (fig. 1), whereas the lateral and anterior chest wall can be examined with the patient in either the lateral decubitus or even supine position. Maximum visualization of the lung and pleura is achieved by examining along the intercostal spaces. Raising the arm above the patient's head increases the intercostal space distance and facilitates scanning in erect or recumbent positions. A patient can fold the arms across the chest in order to displace the scapulae when

Fig. 1. Scanning position for thoracic US. The posterior chest is best scanned with the patient in the sitting position using a bedside table as an armrest. Note the way in which the probe is held. It is important to ask the patient to fold his arms across his chest when surveying the superior posterior chest. The lateral chest wall can be examined with the patient in the lateral decubitus position with the arm raised, and the anterior chest wall with the patient supine (not shown).

surveying the upper posterior thorax. Superior sulcus pathology can be visualized apically with the patient in the supine or sitting position.

Diagnostic Thoracic Ultrasonography

The Normal Thorax

A series of echogenic layers of muscles and fascia planes are seen during the initial surveillance of a normal chest with the low frequency probe (fig. 2a). Ribs appear as curvilinear structures on transverse scans, associated with posterior acoustic shadowing. When the ribs are scanned longitudinally, the anterior cortex appears as a continuous echogenic line.

The visceral and parietal pleura are normally displayed by a low-frequency probe as one highly echogenic line representing the pleura and pleuropulmonary surface. With a high-resolution linear probe, the visceral and parietal pleura can be seen as two distinct echogenic lines, with the latter seemingly thinner in appearance (online suppl. video 1). The two layers can be seen to slide over each other during in- and expiration. The respiratory movement of the lung relative to the chest wall is visible with both probes and is called the 'lung sliding' sign (online suppl. video 2). Its presence on real-time US is strong evidence against the presence of a pneumothorax [7].

The normal diaphragm is best seen through the lower intercostal spaces or via the liver or the spleen. It is seen as an echogenic 1- to 2-mm-thick line which contracts with inspiration.

The 'curtain sign' describes the variable obscuring of underlying structures by air-containing tissue. In normal subjects, the curtain sign is seen in the costophrenic angle. The upper abdominal organs are easily visible on expiration, but during inspiration the normal air-filled lung is moved downwards in front of the probe and temporarily obscures the sonographic window.

The parenchyma of normal aerated lungs is invisible by means of US. The large change in acoustic impedance at the pleura-lung interface causes horizontal artefacts that are seen as a series of echogenic parallel lines equidistant from one another below the pleura. These bright but formless lines are known as reverberation artefacts and diminish in intensity with increasing distance from the pleura. Vertical 'comet-tail' artefacts, caused by fluid-filled subpleural interlobular septa, can also be seen originating at the pleura-lung interface (fig. 2b).

Chest Wall Pathology

Soft-Tissue Masses and Lymph Nodes
Soft-tissue masses arising from the chest wall can readily be detected by high-frequency US. These include abscesses, lipomas and a plethora of other (mostly benign) lesions. Masses generally have variable echogenicity and US findings are too non-specific to differentiate between various aetiologies [1, 4].

Supraclavicular and axillary lymph nodes are accessible by means of US, and US may even aid in distinguishing reactive from malignant lymph nodes [4]. An echogenic fatty hilum and oval or triangular shapes are indicative of inflammatory lymph nodes, whereas lymph nodes with malignant infiltration usually show loss of the fatty hilum leading to a hypoechoic appearance [4, 8]. Malignant nodes also appear bulky, and extracapsular spread is suggested by irregular borders [9].

Skeletal Pathology
Sonography may sometimes detect bony metastases to the ribs, which appear as hypoechoic masses replacing the normal echogenicity of a rib and leading to the disruption of the cortical line [9]. US is also reported to be more sensitive than radiography in the detection of rib fracture [10], which appears as a breach or displacement of the cortex of the rib with or without a localized swelling or haematoma.

Fig. 2. a The typical appearance of a normal chest on US (transverse image through the intercostal space with high frequency probe). The chest wall is visualized as multiple layers of echogenicity representing muscles and fascia. The visceral and parietal pleura appear as echogenic bright lines that slide during respiration. Reverberation artefacts beneath the pleural lines imply an underlying air-filled lung. S = Skin; CW = chest wall; P = pleura; Pp = parietal pleura; Pv = visceral pleura; L = lung; R = reverberation artefact. **b** An example of a comet-tail artefact observed in an otherwise normal subject. C = Comet-tail artefact.
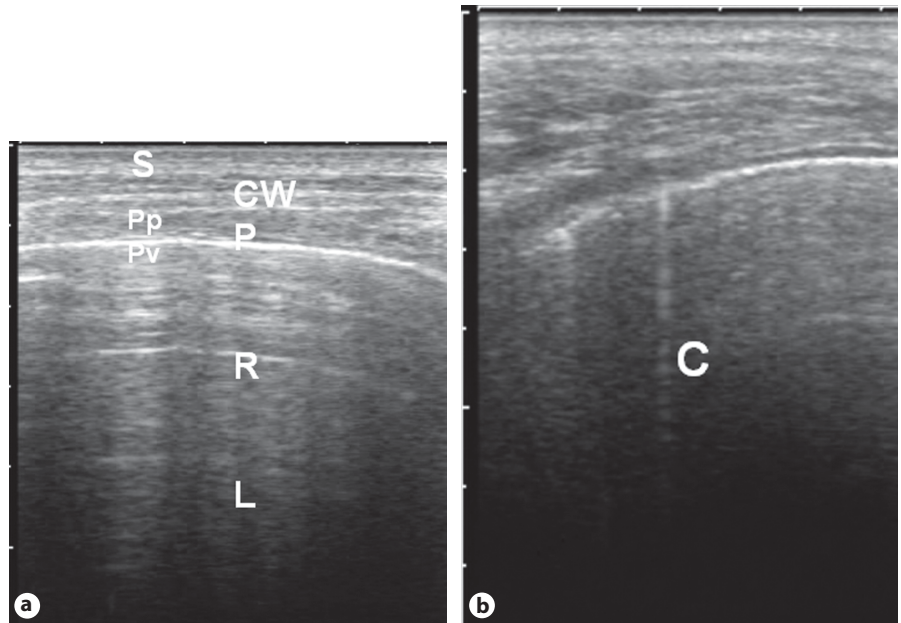
Diaphragmatic Abnormalities

Diaphragmatic movements are best assessed through solid upper abdominal viscera, i.e. the liver or the spleen [1]. A degree of asymmetry in the movement of the hemidiaphragms is considered normal [4]. Sonographic examination of a paralyzed diaphragm will yield paradoxical movement of the diaphragm with respiration [11]. This can be accentuated with forced inspiration ('sniff' test). Long-term paralysis causes muscle atrophy [11].

Pleural Pathology

Pleural Effusions

The value of sonography for the detection and quantification of pleural effusions remains uncontested. US is particularly useful in assessing the nature of localized or diffuse pleural opacities, and is more sensitive than decubitus expiratory films in identifying minimal or loculated effusions [12]. Sonographically, a pleural effusion appears as an anechoic, homogeneous space between parietal and visceral pleura (fig. 3). This space may change in shape with respiration, and the atelectatic lung inside a large effusion may appear as a tongue-like structure within the effusion. In inflammatory effusions, adhesions between the two pleural surfaces may result in the absence of lung motion above the effusion. If an abnormal elevation of a hemidiaphragm is noted on a chest radiograph, subpulmonary effusion can be
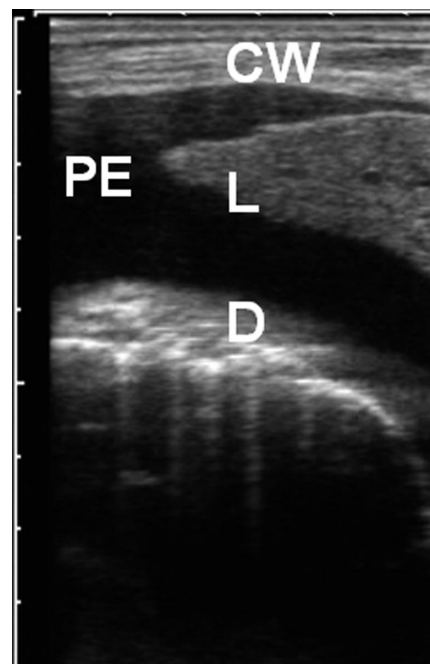
Fig. 3. A pleural effusion is presented as an echo-free space between the visceral and parietal pleura. Compressive atelectasis of the lung is seen on this high-frequency US. This is an example of an anechoic effusion. CW = Chest wall; PE = pleural effusion; L = lung; D = diaphragm.

differentiated from a subphrenic fluid collection and diaphragm paralysis [13].

The US appearance of a pleural effusion depends on its nature, cause and chronicity. Four appearances are recognized
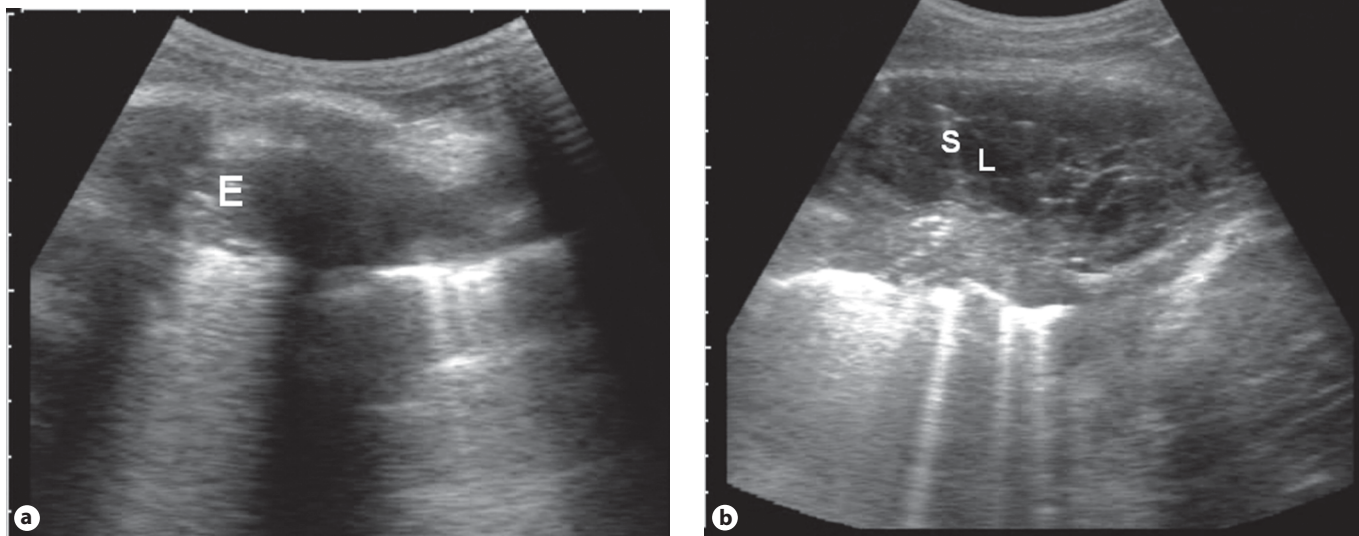
Fig. 4. More examples of pleural effusions. **a** A low-frequency US of a complex non-septated effusion showing movable echogenic shadows (E) within the effusion. **b** A low-frequency US of a complex septated effusion with thick septa (S) and loculations (L) (also see online suppl. video 3).

based on the internal echogenicity: anechoic (fig. 3), complex but non-septated (fig. 4a), complex and septated (fig. 4b), and homogenously echogenic. Transudates are invariably anechoic, unseptated, and free flowing, whereas complex, septated or echogenic effusions are usually exudates [14, 15]. Malignant effusions are often anechoic. Nodular pleural thickening is apparent in the minority of malignant effusions, and echogenic swirling patterns have been linked to these effusions [16]. Inflammatory effusions are often associated with strands of echogenic material and septations (online suppl. video 3) which show more or less mobility with respiration and the cardiac cycle. The presence of septa has several implications. Chen et al. [17] demonstrated that patients with septated effusions needed longer chest tube drainage, longer hospital care, and were more likely to require fibrinolytic therapy or surgery compared with those with unseptated effusions. Tu et al. [18] confirmed some of these findings in medical intensive care unit patients.

Several studies have shown reasonable correlation between the volume of an effusion estimated with planimetric measurements and its square dimensions [19–21]. Such geometric calculations are hampered by the uneven distribution of fluid in the presence of pleuropulmonary adhesions. Although not prospectively tested, we suggest the following practical way to classify the volume of an effusion: minimal, if the echo-free space is confined to the costophrenic angle; small, if the space is greater than the costophrenic angle but still within the range of the area covered with a 3.5-MHz curvilinear probe; moderate, if the space is greater than a

one-probe range but within a two-probe range, and large, if the space is bigger than a two-probe range [1].

Distinguishing small effusions from pleural thickening can be challenging. Both may appear as hypoechoic on US. Furthermore, empyema may also cause a strongly echogenic effusion that may be mistaken for a solid pleural lesion. Mobility is an important sign for effusion. Marks et al. [22] found that if a lesion changed shape with respiratory excursion and if it contained movable strands or echo densities, the lesion was an effusion. If a colour Doppler is available, the fluid colour sign is the most sensitive and specific ultrasonographic evidence of a small effusion. The sign refers to the presence of a colour signal within the fluid collection that is believed to arise from transmitted motion during respiratory or cardiac cycles. This sign has a sensitivity of 89.2% and specificity of 100% in detecting minimal fluid collections [23].

Pleural Thickening

Pleural thickening can be defined as a focal lesion arising from the visceral or parietal pleura that is greater than 3 mm in width with or without an irregular margin (fig. 5). It appears as broadening of the pleura and does not exhibit a fluid colour sign or display movement relative to the chest wall (online suppl. video 4). Pleural thickening most often appears hypoechoic, but increased echogenicity with focal shadowing is sometimes observed and is indicative of calcification and chronicity.
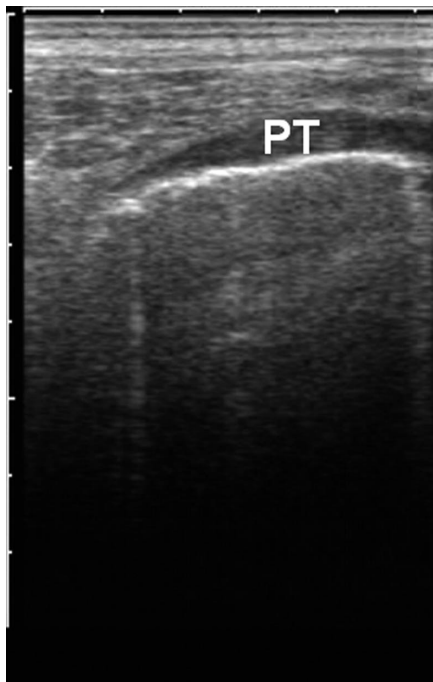
Fig. 5. Pleural thickening (PT). Note the hypoechoic appearance with distal enhancement (suggestive of chronicity). This patient was previously treated for tuberculous pleuritis (also see online suppl. video 4).

Fig. 6. Two examples of the sonographic appearance of pleural tumours, one with a large pleural effusion (**a**) and one without (**b**). Note the posterior echo enhancement (E). PE = Pleural effusion; T = pleural tumour; Pp = parietal pleura; L = lung [from 2, with permission].

Pneumothorax and Hydropneumothorax

The detection of a pneumothorax requires a higher level of skill and experience than the detection of pleural fluid. A pneumothorax (online suppl. video 5) can be diagnosed by means of the absence of normal lung sliding, exaggerated horizontal reverberation artefacts and the loss of comet-tail artefacts, provided that no diaphragmatic paralysis, prior pleurodesis, pleural adhesions or adult respiratory distress syndrome are present [24–27]. Ultrasonography is particularly useful in intensive care units and in other situations where radiographic equipment is unavailable. Herth et al. [26] showed that a pneumothorax following transbronchial biopsy can be reliably excluded with US (sensitivity 100%; specificity 83%). Soldati et al. [27] very recently found US to be superior to chest radiographs in diagnosing pneumothoraces in patients following blunt chest trauma. In their prospective study they were able to show that a rapid US performed by an experienced operator had a sensitivity of 92% (spiral CT was used as the gold standard). Only 52% of pneumothoraces in their study population were visible on routine chest radiographs.

Hydropneumothorax can also be identified with US by means of the visualization of air-fluid boundary [28], which can move with respiration. The sliding sign above the air-fluid level will be absent. The 'curtain sign' describes reverberation artefacts originating from the air within the pleura that obscures the underlying effusion during inspiration, allowing a confident diagnosis to be made.

Pleural Tumours

Benign pleural tumours are rare and appear on US as well-defined rounded masses of variable echogenicity (depending on their fat content) on either the parietal or visceral pleura. Both metastatic pleural tumours and malignant mesothelioma give rise to polypoid pleural nodules or irregular sheet-like pleural thickening [29], often with large pleural effusions (fig. 6).

Pulmonary Pathology

Neoplasms

A peripheral lung tumour will be detectable by US provided that pleural contact is present. These tumours most often appear hypoechoic with posterior acoustic enhancement [3] (fig. 7). Associated pulmonary collapse may cause fluid bronchograms. Visceral pleura or chest wall invasion has important implications for lung tumour staging (T2 or T3 staging, respectively). Although computer tomography is routinely used for determining the extent of invasion, high-resolution real-time US scanning has been found to be
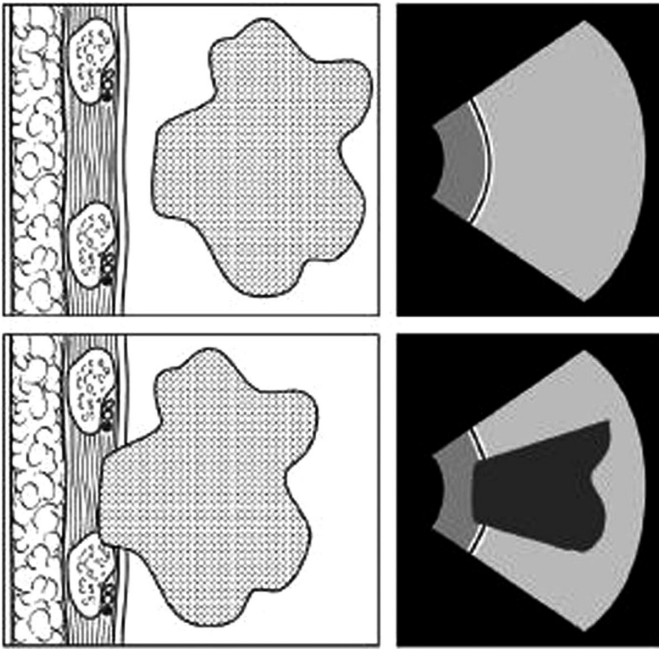
Fig. 7. A peripheral lung lesion is shown schematically without (top) and with (bottom) pleural contact. The corresponding sonar images recorded with a sector scanner are shown on the right. Only the lesion with pleural contact is visible on US. Note that the acoustic window is too narrow to demonstrate the whole circumference of the lesion, but it allows determining its full depth [from 3, with permission].

superior to routine chest CT in evaluating tumour invasion of the pleura and chest wall [30, 31]. When a tumour abutted to the chest wall is visualized with US, all layers of the chest wall, i.e. muscle, fascia, parietal pleura and visceral pleura, can be examined and the extent of tumour invasion can be accurately determined (fig. 8). Loss of movement of a visualized tumour with respiration suggests extension beyond the parietal pleura.

Colour Doppler US may aid in distinguishing malignant from benign pulmonary masses [32–34]. Almost two thirds of peripheral malignant masses will demonstrate a colour Doppler signal (low-impedance flow) due to neovascularity. A constant flow pattern correlates with malignancy, whereas a pulsatile or triphasic flow pattern is often observed in either malignant or benign masses [31]. At least one study has found that residual peripheral metastases showed diminished vascularity at colour Doppler imaging following chemotherapy [35].

Pneumonia and Lung Abscess

Apart from solid tumours, numerous pathological processes can replace the air within lung tissue and thereby become detectable with US, provided that the pleural contact is present. Pleural-based pneumonic consolidation is detectable by means of US, although the extent of disease appears smaller at US than on chest radiographs. In the early phase of consolidation, the lung appears diffusely echogenic, similar to the ultrasonographic texture of the liver. Air and fluid bronchograms appear as echogenic branches that vary with respiration. Fluid bronchograms appear as anechoic tubular structures, representing fluid-filled airways, and are typically seen in bronchial obstruction [9]. Fluid bronchograms should alert the clinician to the possibility of a postobstructive pneumonitis, secondary to a proximal tumour. US may also aid in distinguishing a central obstructive tumour (usually hypoechoic) from distal consolidation (more echogenic) [36]. Sonographically observed consolidation is not synonymous with infective pneumonia. Pulmonary infarction, haemorrhage and bronchoalveolar carcinoma are examples of noninfective causes of consolidations that are similar in appearance on US. US may guide transthoracic needle aspirations or biopsies of peripheral pulmonary infiltrates in cases with diagnostic uncertainty regarding the aetiology [37, 38].

A lung abscess abutting the pleura appears as a hypoechoic lesion with a well-defined or irregular wall (fig. 9) [38]. The centre of the abscess is most often anechoic, but may reveal septations and internal echoes. Abscesses containing air fluid levels are more inhomogeneous.

Pulmonary Oedema and other Alveolar-Interstitial Syndromes

In the setting of patients with acute dyspnoea it has been reported that the presence of bilateral, widespread comet-tail artefacts (fig. 10) is a reliable sign to differentiate patients with pulmonary oedema from those with chronic obstructive airway disease [39]. Lichtenstein et al. [40] reported that comet-tail artefacts were absent in 92% of patients with chronic obstructive airway disease, but detectable in 93% of patients with alveolar-interstitial syndromes.

Pulmonary Embolism

US can aid in the acute bedside assessment of patients presenting with possible pulmonary embolism [41]. Pulmonary infarction is recognized as a peripheral wedge-shaped hypoechoic region, often accompanied by a pleural effusion [42–44]. A central hyperechoic bronchiole and a congested pulmonary vessel can sometimes be
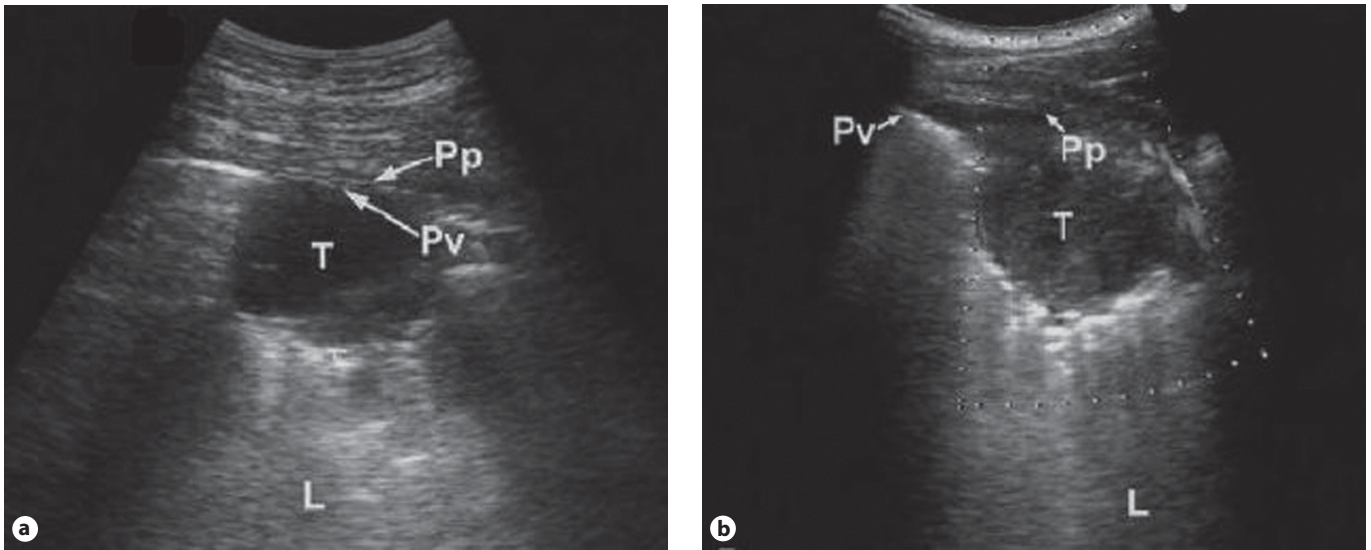
Fig. 8. a An US image showing a lung tumour with posterior echo enhancement. Note that both the visceral as well as the parietal pleural lines are intact. **b** This US shows tumour extension beyond the pleura. The visceral pleural line is interrupted, and the respiratory movement of the tumour is disturbed in real-time US. Invasion of the pleural cavity by the tumour is evident. L = Lung; T = tumour; Pv = visceral pleura; Pp = parietal pleura [from 2, with permission].

Fig. 10. A high-frequency US of a patient with pulmonary oedema showing widespread pronounced comet-tail artefacts (a reliable signs of interstitial pulmonary oedema). C = Comet-tail artefacts; E = pleural effusion.

Fig. 9. A peripheral lung abscess. Note the hypoechoic centre and irregular wall. A = Abscess cavity; L = lung.

observed [4]. The extent of pulmonary infarction is invariably underappreciated at US, as is the case for pneumonic consolidation. US is also useful in detecting the sequelae of thromboembolic disease such as right ventric-

ular overload and dilated hepatic veins. In experienced hands, thoracic US has a sensitivity of 77–89% and specificity of 66–83% for pulmonary embolism [42–44]. However, sonographic detection of pulmonary emboli is currently still reserved for physicians with an interest in US, as pulmonary spiral CT angiography remains the investigation of choice.

Fig. 11. This patient presented with a suspected hydatid cyst. Her CT chest showed cystic mass (pleural based) (**a**), and a FNA was safely performed with the assistance of low-frequency US (**b**). C = Cyst.
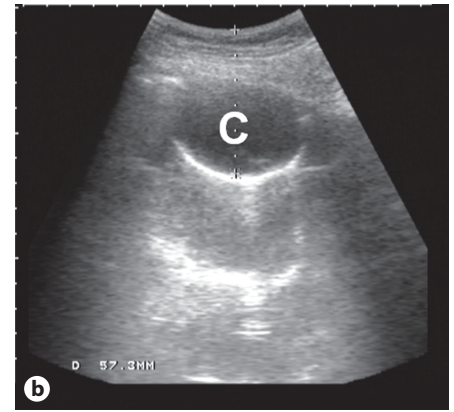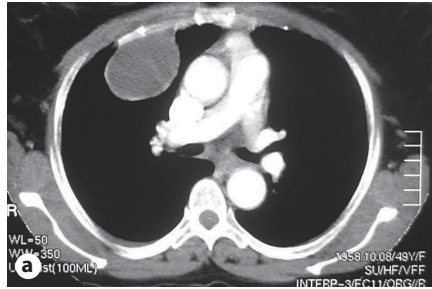
Other Pulmonary Pathology

Pleural-based cysts (e.g. echinococcus cysts) can be visualized as large anechoic (round) lesions (fig. 11). Pulmonary arteriovenous malformations may also be seen at US as these congenital abnormalities are often peripheral. Arteriovenous malformations appear as distinct hypoechoic lesions with posterior acoustic enhancement [45]. Lesions show high vascularity on Doppler with low-impedance flow.

Rounded atelectasis may give rise to a pleural-based mass with associated pleural thickening and extrapleural fat. The invaginated pleura may be seen as an echogenic line running from the pleura into the mass [46].

US-Guided Interventions

Principles

US is ideal for guiding chest wall, pleural and peripheral pulmonary interventions, including diagnostic thoracentesis, closed tube drainage, chest wall and pleural biopsies and biopsies of lung tumours abutting or invading the pleura. The use of US increases the success rate and minimises risk compared to blind procedures [1].

Specific reusable probes for real-time US guidance of needle biopsies are commercially available. Many experienced physicians, however, prefer the so-called 'freehand' technique. Following adequate patient positioning, the intended site of needle insertion is sonographically identified and marked, while the direction, the depth of interest and the safety range for the procedure are determined and memorized [1] (online suppl. video 6). It is essential that the subject must not change position in order to prevent a shift of the area of interest relative to the skin mark. It is occasionally even necessary to ask the patient to hold his breath for the duration of the aspiration. The practice of

identifying a puncture site at a radiology department prior to transporting a patient elsewhere for thoracentesis should be discouraged, particularly in the case of small effusions, as both the fluid collection and the skin mark might shift considerably with minor changes in body position.

Chest Wall Biopsy

Soft-tissue masses of indeterminate aetiology may be sampled by means of US-assisted fine needle aspirations (FNA) or biopsies [4]. US-guided procedures may also be used to detect chest wall invasion by pulmonary tumours. High-resolution US is superior to routine chest CT in evaluating tumour invasion of the pleura and chest wall [30, 31], and Nakano et al. [47] have even suggested US-assisted cutting needle biopsy (CNB) of the chest wall for the preoperative assessment of chest wall invasion by pulmonary neoplasms (specificity: 100%, diagnostic accuracy: 83%).

Pleural Fluid Aspiration

US is superior to chest radiographs for the documentation of the optimal site for diagnostic thoracentesis [48]. The most accessible area of fluid accumulation can be identified, and an aspiration can easily be performed by means of the 'freehand' technique (online suppl. video 7). The success rate of US-guided thoracentesis can be as high as 97% [49]. US-guided thoracocentesis improves the diagnostic yield and decreases the risk of complications in all patients, but is particularly helpful when a safe procedure is mandatory, e.g. in patients with bleeding diathesis.

Intercostal Tube Drainage

Ultrasonography is ideal for identifying the optimal site for safe and effective pleural drainage (fig. 12). This is particu-
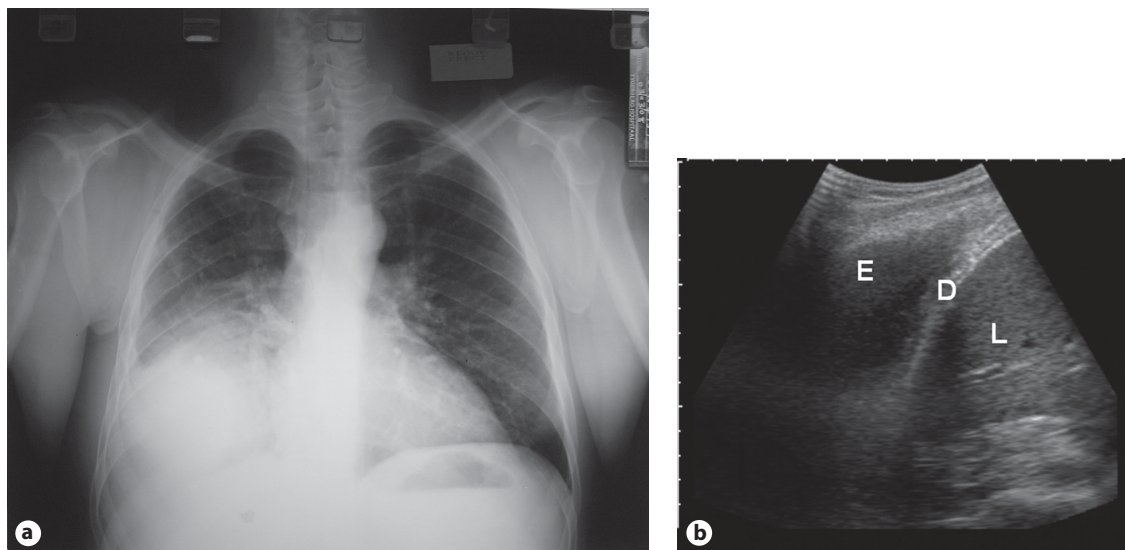
Fig. 12. A low-frequency US was used to guide a diagnostic aspiration and the insertion of an intercostal drain in this patient with empyema. **a** His chest radiograph was suggestive of a large loculated right-sided effusion. **b** US confirmed this, but also revealed a raised right hemidiaphragm. An optimal site for the aspiration and drain insertion was subsequently identified. E = Effusion; D = diaphragm; L = liver.

larly relevant in patients in an ICU setting and with loculated parapneumonic effusions, where thickened parietal pleura, adhesions or loculations often complicate insertion. Depending on operator experience, US may also guide further decisions regarding the need for subsequent intrapleural fibrinolytics, thoracoscopy or for surgical intervention in addition to tube drainage and antibiotics [50].

US-guided drains are most frequently inserted by means of the 'freehand' technique. As an alternative, effusions may also be accessed by means of an 18- or 16-gauge needle under direct (real-time) US visualization. This allows direct fluid aspiration followed by an insertion of a guide wire, which is used to guide dilatation of a tract and deployment of a small-bore catheter (8–14 french). These tubes are better tolerated than large bore (20–24 french) intercostal drains [51], although common sense suggests that smaller bore drains are more likely to fail in the presence of pus with a high viscosity. Some prospective studies have found that 8- to 12-french pigtail catheters or 10- to 14-french catheters inserted with the Seldinger technique under US or CT guidance were at least as effective as larger catheters inserted without imaging [51–53]. However, the positioning of the catheter tips with guidance is likely to be superior compared to a blind insertion, irrespective of drain size. Most of these studies also employed a strict rinsing schedule (often several times a day), which might be difficult to sustain in everyday clinical practice. Moreover, a recent study found a failure rate of 19% with small-bore catheters and concluded that the threshold for using fibrinolytics and large-bore catheters should be low in empyema [54].

Closed Pleural Biopsies

US is an extremely helpful guide for biopsies of the pleura. Focal pleural abnormalities can be identified with US, and biopsy can be aimed at areas of interest. Measuring the size of an associated effusion decreases the risk of visceral lacerations, which is particularly relevant in cases with small pleural effusion [1].

Closed pleural biopsies (e.g. with the Abrams needle) could conventionally only be performed in the presence of a sizeable pleural effusion or pneumothorax visible on chest radiography. Ultrasonography, however, can demonstrate small fluid collections and facilitate the use of devices that were not primarily designed for pleural biopsies in the absence of an effusion. Numerous studies have shown that US-assisted Tru-Cut needle biopsies have higher sensitivity and specificity in the diagnosis of pleural malignancy than unaided Abrams needle biopsies [55–59]. Chang et al. [55] found a sensitivity of up to 86% for pleural malignancies or tuberculosis, whereas Helio et al. [56] showed that US-assisted biopsies had a sensitivity of 77% and a positive predictive value of 100% for malignant mesothelioma. Diacon

Fig. 13. An example of a case suitable for US-guided fine-needle aspiration and/or biopsy. **a** The chest radiograph showed a lesion in the peripheral right mid lung field. **b** The corresponding sonar image shows that good transthoracic access to the tumour is provided. An US-guided FNA and biopsy confirmed small cell lung cancer [from 3, with permission].
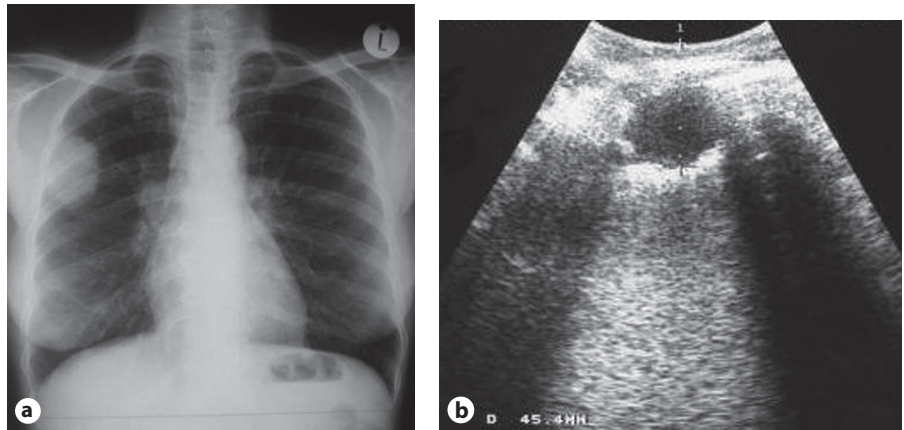
et al. [59] found that US-assisted biopsies had a sensitivity and specificity of 100% for mesothelioma provided the tumours were greater than 3 cm in diameter.

Transthoracic FNA and Needle Biopsies of Solid Tumours
Transthoracic FNA (TTFNA) and needle biopsies of solid tumours by means of US-assisted FNA or cutting biopsy performed under local anaesthesia and by non-radiologists are safe procedures and have high diagnostic yields [59]. Peripheral lung tumours that either abut or invade the pleura or chest wall and anterior mediastinal masses are ideally suited for these procedures (fig. 13). No aerated lung needs to be transversed with the biopsy device, and the risk of pneumothorax is therefore low. Furthermore, US-assisted biopsies can be readily performed outside a theatre, which offers advantages in immobile patients with advanced disease. TTFNA are performed under local anaesthesia, preferably with a 22-gauge injection-type or spinal needle (online suppl. video 8). CNB follow the same principles as TTFNA, but such devices are more invasive and carry the risk of vascular trauma if the anatomical locations of subclavian, brachial, intercostal and mammarian arteries are not respected.

A prospective study by Diacon et al. [59] found that TTFNA and closed needle biopsies performed by pulmonologists corresponded well in the diagnosis of epithelial lung carcinoma and in the distinction of small cell and non-small cell bronchogenic carcinoma. They were able to show that US-guided 'free-hand' CNB of lung tumours abutting the chest wall had a diagnostic sensitivity of 85.5%. The same investigators also found that US-assisted TTFNA with rapid on-site evaluation by a cytopathologist of tumours abutting the chest wall were diagnostic in 82% [60].

Subanalyses of their data proved that US-guided TTFNA, compared to CNB, had a superior yield for bronchial carcinoma whereas CNB was superior in the minority of cases with non-carcinomatous tumours and non-malignant lesions [60]. CNB should therefore be performed in all cases where cytology is non-contributory and in cases where a diagnosis other than lung cancer is suspected. Both US-guided CNB and FNA had a low complication rate, with pneumothoraces observed in 4 and 1.3%, respectively [60].

US is not only used to assist transthoracic procedures, but also to exclude a pneumothorax post-TTFNA or biopsy. If the lesion remains visible and unchanged in location, shape and size, it implies that no free air is present between the sampled lesion and the visceral pleura, and that a clinically relevant pneumothorax is unlikely [1, 3].

TTFNA and/or Needle Biopsies of Diffuse Parenchymal Infiltrates, Consolidations and Lung Abscesses
The indications for US-assisted TTFNA and biopsies are not limited to solid tumours but can be helpful in other aetiologies of lung consolidation. Yang et al. [37] reported a diagnostic yield of as high as 93% with US-assisted biopsies of pulmonary consolidation of unknown aetiology. This procedure is particularly useful in the immunocompromised patient, given the extensive differential diagnosis. The same author was able to sonographically demonstrate abscess cavities in 94% of 35 patients with radiologically confirmed lung abscesses [61]. At US, lung abscesses were depicted as hypoechoic lesions with irregular outer margins and an abscess cavity that was manifested as a hyperechoic ring. More than 90% of all aspirates of these abscesses yielded pathogens, whereas less than 10% of patients had positive blood cultures.

Conclusion

The value of US for chest physicians is firmly established. Basic thoracic ultrasonography is an elegant and inexpensive investigation that extends the physicians' diagnostic and interventional potential at the bedside in peripheral lung, pleural, and chest wall disease. It has the potential to replace CT-guided FNA or biopsies of all lesions involving the pleura and chest wall as well as lung masses or consolidations abut-

ting the pleura. Academic institutions should strive to have a basic training program in thoracic ultrasonography in place in order to ensure that all aspiring chest physicians are familiar with the basic aspects of chest ultrasonography.

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Chapter 3

THE DIAGNOSTIC YIELD OF TRANSTHORACIC FINE NEEDLE ASPIRATION WITH RAPID ON-SITE EVALUATION IN A NOVEL CLINICAL SETTING

> **Koegelenberg CFN, Bolliger CT, Irusen EM, Wright CA, Louw M, Schubert PT, Diacon AH. The diagnostic yield and safety of ultrasound-assisted transthoracic fine needle aspiration of drowned lung. Respiration 2011;81:26–31**

Respiration

The Diagnostic Yield and Safety of Ultrasound-Assisted Transthoracic Fine-Needle Aspiration of Drowned Lung

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Abstract

Background: Proximal lung tumors, though not discernable by means of transthoracic ultrasound (US), may cause varying degrees of pulmonary collapse and postobstructive pneumonitis which may give rise to a 'drowned lung' appearance on chest computed tomography (CT) and US. The diagnostic yield for malignancy of US-assisted transthoracic fine-needle aspiration (FNA) of these areas of drowned lung is unknown. **Objectives:** We aimed to explore the feasibility of US-assisted FNA in this setting by prospectively investigating its diagnostic yield and safety. **Methods:** We enrolled 31 patients (aged 59.4 ± 9.7 years, 17 males) with central tumors and secondary drowned lung on CT scan. A respiratory physician performed transthoracic US to identify the target drowned lung tissue. Three US-assisted superficial FNA passes (≤20 mm from the pleura) were followed by 3 deeper FNA passes (>20 mm) aimed in the direction of a visible or approximated central mass. Rapid on-site evaluation of specimens was used. **Results:** Superficial FNA was diagnostic in 11 patients (35.5%), whereas deeper FNA was diagnostic in 23 patients (74.2%, p = 0.002). Deeper FNA confirmed malignancy in all cases with diagnostic superficial FNA. We observed no pneumothoraces or major hemorrhage. All patients were ultimately diagnosed with malignancy (bronchogenic carcinoma, n = 30; lymphoma, n = 1). **Conclusions:** US-assisted FNA of drowned lung has an acceptable diagnostic yield and is safe.

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Introduction

Transthoracic ultrasound (US) has become a valuable diagnostic aid for respiratory physicians [1–6] and is increasingly being used to guide interventional procedures such as thoracentesis and biopsies of the pleura and lung tumors that abut the chest wall [1, 2, 7–9]. Studies have shown that US-assisted transthoracic fine-needle aspiration (FNA) in the setting of intrathoracic malignancies that extend to the chest wall is safe and has a high diagnostic yield, particularly in the setting of bronchogenic carcinoma where the diagnostic sensitivity is greater than 90% [7–9].

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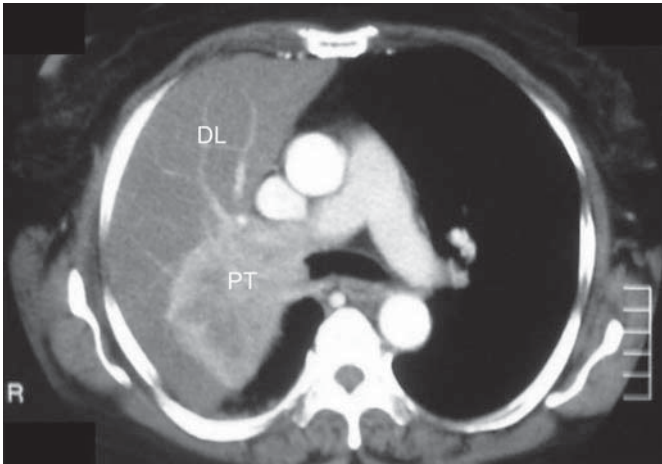Tel. +27 21 938 9243, Fax +27 21 933 3591, E-Mail coeniefn@sun.ac.za

Fig. 1. This CT scan of one of the study subjects shows a distinct central mass lesion (primary tumor) with secondary drowned lung. Note the enhanced pulmonary vasculature. In this particular patient, aspirates were taken in the supine position anterolaterally in order to transect at least 40 mm of drowned lung (as measured from the visceral pleural to the drowned lung-tumor interface). PT = Primary tumor; DL = drowned lung.

Fig. 2. An example of the US appearance of drowned lung. The arrow depicts the preserved bronchovascular bundle appearing as fluid-filled tubular structures. Note that the fluid bronchograms are best appreciated on real-time US. No clear plane between the drowned lung and tumor mass could be identified in this particular case.

The parenchyma of normal aerated lungs is not discernable by means of US. Proximal lung tumors are therefore not considered amenable to US-assisted transthoracic FNA or cutting-needle biopsies. Proximal lung tumors may, however, cause varying degrees of pulmonary collapse (resorptive atelectasis) and postobstructive pneumonitis. 'Drowned lung' is a radiological term often used to describe these areas which are considered to represent accumulated secretions and are typified on chest computed tomography (CT) by enhanced pulmonary vasculature contrasted against the surrounding pulmonary consolidation (fig. 1) [10, 11]. The fluid-filled airways are detectable on US as fluid bronchograms, which are dynamic anechoic tubular structures within consolidated lung that fluctuate with respiration, provided the consolidation extends to the chest wall (fig. 2) [2, 12].

The diagnostic yield for malignancy of US-assisted FNA of areas of drowned lung secondary to proximal tumors is not known. Moreover, endobronchial inspection and sampling by means of flexible bronchoscopy is generally considered the standard diagnostic approach in this scenario [10, 13, 14]. We therefore aimed to explore the feasibility of US-assisted transthoracic FNA in this setting by prospectively investigating its diagnostic yield and safety. Furthermore, we tested the hypothesis that aspirations performed close to the primary tumor would have a greater chance of yielding diagnostic material than more superficial passes.

Materials and Methods

Study Population

Our institution is a 1,200-bed academic hospital in Cape Town, South Africa. It is 1 of 2 referral centers and renders a tertiary service to a population of approximately 1.5 million people. Over a 3-year period (from May 2007 to April 2010) we screened the CT scans of all adult patients (>18 years) with suspected bronchogenic carcinoma reviewed at the Division of Pulmonology's daily radiology meeting, which acts as a forum where all internal and external referrals of patients with potential bronchogenic carcinoma are routinely presented (from January 2007 to December 2009, 906 cases of confirmed primary lung cancer were presented at this meeting according to our divisional cancer registry). All patients with an unequivocal central mass lesion with secondary drowned lung (on CT scan) were subsequently invited to participate in this prospective observational study, provided that the suspected carcinoma did not extend to the visceral pleura, at least 1 lobe was involved, at least 40 mm of drowned lung (minimal distance measured from visceral pleura) was present, and a tissue diagnosis was not known. For the purposes of this study, drowned lung was defined on contrasted CT scan as consolidated lung parenchyma with enhanced pulmonary vasculature distinct from and distal to a central mass lesion. The Health Research Ethics

Committee of Stellenbosch University approved the study (project No. N08/01/010). Written informed consent was obtained from all subjects upon enrolment and also prior to any invasive procedures.

Transthoracic US

A consultant respiratory physician performed the sonography (Toshiba JustVision 200 SSA-320A; Toshiba Medical Systems Corporation, Utsunomiya, Japan). A standard 3.75-MHz sector probe was used and the patients' positions for US scanning were determined by the corresponding CT scan, e.g. patients with lower-lobe involvement were generally examined in the sitting position using a bedside table as an armrest, whereas patients with upper-lobe involvement were scanned in the supine position. All procedures were performed in a bronchoscopy suite without the support of a specialist radiologist. The physician was asked to specifically comment on the presence of drowned lung and whether a distinct border between the apparent proximal mass and distal drowned lung could be observed. An associated effusion, if present, was documented as follows: minimal (if the echo-free space was confined to the costophrenic angle), small (if the space was greater than the costophrenic angle but still within the range of the area covered with a 3.75-MHz curvilinear probe), moderate (if the space was greater than a 1-probe range but within a 2-probe range, and large (if the space was larger than a 2-probe range) [1]. The intended puncture site was subsequently identified and marked, and the direction and the depth of interest for the procedure were documented. The site of aspirations was the epicenter of pleural contact, and the intended direction was towards the observed or anticipated location of the central mass lesion while care was taken to avoid any major blood vessels or viscera. All procedures were subsequently performed 'freehand' (not under direct real-time US guidance).

Transthoracic FNA

Aspirations were performed with 22-gauge spinal needles of 40- or 90-mm length as needed (Tae-Chang, Kong Ju City, Korea) connected to a 10-ml syringe under sterile conditions with local anesthesia (lignocaine 1%) and no sedation. Three superficial passes at a depth not greater than 20 mm from the visceral pleura were performed, followed by 3 deeper passes ranging from 20 to 60 mm. For the purposes of the study, care was taken not to aspirate pleural fluid or to contaminate the needles with pleural effusion. The inner stylet of the spinal needle was only removed once the target area had been reached, and no suction was applied while the needle was withdrawn. Aspirates (all from slightly different directions and depths) were directly expressed onto slides, smeared, and submitted for rapid on-site evaluation (ROSE) using both Diff-Quik (Rapidiff; Clinical Sciences Diagnostics, Johannesburg, South Africa) and rapid Papanicolaou staining methods [15].

ROSE of Cytology Specimens

The cytopathologist present in theater was experienced in ROSE and was asked to comment on the presence or absence of diagnostically useful material obtained during each individual pass. Material that was considered not diagnostically useful included exclusively blood, necrotic tissue, or the total absence of cellular material. The cytopathologist was subsequently asked to comment on cytological evidence of drowned lung, which for the purposes of this study was defined as an aspirate that contained a paucity of bronchial cells with a predominance of alveolar macrophages or pneumocytes (75% or more). Finally, he or she was asked to comment on the presence of malignant cells and, if present, whether they could be provisionally categorized as non-small cell lung carcinoma, small cell lung carcinoma, epithelial carcinoma not otherwise specified, or malignant cells of unknown origin.

Immediate Postprocedure Care

The FNA site was reexamined by means of US immediately after the procedures, and a chest radiograph was obtained if the pre- and postprocedure US findings differed and at the discretion of the attending physician. All patients were observed for at least 2 h prior to discharge and complications were noted. The presence or absence of chest wall hemorrhage and a pneumothorax was specifically documented.

Further Assessment and Statistical Analysis

All cytology slides were reviewed in the laboratory by a second experienced cytopathologist who had an array of special stains (including immunohistochemistry) at his or her disposal and had to concur with the original cytopathologist prior to issuing a final cytological diagnosis. In case of disagreement, a third cytopathologist was consulted to resolve the case.

Further investigations for patients who remained undiagnosed or who required additional staging were guided by the patient's attending respiratory physician. These investigations potentially included bronchoscopy with direct forceps and/or transbronchial needle aspiration biopsies (TBNA), CT-guided FNA, or even surgical biopsies. All patients were followed up until a tissue diagnosis could be confirmed. All cases of bronchogenic carcinoma were staged according to the 2002 Union Internationale Contre le Cancer staging system for lung cancer [16].

Descriptive statistics and McNemar's test (performed to assess whether the proportion of positive diagnoses was the same between deep and superficial passes) were utilized. $p \leq 0.05$ in a 2-tailed test was considered statistically significant. Unless stated otherwise, data are displayed as means $\pm$ standard deviation (SD). We used standard methods to calculate the sensitivity [17]. We had no firm data to base the sample size estimation of this proof-of-concept study on; therefore, we only used approximations. We considered a difference of 50% between superficial and deeper passes worth detecting, and posited a yield of 25 and 75%, respectively. A study population of 30 subjects was therefore considered sufficient (with a 5% confidence level allowing for 25% nondiagnostic aspirations).

Results

Patients

Over the 3-year period we screened >1,000 CT scans and identified 39 patients with drowned lung. We enrolled all 31 patients (aged 59.4 $\pm$ 9.7 years, 17 males) who fulfilled the inclusion criteria. Of these, 30 patients were ultimately diagnosed with bronchogenic carcinoma and

1 with a lymphoma (tables 1, 2). Eight patients were not included as they had an established tissue diagnosis (all bronchogenic carcinoma) at the time of screening. Only 1 of the 31 patients enrolled had undergone a preceding bronchoscopy, which was nondiagnostic (the single case of Hodgkin's lymphoma).

Imaging

On CT scan the central mass lesions' maximum diameter in any plane ranged from 12 to 60 mm. The extent of pulmonary involvement with regard to drowned lung ranged from 40 to 61 mm (52.6 ± 5.8 mm) expressed as the shortest distance between the pleura and the central mass. Anatomically the areas of drowned lung varied from total lung (n = 8, 25.8%) to bilobar lung (n = 1, 3.2%) to unilobar right lung (n = 22, 71.0%) (table 3).

Drowned lung was confirmed in all cases on US and measured from 40 to 62 mm (54.3 ± 8.9 mm) from the visceral pleura. A clear plain of separation between areas of distal drowned lung and the proximal mass lesion was only observed in 10 cases (32.3%). Twelve patients (38.7%) had evidence of an associated effusion ranging from minimal (n = 5, 16.1%) to small (n = 7, 22.6%).

Fine-Needle Aspirations

A total of 93 superficial FNA passes (range 9–20 mm from the pleura) and 94 deep FNA passes (range 25–60 mm) were performed. Laboratory confirmation of bronchogenic carcinoma was possible in 11 of the 31 patients based on specimens obtained by means of superficial passes (sensitivity 35.5%) and in 23 patients based on specimens obtained with deep FNA passes (sensitivity 74.2%, p = 0.002). Deep passes confirmed malignancy in all cases in which superficial passes were diagnostic (in no case was a diagnosis made based solely on a superficial FNA). Cytological evidence of drowned lung was present in 28 patients based on superficial passes (90.3%) and in 24 patients based on deep passes (77.4%, p = 0.343).

At least 1 of the 3 deep FNA passes was performed to a depth greater than that of the measured (on US) or estimated (on CT scan) tumor-drowned lung interface in 8 patients. These passes yielded the only positive specimens in 3 patients, whereas both sets (including passes that did not cross this interface) were positive in 3 more cases. Both were negative in 2 cases.

Further Investigations

Of the 23 patients with a firm cytological diagnosis of bronchogenic carcinoma, most had either advanced non-small cell lung cancer (table 2) or small cell lung cancer. Only 3 patients required a subsequent bronchoscopy with TBNA to clarify the staging. Of the 8 cases in which a diagnosis could not be established by means of US-assisted transthoracic FNA, 7 were diagnosed by bronchoscopy with TBNA and 1 by mediastinoscopy (the solitary case of lymphoma). In total, 11 patients (35.5%) required further investigation, which in no case was deemed high risk.

Table 1. Final established diagnoses of all study subjects (n = 31)

Diagnoses	n	%
Non-small cell lung cancer		
Adenocarcinoma	10	32.3
Squamous cell carcinoma	12	38.7
Undifferentiated/large cell	3	9.7
Small cell lung cancer	5	16.1
Hodgkin's lymphoma (nodular sclerosing type)	1	3.2

Table 2. Final TNM staging[1] of all cases of non-small cell lung cancer (n = 25)

Stage	n	%
I	0	0
II	2	8
IIIA	2	8
IIIB	10	40
IV	11	44

[1] According to the 2002 Union Internationale Contre le Cancer staging system [16].

Table 3. Anatomical extent of drowned lungs (n = 31)

Lobes involved	n	%
Complete right lung	5	16.1
Isolated right upper lobe	11	35.5
Isolated right middle lobe	1	3.2
Isolated right lower lobe	1	3.2
Right lower and middle lobes	1	3.2
Complete left lung	3	9.7
Isolated left upper lobe	9	29.0
Isolated left lower lobe	0	0.0

Complications

The procedures were well tolerated and no pneumothoraces were noted. Only 1 case of minor hemorrhage which subsided upon compression alone and did not require surgical sutures was documented.

Discussion

This prospective study is, to the best of our knowledge, the first to investigate US-assisted transthoracic FNA of drowned lung to determine the diagnostic yield for malignancy. We found that FNA passes at a depth greater than 20 mm from the visceral pleura had a diagnostic sensitivity of 74.2% and that they were more likely to contain malignant cells than more superficial passes (74.2 vs. 35.5%, p = 0.002). Furthermore, we observed no serious complications.

We previously showed that transthoracic US-assisted FNA with ROSE and cutting-needle biopsies had a combined sensitivity of 81% for a spectrum of benign and malignant lesions that abutted the pleura [8]. More importantly, this technique had a sensitivity of 95% for bronchogenic carcinoma and a pneumothorax rate of only 1.3% [8]. In another study we found that this modality had a diagnostic sensitivity of 96% in patients who presented with superior vena cava syndrome with an associated mass lesion abutting the chest wall [9]. Yang et al. [18] previously found that US-guided cutting-needle biopsies have a diagnostic yield of 94.6% for subpleural pulmonary tumors. Although the diagnostic yield in the present study is certainly not on par with these figures, our data provides novel evidence that transthoracic US-assisted FNA may even be useful in cases where the primary tumor does not extend to the chest wall.

Approximately 35% of patients had cytological evidence of bronchogenic carcinoma on superficial FNA passes. Although this figure was significantly less than on deeper passes, it remained an important observation as these aspirates were obtained at a distance from the associated pulmonary mass. Interestingly this yield is very similar to that of sputum cytology [13, 19, 20], suggesting that endobronchial shedding and pooling of tumor cells may be the source of the diagnostic material obtained by means of superficial sampling from the drowned lung. We specifically aimed to avoid the potential contamination of specimens with malignant cells inadvertently obtained from pleural fluid, making it a much less likely source.

Bronchoscopy has an overall sensitivity of 88–95% for malignancy in patients with centrally located lung lesions [13, 21], which is superior to the sensitivity of US-assisted transthoracic FNA. It allows for the inspection of central airways, evaluation for therapeutic airway management, and the acquisition of histological samples that may allow for superior subtyping and immunohistochemistry [13]. Furthermore, mediastinal nodal staging by means of TBNA has important implications for the staging and management of lung cancer [16, 22]. Ten patients underwent bronchoscopy in our study, which in 3 patients only indicated the need for endobronchial mediastinal staging. In fact, the vast majority of our study population had advanced lung cancer.

As this study was purely a proof-of-concept study designed to explore the feasibility of US-assisted transthoracic FNA in a novel setting, it was not designed to compare US-assisted transthoracic FNA with bronchoscopy (or CT-guided FNA) or to define which patient may be best suited for a particular procedure. Notwithstanding these important considerations, our findings suggest that transthoracic US-assisted FNA of drowned lung may be utilized in specific circumstances, which may include patients who are considered high risk for bronchoscopy, those who refuse to undergo bronchoscopy, and those in whom a preceding bronchoscopy had been nondiagnostic. Moreover, it may be viewed as an acceptable alternative when endoscopic mediastinal staging is irrelevant [1] or when bronchoscopy is unavailable. Only future randomized studies will, however, be able to specifically delineate the subgroup of patients with drowned lung in whom a bronchoscopy may be considered superfluous.

Some practical considerations need to be emphasized. US-assisted FNA can be performed by a single clinician with no sedation and minimal monitoring, even potentially outside of theater [1]. The disposables (especially the needles) are cheap, and we once again showed that the procedure is safe even without the assistance of specialist radiologists. We observed no pneumothoraces or major hemorrhage, a finding that was not unexpected as no aerated lung was transversed and only 22-gauge needles were utilized.

We specifically only included cases with at least 40 mm of drowned lung (as measured from the visceral pleura) in order to have ample drowned lung to sample and to avoid direct sampling of the primary tumor by means of superficial FNA passes. A clear plane between the drowned lung and tumor mass could, however, only be identified in a minority of subjects with the aid of US, and in the majority this plane was purely an estimation

based on CT scan findings. The relative contribution of FNA passes from the actual tumor mass and from surrounding drowned lung to the reported diagnostic yield for deep passes is therefore uncertain. Although this may be viewed as a limitation of the study, this distinction seems irrelevant, as in practice knowing which specimen confirmed a cytological diagnosis of bronchogenic carcinoma would seem immaterial.

Our study was not designed to establish the true incidence of drowned lung secondary to lung cancer in our population, but our data suggest it to be a relatively rare presentation. Over a 3-year period we identified only 39 patients with central tumors and drowned lung, 38 of whom were diagnosed with lung cancer. We recorded 906 cases of primary lung cancer during that period, suggesting that approximately 4% of all patients with lung cancer had drowned lung at the time of initial presentation.

In conclusion, US-assisted FNA of drowned lung is safe and has an acceptable diagnostic yield, particularly when deep passes are performed. It may be a feasible alternative to bronchoscopy where endoscopy is considered high risk, where bronchoscopy has failed to yield a diagnosis, or where mediastinal staging is considered unnecessary. Future studies aimed at specifically delineating the subgroup of patients in whom a bronchoscopy may be considered superfluous are therefore indicated.

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Financial Disclosure and Conflicts of Interest

The authors report no conflicts of interest.

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Chapter 4

THE DIAGNOSTIC YIELD AND SAFETY OF A NOVEL, SINGLE-SESSION SEQUENTIAL APPROACH OF ULTRASOUND-ASSISTED TRANSTHORACIC FINE NEEDLE ASPIRATION WITH RAPID ON-SITE EVALUATION FOLLOWED BY CUTTING NEEDLE BIOPSY PERFORMED BY PHYSICIANS IN THE SPECIFIC CLINICAL SETTINGS

➢ **Koegelenberg CF, Bolliger CT, Plekker DP, Wright CA, Brundyn K, Louw M, Schubert P, van den Heuvel MM, Diacon AH. Diagnostic yield and safety of ultrasound-assisted biopsies in superior vena cava syndrome. Eur Respir J 2009;33:1389-1395**

➢ **Koegelenberg CF, Bolliger CT, Irusen EM, von Groote-Bidlingmaier F, Mowlana A, Wright CA, Louw M, Schubert PT, Diacon AH. The diagnostic yield and safety of ultrasound-assisted biopsy of mediastinal masses. Respiration 2011;81:134-141**

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Diagnostic yield and safety of ultrasound-assisted biopsies in superior vena cava syndrome

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ABSTRACT: The yield and safety of ultrasound (US)-assisted transthoracic fine needle aspirations (TTFNA) and cutting needle biopsies (CNB) in the setting of superior vena cava (SVC) syndrome are unknown. The aims of the present prospective study were to asses the diagnostic yield and safety of US-assisted TTFNA and CNB in SVC syndrome with an associated mass lesion abutting the chest wall.

Over a 3-yr period, the present authors screened 59 patients with SVC syndrome, and enrolled 25 patients who had an associated mass lesion that extended to the chest wall. US-assisted TTFNA with rapid on-site evaluation (ROSE) was performed in all cases. CNBs were performed where a provisional diagnosis of bronchogenic carcinoma could not be established, and in 57.1% of patients with bronchogenic carcinoma (limited due to safety constraints).

ROSE of US-assisted TTFNA confirmed diagnostically useful material in 24 patients, and cytological diagnoses were ultimately made in all of these cases (diagnostic yield 96%). US-assisted CNB had a diagnostic yield of 87.5%. Minor haemorrhage occurred in one out of 25 TTFNA and three out of 16 CNB. Neither procedure resulted in major haemorrhage nor pneumothoraces.

US-assisted TTFNA and CNB have a high diagnostic yield and are safe in the setting of SVC syndrome with an associated mass lesion abutting the chest wall.

KEYWORDS: Bronchogenic carcinoma, cutting needle biopsy, superior vena cava syndrome, transthoracic fine needle aspiration, ultrasound

The superior vena cava (SVC) syndrome is a clinical entity caused by obstruction of the superior vena cava by infiltration, compression or thrombosis [1]. Intrathoracic neoplasms, mainly bronchogenic carcinomas and lymphomas, are by far the most common causes [1–3]. An SVC syndrome secondary to an intrathoracic neoplasm is generally considered an oncological emergency that requires an expedient diagnostic evaluation and initiation of treatment [1, 4]. Bronchoscopy and associated procedures have a reported diagnostic yield of >70% in this setting, whereas mediastinoscopy or mediastinotomy have a diagnostic yield of >90% [5, 6]. The latter procedures are associated with a high anaesthetic risk and a relatively high complication rate, and major haemorrhage is seen in a significant percentage of cases due to high venous pressure [5, 6]. Moreover, associated brain oedema may complicate mediastinoscopy or mediastinotomy, as patients may experience significant discomfort in the supine position [1].

Thoracic ultrasound (US) is a well-established diagnostic aid to the clinician [7–10]. The major advantages of this modality include its dynamic properties, low cost, lack of radiation, mobility and short examination time [7–12]. US of the chest is increasingly being used to guide interventional procedures, such as thoracentesis, and biopsies of tumours of the chest wall, pleura or peripheral lung [7]. Intrathoracic mass lesions abutting or invading the chest wall are visible at US [7–9]. Recent studies on US-guided transthoracic fine needle aspirations (TTFNA) utilising rapid on-site evaluation (ROSE) and US-assisted cutting needle biopsies (CNB) of mass lesions involving or abutting the pleura have shown that these procedures are not only safe but also have a high diagnostic sensitivity [13, 14].

There is, however, a paucity of data on the diagnostic yield and safety of US-assisted TTFNA with ROSE and CNB in the setting of SVC syndrome caused by mass lesions that either

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abut or invade the chest wall. The aims of the present prospective study were to assess the feasibility, diagnostic yield and safety of these investigations in the setting of SVC syndrome and, specifically, in the hands of nonradiologists.

METHODS

Study population

All adult patients ($\geqslant$18 yrs of age) with a clinical diagnosis of SVC syndrome referred to the Division of Pulmonology of Tygerberg Academic Hospital, Cape Town, South Africa, were potential candidates for the present 3-yr prospective analytical observational study. Tygerberg Academic Hospital is a 1,200-bed university hospital. It is one of two referral centres and renders a tertiary service to a population of ~1.5 million people. The Committee for Human Research of the University of Stellenbosch, Cape Town, South Africa, ethically approved the study. Written informed consent was obtained from all subjects on enrolment and also prior to any invasive procedures.

A contrasted computed tomography (CT) scan of the chest and upper abdomen was performed on all patients, according to standard operating procedure at the Tygerberg Academic Hospital. Studies routinely included the supraclavicular fossae and lesions were classified on radiological appearance as to the most likely origin: ''mediastinal'' (lesions predominantly located in the anterior mediastinum with extension to the pleura), ''pulmonary'' (lesion with centre in the lung, acute angle to the pleura), ''pleural'' (pleural based, blunt angle to the lung) or ''chest wall'' (lesions centred in the chest wall with pleural involvement). All CT scans were scored by an independent radiologist with regards to the maximum length of the interface between the particular lesion and the thoracic wall (in the longest plane). The depth of lesions relative to the pleural surface and the presence of chest wall invasion were also documented.

The initial evaluation of all patients included, where applicable, fine needle aspiration (FNA) of palpable and/or radiologically detectable supraclavicular lymph nodes or diagnostic pleural aspirations. Only cases with confirmed partial or complete SVC obstruction that remained undiagnosed following these investigations and where an intrathoracic mass lesion abutted the chest wall to an extent that it made a FNA feasible were enrolled onto the present prospective observational study.

Thoracic US

A consultant respiratory physician or a senior registrar under supervision performed the sonography (Toshiba Just Vision 200 SSA-320A; Toshiba Medical Systems Corporation, Tochigi-ken, Japan). All procedures were performed in a bronchoscopy suite without the support of a specialist radiologist. Although the preferred patient position for the procedure was supine, with a parasternal approach, the clinician could employ a more lateral or apical approach if this was deemed feasible and safe. The operator reviewed the thoracic CT scan prior to performing the transthoracic US. The interface between the intrathoracic mass lesion and chest wall was then identified by means of a standard 3.75-MHz sector probe. An interface of $\geqslant$1 cm^2 visible throughout inspiration and expiration in an area not covered by bony elements was considered the minimal

requirement for an US-assisted procedure. Procedures were performed ''freehand'' (i.e. not under direct US guidance). The intended site was marked, and the direction, the depth of interest and the safety range for the procedure documented. The patient was instructed not to change position in order to prevent a positional shift of the area of interest relative to the skin mark. Care was taken to avoid the major intrathoracic blood vessels, and the intercostal and mammarian arteries, as well as any major collateral veins that may have formed secondary to the SVC obstruction.

TTFNA

Under sterile technique and local anaesthesia with lignocaine 1%, aspirations were performed with a 22-G spinal needle (40 or 90 mm; Becton Dickinson, Madrid, Spain) connected to a 10-mL syringe. Aspirates from at least four slightly different directions and depths were directly expressed onto slides, smeared and submitted for ROSE using Diff-Quik (Rapidiff; Clinical Sciences Diagnostics, Southdale, South Africa) and rapid Papanicolaou staining methods.

ROSE of cytology specimens

The cytopathologist present in theatre was experienced in ROSE and was asked to comment on the presence or absence of diagnostically useful material obtained during each individual pass. Material that was considered not diagnostically useful included blood, necrotic tissue or the total absence of cellular material. Where diagnostically useful material was present, the cytopathologist was asked to make a provisional diagnosis of malignant or nonmalignant pathology. Where malignant cells were present, the pathologist provisionally typed the specimens into one of two main categories: 1) epithelial carcinomas of the lung, or 2) other malignancies. Furthermore, epithelial carcinomas were subtyped into nonsmall cell lung cancer (NSCLC), small cell lung cancer (SCLC) or epithelial carcinoma of unsure type. Finally, the cytopathologist was asked to further provisionally subtype NSCLC into one of the following: 1) adenocarcinoma, 2) squamous cell carcinoma, 3) undifferentiated carcinoma, or 4) NSCLC, unsure subtype.

In the case of nonmalignant pathology or malignancies other than epithelial carcinoma, the cytopathologist was asked to give an opinion on the representative nature of the specimen and, if considered representative, which further investigations were appropriate (e.g. performing a cutting needle biopsy or collecting further aspirates for cultures for mycobacteria or fungi).

Cutting needle biopsies

Cutting needle biopsies were obtained following TTFNA in all cases where the provisional on-site diagnosis was not an epithelial carcinoma of the lung. In cases where the on-site diagnosis was epithelial carcinoma, biopsies were only performed if $\geqslant$2 cm of safe range could be assured (i.e. no major mediastinal organs, blood vessels and collateral veins were within 2 cm of the intended CNB path). Superficial veins were avoided. Manually operated 14-gauge Tru-cut biopsy needles with a specimen notch of 20 mm (Allegiance, Chateaubriand, France) were used. Two or more passes were performed until macroscopically satisfactory material was

harvested. These specimens were harvested in 4% formalin and routinely processed for histological evaluation.

Immediate post-procedure care

The TTFNA and CNB site were re-examined by means of US immediately after the procedures, and a chest radiograph was obtained if the pre- and post-procedure US findings differed and at the discretion of the attending physician. All patients were observed for $\geqslant 2$ h prior to discharge, and complications were noted. The presence or absence of minor or major haemorrhage, as well as iatrogenic pneumothoraces, was specifically documented. Major haemorrhage was defined as any haemorrhage that required additional measures above and beyond localised pressure and superficial sutures.

Further assessment and statistical analysis

All cytology slides were reviewed in the laboratory by two other cytopathologists, who were blinded to the on-site findings. These cytopathologists had an array of special stains (including immunohistochemistry) at their disposal, and had to concur prior to issuing a final cytological diagnosis. They also had access to the results of the flow cytometry in case of suspected lymphoma. The histological specimens were reviewed by two independent pathologists. Histology was classified as either ''diagnostic'' or ''nondiagnostic'' (normal tissue, not representative tissue, or representative but necrotic tissue). Only histological diagnoses or unequivocal cytology (where histology was unavailable and as reported by two laboratory-based cytopathologist) were accepted as diagnostic and used as the gold standard for statistical analyses. Patients in whom the initial procedures failed to yield diagnosis underwent further special investigations in order to obtain a diagnosis. The choice of further invasive investigations was guided by the patient's attending chest physician, and could potentially have included bronchoscopy with direct forceps or transbronchial needle aspiration biopsies (TBNA), CT-guided biopsies, medical thoracoscopy, video-assisted thoracoscopy, and mediastinoscopy or open surgical procedures.

Descriptive statistics and Chi-squared comparisons of proportional data were performed. Unless otherwise stated, data are displayed as mean±SD. Standard methods were used to calculate the sensitivity [15].

RESULTS

Patients and lesions

Over the 3-yr period of the present study, a total of 59 consecutive patients with clinical and radiological evidence of SVC obstruction were reviewed by the investigators. Of these, 25 patients (42.4%) were included in the study as they remained undiagnosed following the initial special investigations and had an SVC syndrome with an associated mass lesion that abutted or infiltrated the chest wall with an interface of $\geqslant 1$ cm. These patients had a mean±SD age of 55.8±11.6 yrs, and 16 were male. Fifteen patients had a pulmonary mass lesion, nine patients had a mediastinal mass and only one patient had a pleural-based mass. Of the pulmonary lesions that abutted the chest wall, only four were considered possibly metastatic in nature (all with an associated primary tumour elsewhere in the lungs). The mean depth of lesions (as measured on CT scans, and measured from the point of probable entrance, *i.e.* measured from the pleural surface, to the most distal tumour limit) was 78±17 mm. The maximum length of the interface between the lesions and the thoracic wall ranged 10–78 mm, with a mean of 26 mm. Radiological evidence of chest wall invasion was present in nine cases.

Each of the 25 patients enrolled were eventually found to have some form of neoplasm (table 1). Bronchogenic carcinoma was the most common diagnosis, with 11 NSCLC and 10 SCLC diagnosed. The remaining four patients had T-cell lymphoblastic lymphoma, B-cell lymphoma, thymoma and malignant mesothelioma, respectively.

The diagnoses established in the 34 subjects not included in the study population are summarised in table 2. These diagnoses were established by means of supraclavicular lymph node FNA (diagnostic in four out of six subjects, 67%), pleural fluid aspirations (diagnostic in one out of 16, 6%), bronchoscopy with TBNA (diagnostic in 21 out of 25, 84%), mediastinoscopy (diagnostic in two out of three, 67%) and open surgical biopsy (diagnostic in one out of one, 100%). Three patients had clear evidence of SVC thrombosis on contrasted CT scan (all occurred in the setting of intravascular devices) and two remained undiagnosed. Three patients (11%) who underwent a

TABLE 1	Final established diagnoses of all study subjects (n=25)
Diagnosis	**Subjects**
Nonsmall cell lung cancer	11 (44)
Adenocarcinoma	5 (20)
Squamous cell carcinoma	1 (4)
Undifferentiated	5 (20)
Small cell lung cancer	10 (40)
Lymphoma	2 (8)
Thymoma	1 (4)
Mesothelioma	1 (4)

Data are presented as n (%).

TABLE 2	Final established diagnoses of subjects not included in the study (n=34)
Diagnosis	**Subjects**
Nonsmall cell lung cancer	16 (47)
Adenocarcinoma	7 (20)
Squamous cell carcinoma	4 (12)
Undifferentiated	5 (15)
Small cell lung cancer	9 (26)
Metastatic breast carcinoma	1 (3)
SVC thrombosis	3 (9)
Fibrosing mediastinitis	2 (6)
Immature teratoma	1 (3)
Undiagnosed	2 (6)

Data are presented as n (%). SVC: superior vena cava.

US-ASSISTED BIOPSIES IN SVC SYNDROME
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bronchoscopy experienced minor haemorrhage, while all other procedures were uncomplicated.

US-assisted TTFNA

US-assisted TTFNAs were performed on all study subjects. Diagnostically useful specimens were obtained from 24 of the 25 study subjects. The on-site cytopathologist identified 21 cases of epithelial carcinoma of the lung and three other malignancies. No ROSE diagnosis was made in one subject. Of the 21 cases of malignant epithelial neoplasm of the lung, 12 were subtyped on ROSE as NSCLC and three as SCLC, whereas six cases could only be subtyped on morphological criteria as unsure type epithelial carcinomas.

After incorporating the results of the immunohistochemistry and flow cytometry (where applicable), two cytopathologists were able to reach a definite diagnosis in 24 out of the 25 cases. It was found that one patient with SCLC was erroneously diagnosed as adenocarcinoma on-site, as both the final cytology and histology confirmed SCLC (fig. 1). The formal laboratory assessment confirmed all other diagnoses, and the 21 cases of epithelial carcinoma of the lung could be subtyped (fig. 1). Furthermore, three cytological diagnoses other than lung cancer could be made in the laboratory: T-cell lymphoma, thymoma and malignant mesothelioma. In all three cases, these diagnoses were confirmed on histology (CNB). The overall diagnostic yield of US-assisted TTFNA was 96%.

CNB

CNB were performed in all four patients who did not have an on-site diagnosis of epithelial carcinoma and in 12 out of the 21 patients with epithelial carcinoma (57.1%). Reasons for not performing CNB included the close proximity of major blood vessels or superficial collateral veins (n=8) and a poor general state (n=1). Diagnostically useful material was obtained in 14 biopsies and the diagnoses made corresponded to the final
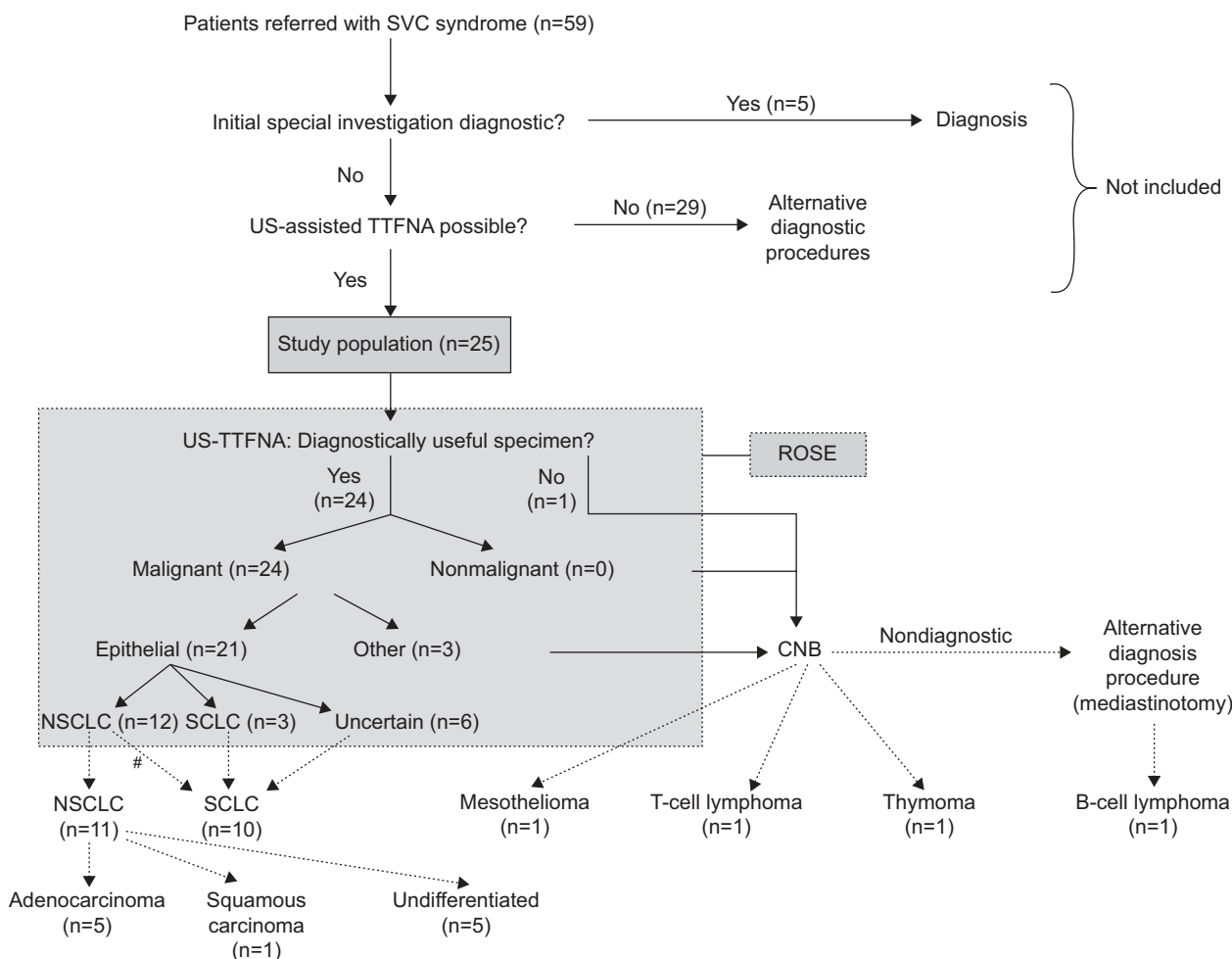
FIGURE 1. The diagnostic pathway followed in the present study. Initial (basic) special investigations included fine needle aspiration (FNA) of supraclavicular lymph nodes and pleural fluid cytology. Of the initial 25 patients, rapid on-site evaluation (ROSE) showed 24 patients to have diagnostically useful specimens obtained by means of ultrasound (US)-assisted transthoracic FNA (TTFNA). Cutting needle biopsies (CNB) were performed in all patients who did not have an on-site diagnosis of epithelial carcinoma of the lung and were deemed safe in 12 out of the 21 patients with epithelial carcinoma. In the case of nonmalignant pathology, further investigations may have included cultures for mycobacteria or fungi (not shown). The final pathological diagnosis was based on histology and unequivocal cytology (reviewed in the laboratory with special stains including immunohistochemistry; see text for detail). SVC: superior vena cava; NSCLC: nonsmall cell lung cancer; SCLC: small cell lung cancer. #: one case of SCLC was erroneously provisionally diagnosed as NSCLC.

cytological diagnoses in every case. Nondiagnostic specimens were obtained from two subjects: one patient with undifferentiated NSCLC was convincingly diagnosed on cytology. The other subject, who also escaped diagnosis by TTFNA, was eventually diagnosed as having a B-cell lymphoma by means of an open surgical biopsy (mediastinotomy). The overall diagnostic yield of CNB was 87.5%.

Complications

The procedures were well tolerated and no pneumothoraces were noted. Only five cases of haemorrhage were documented. One of the 25 patients (4%) experienced minor haemorrhage following TTFNA, and three out of 16 patients (18.8%) following CNB. One patient required a single superficial suture in order to achieve haemostasis. No procedure was complicated by major haemorrhage.

DISCUSSION

The present prospective study is, to the best of the present authors' knowledge, the largest single-centre study on US-assisted TTFNA with ROSE and CNB in the setting of SVC syndrome ever reported. Utilising these minimally invasive techniques, it was possible to accurately diagnose 96% of all patients who presented with an SVC syndrome with an associated mass lesion that either abutted or infiltrated the chest wall. US-assisted TTFNA with ROSE by a cytopathologist yielded specimens that had a diagnostic yield of 96%. CNB were performed in all cases where a provisional on-site diagnosis of malignant epithelial neoplasm of the lung could not be established, and in 57.1% of patients with malignant epithelial neoplasm of the lung (biopsies limited due to safety constraints). In this pre-selected group, CNB had a diagnostic yield of 87.5%. A paucity of complications was observed. No pneumothoraces or major haemorrhage was caused, and only mild haemorrhage occurred in 4% of needle aspirations and 18.8% of biopsies. These findings are comparable to case series not limited to SVC syndrome [13, 14].

Most experts still utilise cervical mediastinoscopy and anterior mediastinotomy to establish a diagnosis in patients with SVC syndrome secondary to anterior mediastinal mass lesions [5, 6]. These procedures have a diagnostic yield of almost 100%, but >15% of patients suffer a major complication [5, 6]. Furthermore, patients need to be able to withstand a general anaesthetic and lie in a supine position. The present data suggest that TTFNA and CNB, either US-assisted or CT-guided, should be the primary investigation, given the speed, low cost, safety and sensitivity of these minimally invasive techniques. US-assisted TTFNA has many added potential benefits: it can be performed in practically any setting (even outside theatre), on a patient in a variety of positions (including sitting), and a provisional result can be available within minutes if ROSE is utilised [7].

US-assisted biopsy performed by clinicians on peripheral pulmonary and mediastinal mass lesions in the absence of SVC syndrome is a well-established practice [7, 10, 13, 14, 16–24]. SAITO et al. [16] described US-guided mediastinal biopsies >20 yrs ago. They were able to diagnose 87% of all malignant tumours and 67% of benign masses [16]. YANG et al. [17] showed that US-guided CNB had a diagnostic yield of 94.6% for subpleural pulmonary tumours, and 88.9% for mediastinal

tumours. The same investigators also pioneered anterior mediastinal biopsies *via* the supraclavicular approach [18]. Numerous subsequent studies firmly established transthoracic mediastinal FNA and CNB as investigations with a diagnostic sensitivity ranging 80–90% [19–22] and as feasible alternatives to mediastinoscopy or diagnostic thoracotomy [23, 24]. The present authors previously reported a combined diagnostic yield for US-assisted TTFNA and CNB of 89% in 155 consecutive patients with mass lesions that abutted the chest wall [14]. In that study, TTFNA had a significantly higher sensitivity than CNB in diagnosing bronchogenic carcinoma (95 *versus* 81%; p=0.006), but CNB was superior in noncarcinomatous tumours and in benign lesions. SCHUBERT et al. [25] reported similar findings. These observations provide two plausible explanations for the high diagnostic yield observed in the present study. First, 84% of the present study population had bronchogenic carcinoma and, secondly, biopsies (CNB) were performed in all noncarcinomatous tumours. Decisions concerning the need for biopsies should therefore ideally be guided by the provisional results on ROSE, particularly when CNB are deemed to be risky.

There is a paucity of prospective data on the use of bronchoscopy in the setting of SVC syndrome. SELçUK and FIRAT [26] reported a very high diagnostic yield with TBNA and were able to diagnose 96% of patients. In fact, only a single case of non-Hodgkin's lymphoma escaped diagnosis in their series. Other smaller studies have reported similar findings [1, 27]. BLACK and ELOUBEIDI [28] were the first to describe the use of oesophageal US-guided FNA specifically in the setting of SVC syndrome.

The findings of the present study support earlier recommendations with regard to the early utilisation of contrasted CT scans in patients who present with suspected SVC obstruction secondary to malignant disease [1, 4, 29–31]. A CT scan can confirm SVC obstruction and the presence of an intrathoracic mass lesion [1, 29–31]. Moreover, in cases where basic investigations, such as sputum cytology, supraclavicular lymph node FNA and pleural aspiration, fail to yield a diagnosis, the findings of a CT scan may guide the choice between further special investigations, chiefly bronchoscopy with TBNA (in the case of more central tumours with mediastinal lymphadenopathy) or US-assisted TTFNA where tumours abut the chest wall [23, 24]. Mediastinoscopy and surgical biopsies should be reserved for patients who remain undiagnosed [23, 24].

Thoracic US has limitations; the most relevant and obvious limitation to the present study is its technical inability to visualise mass lesions that do not abut or invade the chest (fig. 2a). Hence, cases not amenable to US-assisted TTFNA were not included in the study (fig. 2b). US-assisted TTFNA was therefore the preferred procedure in only 42.2% of patients screened, while the majority of the remaining patients were diagnosed by means of bronchoscopy with TBNA.

The present study has limitations. We specifically evaluated the diagnostic yield and safety of US-assisted TTFNA and CNB, and immediately excluded cases that were diagnosed by means of supraclavicular lymph node FNA. High frequency ultrasonography of the supraclavicular fossae might have revealed pathological lymph nodes that escaped palpation [7],
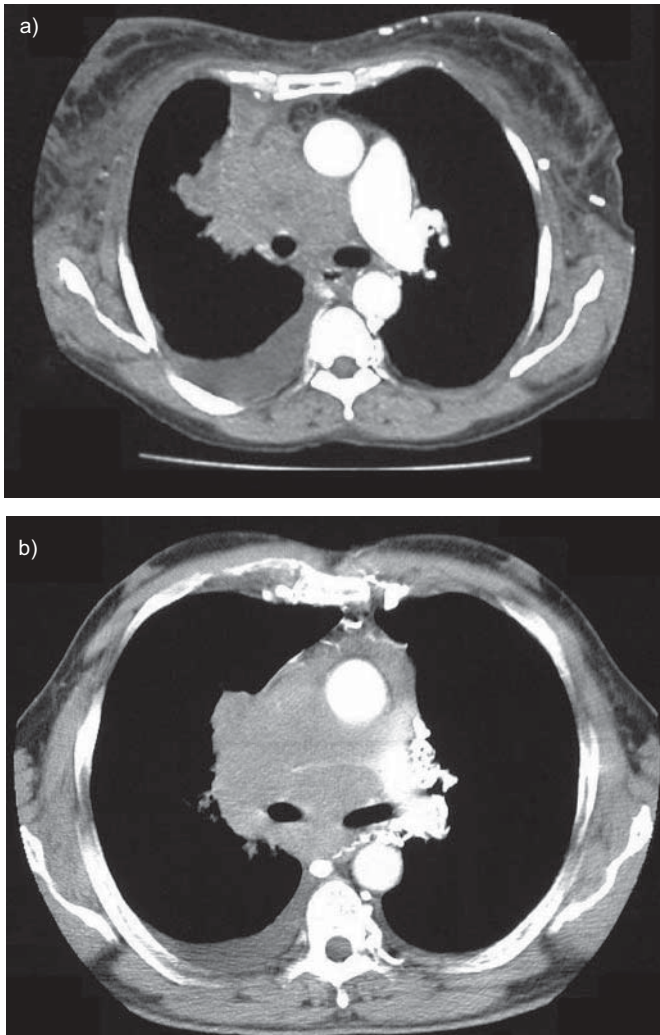
FIGURE 2. Two examples of contrast-enhanced computed tomography (CT) images from patients with superior vena cava (SVC) obstruction that were screened during the present study period. a) The study patient presented with complete SVC obstruction secondary to a tumour that abutted the chest wall, and was included into the study population. b) This CT scan shows a central mass lesion not amenable to ultrasound-assisted transthoracic fine needle aspiration or cutting needle biopsies. Patients with mass lesions not extending to the chest wall were excluded from the present study, and alternative diagnostic techniques were employed in these cases (bronchoscopy with transbronchial needle aspiration in this particular case).

particularly in patients with severe supraclavicular swelling from their SVC syndrome, and in those with radiologically negative nodes on CT scan. This study was not designed to address this issue. Furthermore, we did not compare the diagnostic yield and safety of US-assisted TTFNA and CNB to bronchoscopy in cases amenable to both procedures, nor did we compare clinicians to radiologists with regard to efficiency and healthcare cost.

The single case with an erroneous on-site typing of bronchogenic carcinoma deserved to be highlighted. The diagnosis was revised on the same cytological specimen after full laboratory assessment. More errors in typing may have been made by inexperienced personnel. It should therefore be stressed that the main purpose of ROSE is to ascertain the presence of diagnostically useful material and not to make final diagnoses *per se* [14, 16]. Vital decisions on patient management should therefore never be solely based on the ROSE diagnosis.

In conclusion, we were able to show that US-assisted TTFNA with rapid on-site evaluation and CNB performed by a clinician had a high diagnostic yield and were safe in the setting of SVC syndrome with an associated mass lesion that abutted the chest wall. US-assisted TTFNA (with ROSE) may be the initial investigation of choice in suspected bronchogenic carcinoma, whereas both TTFNA and CNB need to be performed in all other cases.

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Respiration

Interventional Pulmonology

The Diagnostic Yield and Safety of Ultrasound-Assisted Transthoracic Biopsy of Mediastinal Masses

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Abstract
Background: Ultrasound (US)-assisted transthoracic biopsy offers a less invasive alternative to surgical biopsy in the setting of mediastinal masses. **Objectives:** The aim of this 1-year prospective study was to assess the diagnostic yield and safety of a novel single-session sequential approach of US-assisted transthoracic fine-needle aspirations (TTFNA) with rapid on-site evaluation (ROSE) followed by cutting needle biopsies (CNB) performed by physicians on patients with anterosuperior mediastinal masses. **Methods:** US-assisted TTFNA with ROSE was performed on 45 consecutive patients (49.5 ± 27.7 years, 24 males), immediately followed by CNB where a provisional diagnosis of epithelial carcinoma or tuberculosis could not be established, provided a safety range could be assured. **Results:** TTFNA alone was deemed adequate by means of ROSE in 27 (60%) patients. CNB could be performed in 17 of the remaining 18. The on-site diagnosis corresponded to the final diagnosis in 26/45 (57.8%). An accurate cytological diagnosis was made in 33 (73.3%), and was more likely to be diagnostic in epithelial carcinoma and tuberculosis (28/30) than all other pathologies (5/15, p < 0.001). CNB yielded a diagnosis in 15/17 (88.2%). Overall, 42/45 patients were diagnosed by the single-session approach (93.3%). The final diagnoses included 41 neoplasms, with small cell lung cancer (n = 13) the commonest diagnosis. We observed no pneumothorax or major haemorrhage. **Conclusions:** A single-session sequential approach of US-assisted TTFNA with ROSE followed by CNB, where indicated, has a high diagnostic yield for anterosuperior mediastinal masses, is safe and offers an alternative to surgical biopsy.

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Introduction

The differential diagnosis of mediastinal masses is broad and computed tomography (CT) scanning followed by biopsy is indicated in practically all cases [1–5]. Tissue is most often harvested by means of mediastinoscopy, mediastinotomy or related surgical procedures [2–6]. Although the diagnostic yield of such an approach exceeds 90%, surgical biopsies carry a complication rate

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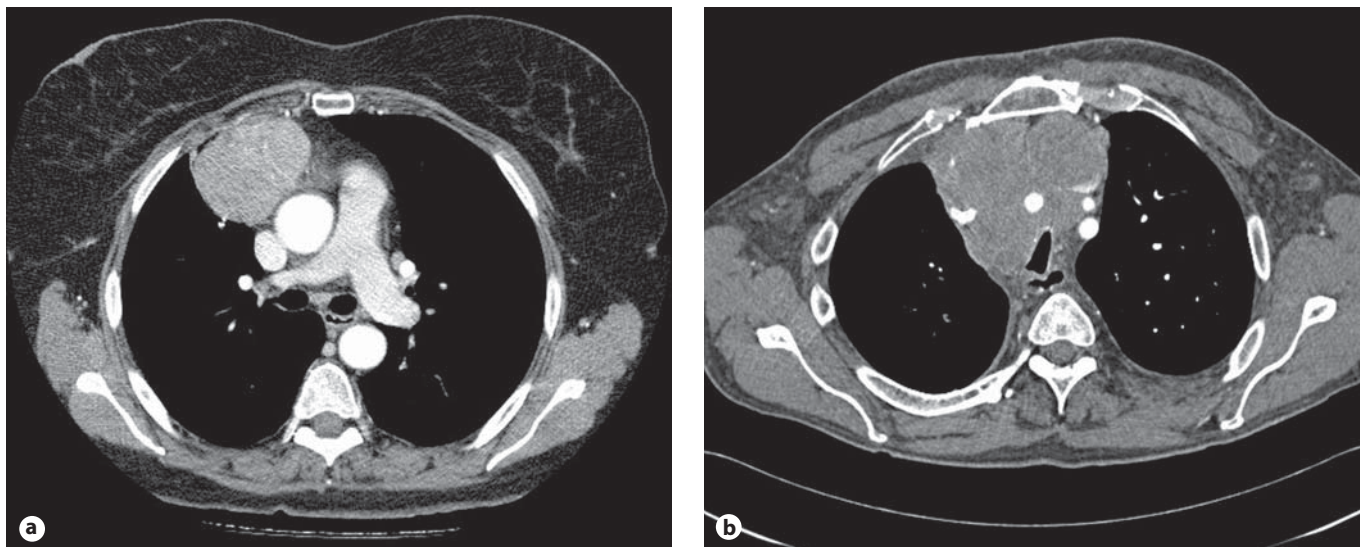Tel. +27 21 938 9243, Fax +27 21 933 3591, E-Mail coeniefn@sun.ac.za

Fig. 1. a CT scan of one of the study subjects shows a distinct anterosuperior mediastinal mass, which was proven to be a thymoma. **b** An example of an extensive mediastinal mass lesion which in this particular case was found to be due to small cell lung cancer.

of up to 5% [2–5]. Moreover, these procedures usually need to be performed in theatre under general anaesthesia and require significant expertise and resources [3–5].

Transthoracic ultrasound (US) has become a valuable guide for interventional procedures [7, 8], and plays an increasing role in biopsies of the chest wall, pleura and peripheral lung [9–13]. US-assisted biopsies of mediastinal masses were first described by Saito et al. [14] two decades ago, enabling them to diagnose 87% of all malignant tumours and 67% of benign masses. Despite these promising findings, US-assisted biopsies have as yet failed to gain popularity amongst clinicians, possibly because subsequent investigators generally utilised only cutting needle biopsies (CNB) [15, 16] and were almost exclusively specialist interventional radiologists [17–21].

US-assisted transthoracic fine-needle aspiration (TTFNA) and CNB in the setting of chest wall, pleural and pulmonary malignancies abutting the chest wall have a very high diagnostic yield and are safe, even in the hands of non-radiologists [10–12]. The use of TTFNA with rapid on-site evaluation (ROSE) and CNB has been shown to be complementary [11, 12, 22]. In our previous studies, we found that TTFNA with ROSE of intrathoracic mass lesions has a significantly higher sensitivity than CNB alone in diagnosing bronchogenic carcinoma, but that CNB remains superior in noncarcinomatous tumours and in benign lesions [10–12, 22]. The addition of ROSE therefore potentially allows for a single-session approach, with US-assisted TTFNA followed by CNB limited to those cases where diagnostically useful material could not be confirmed [11, 12, 22].

The main aim of this prospective study was to assess the diagnostic yield and safety of a novel, single-session sequential approach of US-assisted TTFNA with ROSE followed by CNB performed by physicians in the setting of anterosuperior mediastinal masses.

Materials and Methods

Study Population

All adult patients ($\geq$18 years) referred to the Division of Pulmonology of Tygerberg Academic Hospital with an anterosuperior mediastinal mass lesion on contrasted CT scan were potential candidates for this 1-year prospective observational study. Our institution is a 1,200-bed academic hospital in Cape Town, South Africa. It is one of two referral centres and renders a tertiary service to a population of approximately 1.5 million people. The Health Research Ethics Committee of Stellenbosch University approved the study (project No. N09/05/136). Written informed consent was obtained from all subjects on enrolment and prior to any invasive procedures.

For the purposes of the study we considered the anterosuperior compartment of the mediastinum as the space posterior to the sternum and anterior to the heart and brachiocephalic vessels, extending from the thoracic inlet to the diaphragm [23]. Patients with a distinct mass lesion that was either confined to the anterosuperior mediastinum (fig. 1a) or where the mediastinum was extensively involved by a mass lesion with the epicentre in the an-
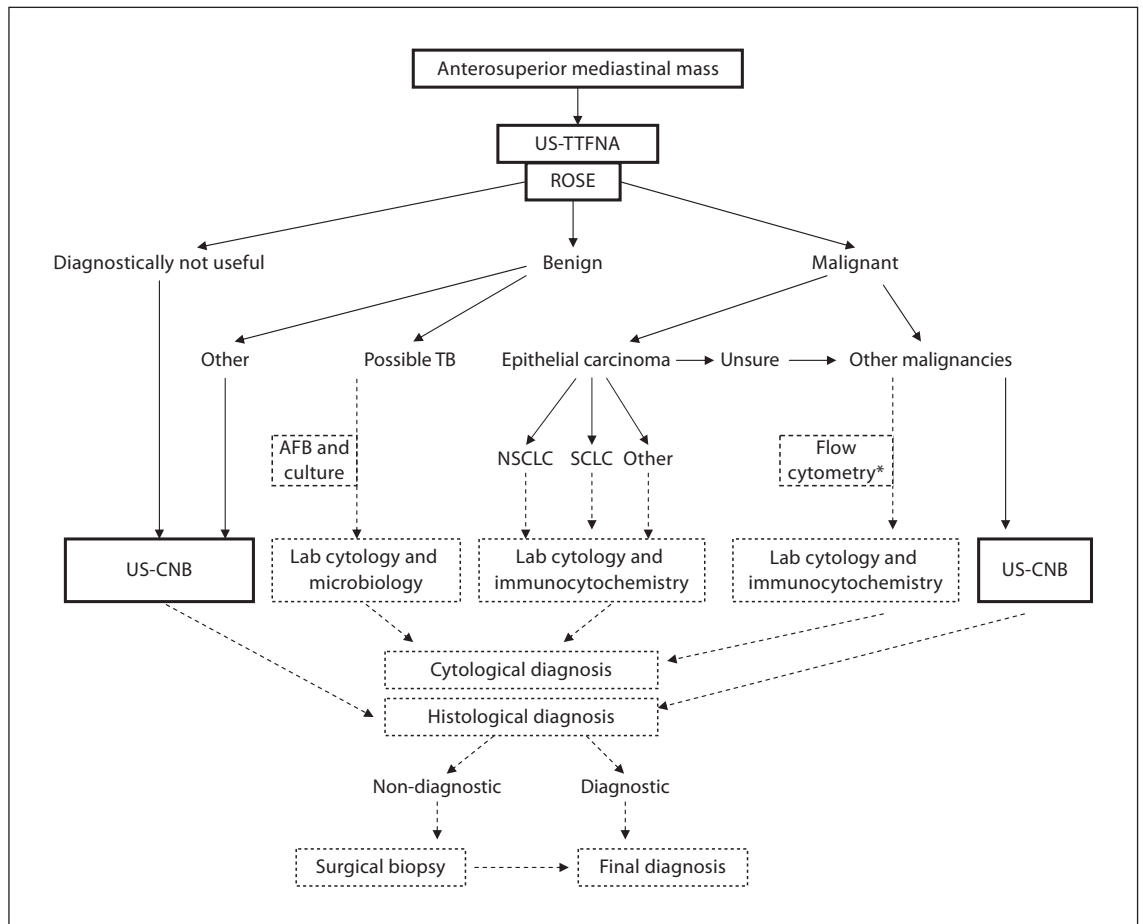
Fig. 2. Scheme of the general diagnostic approach. Solid lines refer to on-site activities, and dotted lines to all laboratory and subsequent procedures. The cytopathologist first commented on the presence or absence of diagnostically useful material obtained during each individual pass. Where diagnostically useful material was present, the cytopathologist was asked to make a provisional diagnosis of malignant or benign pathology. Where malignant cells were present, the pathologist provisionally typed the specimens into one of two main categories: (1) epithelial carcinomas or (2) other malignancies. Epithelial carcinomas were subtyped into either non-small cell lung cancer, small cell lung cancer, other epithelial carcinomas (including thyroid) or epithelial carcinoma of unsure origin. In case of malignancies other than epithelial carcinoma, the cytopathologist was asked to provide provisional diagnosis where possible and to suggest further investigations including flow cytometry. In the case of benign pathology, the specimens were typed into two main categories: (1) suspected tuberculosis and (2) other pathology. Further aspirates for cultures for mycobacteria were obtained in case of suspected tuberculosis. CNB were performed on all cases except those with an on-site diagnosis of either epithelial carcinoma of known origin or tuberculosis. * Flow cytometry was performed on all cases with an on-site diagnosis of possible non-Hodgkin's lymphoma. US-TTFNA = ultrasound-assisted transthoracic fine needle aspiration; ROSE = rapid on-site evaluation; US-CNB = ultrasound-assisted cutting needle biopsy; TB = tuberculosis; AFB = acid-fast bacilli (stain); NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

terosuperior mediastinum (fig. 1b) were invited to participate in the study, provided that the mass lesion abutted the anterior chest wall with an interface of at least 1 cm in two dimensions and no known coagulopathy was present.

Transthoracic US

A consultant respiratory physician performed the sonography (Toshiba Just Vision 200 SSA-320A; Toshiba Medical Systems Corporation, Tochigi-ken, Japan) in a bronchoscopy suite without the support of a specialist radiologist. The preferred patient position for the procedure was supine, using a standard 3.75-MHz sector probe in a parasternal approach. The interface between the intrathoracic mass lesion and chest wall was identified. An interface of at least 1 cm in two dimensions visible throughout inspiration and expiration in an area not covered by bony elements was considered the minimal requirement for a US-assisted procedure. Procedures were performed 'freehand' (not under direct US guidance). The intended site was marked, and the direction, the depth
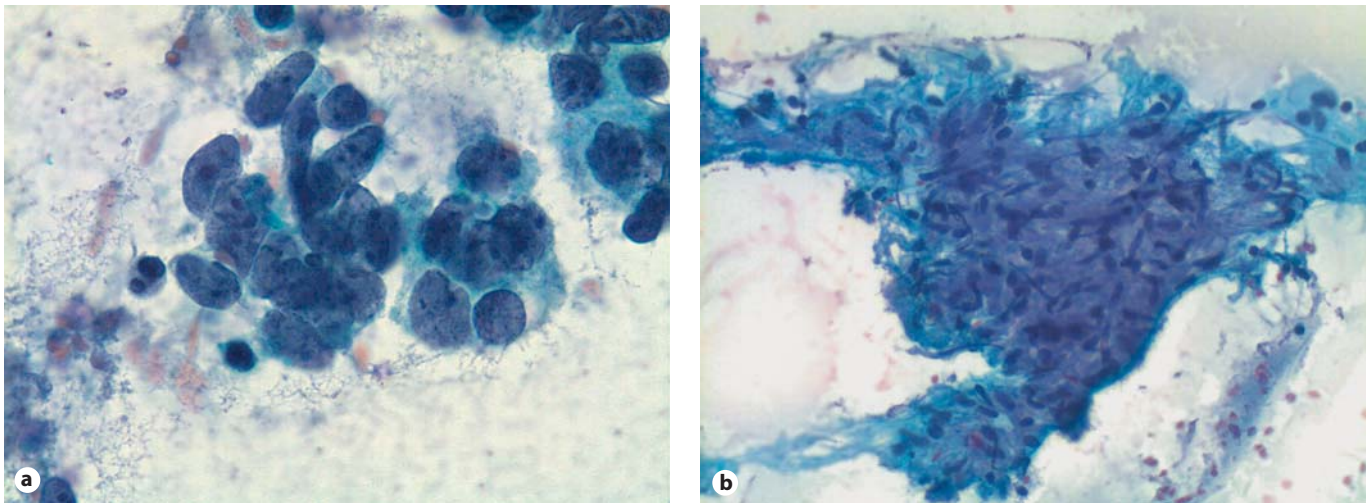
Fig. 3. a An example of an aspirate obtained from a patient with small cell lung cancer showing hyperchromatic nuclei with scanty cytoplasm and nuclear moulding. (Papanicolaou stain, ×1,000). **b** This aspirate was obtained from a patient with tuberculosis. Note the poorly formed granuloma consisting of epithelioid histiocytes. This slide subsequently stained positive for acid-fast bacilli in the laboratory; cultures confirmed these bacilli to be *Mycobacterium tuberculosis*. (Papanicolaou stain, ×400).

of interest and the safety range for the procedure documented. Care was taken to avoid the major intrathoracic blood vessels and the internal thoracic arteries, as well as any major collateral veins that may have formed in cases with superior vena cava obstruction.

Transthoracic Fine-Needle Aspirations

Aspirations were performed with 22-G spinal needles of 40 or 90 mm length as needed (Tae-Cang, Kong Ju City, Korea) connected to a 10-ml syringe under sterile conditions with local anaesthesia (lignocaine 1%). Aspirates from at least 4 slightly different directions and depths were directly expressed onto slides, smeared and submitted for ROSE using both Diff-Quik (Rapidiff; Clinical Sciences Diagnostics, Southdale, South Africa) and rapid Papanicolaou staining methods [24].

ROSE of Cytology Specimens

The cytopathologist present in theatre was asked to comment on the presence of diagnostically useful material obtained (fig. 2) and to provisionally type the diagnostically useful specimens into 1 of 4 main categories: (1) epithelial carcinomas of known origin (including non-small cell lung carcinoma, thyroid carcinoma and small cell carcinoma; fig. 3a), (2) other malignancies, (3) probable tuberculous disease (necrotising and/or granulomatous inflammation; fig. 3b) and (4) other benign pathology. We considered specimens with a provisional on-site diagnosis of either epithelial carcinomas of known origin or probable tuberculosis as sufficient for a potential final cytological diagnosis (that is, no histology was obtained). In case of malignancies other than epithelial carcinoma, the cytopathologist was asked to provide a provisional diagnosis where possible and to suggest further investigations, for example flow cytometry for non-Hodgkin's lymphoma or aspirates for mycobacterial cultures in case of suspected tuberculosis.

Cutting Needle Biopsies

CNB were obtained in the same session immediately following TTFNA in all cases where the provisional on-site diagnosis was not an epithelial carcinoma of a known origin or tuberculosis, provided at least a 1-cm safety range could be assured (that is, no mediastinal organs or blood vessels within 1 cm of the intended CNB path). Manually operated 14-gauge Tru-cut biopsy needles (Allegiance, Chateaubriand, France) were used. Two or more passes were performed until macroscopically satisfactory material was harvested. These specimens were harvested in 4% formalin and routinely processed for histological evaluation.

Immediate Post-Procedure Care

The TTFNA and CNB site were re-examined by means of US immediately after the procedures, and a chest radiograph was obtained if the pre- and post-procedure US findings differed and at the discretion of the attending physician. All patients were observed for at least 2 h prior to discharge. Minor or major haemorrhage, as well as iatrogenic pneumothoraces, was documented. Major haemorrhage was defined as any haemorrhage that required additional measures above and beyond localised pressure and superficial sutures.

Further Assessment

All cytology slides were reviewed in the laboratory by a second cytopathologist, who had an array of special stains (including immunocytochemistry and stains for acid-fast bacilli) at his or her disposal, and had to concur with the original cytopathologist prior to issuing a final cytological diagnosis. In case of disagreement a third cytopathologist was consulted to resolve the case. The histological specimens were reviewed by two independent pathologists. Only histological diagnoses, unequivocal cytology in case of epithelial carcinoma or aspirates that were culture positive for

Table 1. Final diagnoses of all study subjects (n = 45)

Diagnoses	n	%
Non-small cell lung cancer		
Adenocarcinoma	6	13.3
Squamous carcinoma	5	11.1
Undifferentiated	1	2.2
Small cell lung cancer	13	28.9
Lymphoma		
Hodgkin's lymphoma	2	4.4
B-cell non-Hodgkin's lymphoma	3	6.7
T-cell non-Hodgkin's lymphoma	2	4.4
Other malignancies		
Papillary thyroid carcinoma	2	4.4
Breast cancer[1]	1	2.2
Germ cell tumour (embryonal carcinoma)	1	2.2
Leiomyosarcoma	1	2.2
Pleomorphic sarcoma	1	2.2
Osteosarcoma[1]	1	2.2
Thymoma	2	4.4
Tuberculosis (adenitis)	2	4.4
Retrosternal thyroid (normal thyroid tissue)	1	2.2
Complicated hydatid cyst	1	2.2

[1] The single cases of breast cancer and osteosarcoma were deemed to be metastatic, as both were diagnosed in patients who had been treated for primary neoplasms in the preceding 2 years.

Mycobacterium tuberculosis were accepted as the gold standard for statistical analyses. Patients in whom the initial investigations (TTFNA and CNB) failed to yield a diagnosis were referred for surgical biopsy. All patients were followed up until a tissue diagnosis could be confirmed, and in the case of bronchogenic carcinoma, until they were staged according to the 2009 International Association for the Study of Lung Cancer staging system [25].

Statistical Analysis
Descriptive statistics as well as Fisher's exact test were employed. A p value of ≤ 0.05 in a two-tailed test was considered significant. Unless stated otherwise, data are displayed as means $\pm$ standard deviation.

Results

Patients
Over the 1-year period (July 2009 to June 2010) we enrolled 45 consecutive patients (49.5 $\pm$ 27.7 years, 24 males). No patient was excluded or declined to give consent. In total, 20 patients (44%) had clinical evidence of SVC syndrome. Bronchogenic carcinoma (n = 25) was responsible for the majority of anterosuperior mass lesions (table 1), with small cell lung cancer being the most fre-

quent final established diagnosis (n = 13). Eight of the patients with small cell lung cancer were considered to have limited disease. Of the patients with non-small cell lung cancer, all had either stage IIIB (n = 7) or stage IV disease (n = 5).

Imaging
Distinct lesions confined to the anterosuperior mediastinum were present in 26 patients and a further 19 had more extensive mediastinal involvement on CT scan (predominantly involving the anterosuperior compartment). The maximum anteroposterior dimensions ranged from 24 to 119 mm, with a mean of 69 mm ($\pm$19 mm). All lesions were visible at US and TTFNA was possible in all patients enrolled.

Fine-Needle Aspirations
Specimens that were considered potentially useful by the on-site pathologist were obtained from 37 of the 45 subjects (82.2%). Of these, the TTFNA were considered as being sufficient for a cytological diagnosis (provisional diagnosis either epithelial carcinoma or probable tuberculosis adenitis) in 27 patients (60.0%). In total, 26 on-site diagnoses (57.8%) corresponded with the final diagnoses (table 2), including single cases of breast carcinoma, papillary thyroid carcinoma and normal thyroid tissue. Two cases of small cell lung cancer were provisionally erroneously typed as non-small cell lung cancer. Provisional on-site diagnoses made in the remaining patients with cellular aspirates (not considered sufficient) included possible lymphoma (n = 3), possible thymoma (n = 1) and malignant cells of unknown origin (n = 5).

A final laboratory cytological diagnosis was possible in 33 patients (73.3%) after incorporating immunocytochemistry, flow cytometry and stains for acid-fast bacilli (table 2). US-assisted TTFNA was diagnostic in 26 of 28 patients with epithelial carcinoma (92.8%), with 23 of 25 lung cancers, 2 papillary thyroid carcinomas and 1 case of metastatic breast cancer having diagnostic morphological and immunocytochemical features. Included in the 2 cases of papillary thyroid carcinoma was 1 case that was typed on-site as 'malignant cells of unknown origin' (laboratory cytology and histology were diagnostic). Both patients with tuberculosis had acid-fast bacilli on the smears and were culture positive for *M. tuberculosis*. US-assisted TTFNA was therefore diagnostic in 28 of 30 cases of either epithelial carcinoma or tuberculosis. Three cases yielding malignant cells of unknown origin could not be accurately subtyped on cytology (the final histological diagnoses were germ cell tumour, leiomyosarco-

Table 2. Diagnostic yield in order of procedural sequence

Diagnoses	TTFNA: ROSE	TTFNA: laboratory	CNB	Surgical biopsy
Epithelial carcinoma				
Small cell lung cancer (n = 13)	11/13 (84.6%)[1]	13/13 (100%)	–	–
Non-small cell lung cancer (n = 12)	10/12 (83.3%)	10/12 (83.3%)	2/2 (100%)	–
Other (n = 3)	2/3 (66.7%)	3/3 (100%)	1/1 (100%)	–
Lymphoma (n = 7)	0/7 (0%)	3/7 (42.9%)	5/6 (83.3%)[2]	2/2 (100%)
Thymoma (n = 2)	0/2 (0%)	1/2 (50%)	2/2 (100%)	
Other neoplasms (n = 4)	0/4 (0%)	0/4 (0%)	4/4 (100%)	–
Non-neoplastic pathology				
Tuberculosis (n = 2)	2/2 (100%)	2/2 (100%)	–	–
Other (n = 2)	1/2 (50%)	1/2 (50%)	1/2 (50%)	1/1 (100%)
All patients (n = 45)	26/45 (57.8%)	33/45 (73.3%)[3]	15/17 (88.2%)	3/3 (100%)

[1] Two cases of small cell lung cancer were provisionally erroneously typed as non-small cell lung cancer and therefore did not undergo CNB.
[2] No CNB was performed in one case due to safety concerns.
[3] A cytological diagnosis on TTFNA specimens were more likely to be made in epithelial carcinomas and tuberculosis (28/30) than all other diagnoses (5/15, $p < 0.001$).

ma and osteosarcoma). Only 5 of the remaining 15 patients (33.3%) had accurate cytological diagnoses, and the diagnoses made were diffuse large B-cell lymphoma (n = 2), T-cell lymphoblastic lymphoma (n = 1), thymoma (n = 1) and normal thyroid tissue (n = 1). US-assisted TTFNA was therefore more likely to be diagnostic in patients with either epithelial carcinoma or tuberculosis than in patients with all other diagnoses ($p < 0.001$).

Cutting Needle Biopsies

US-assisted CNB were performed in all but one patient with insufficient on-site cytology (in a single case a 1-cm safety range could not be assured). Diagnostic histology was obtained from 15 of 17 patients who underwent CNB (88.2%). Laboratory cytology was also non-diagnostic in both patients with negative histology and in the single case where CNB was deferred. The combined approach of US-assisted TTFNA with ROSE and CNB (where indicated) therefore yielded a diagnosis in 42 patients (93.3%).

Complications

All procedures were well tolerated and no pneumothoraces were noted. Only one case of minor haemorrhage necessitating a single superficial suture following a CNB was observed.

Further Investigations

Three patients were referred for surgical biopsy. The diagnoses made in these three cases were Hodgkin's lym-

phoma (nodular sclerosing), non-Hodgkin's lymphoma (diffuse large B-cell lymphoma) and complicated hydatid cyst *(Echinococcus granulosus)*. No further invasive diagnostic procedures were deemed necessary in the 24 patients with lung cancer.

Discussion

Using a sequential diagnostic approach of US-assisted TTFNA which was immediately followed by US-assisted CNB where indicated, we were able to diagnose 93.3% of all patients with anterosuperior mediastinal masses after a single visit to theatre and without the aid of a specialist radiologist or thoracic surgeon. TTFNA yielded a final cytological diagnosis in 73.3%, and was more likely to be diagnostic in the cases of epithelial carcinoma and tuberculosis than all other diagnoses ($p < 0.001$). CNB yielded diagnostic histology in 88.2%. Furthermore, all procedures were well tolerated and we observed no pneumothoraces or major haemorrhage.

Saito and co-workers were able to diagnose 31 of 45 mediastinal masses by means of US-guided needle biopsies in their landmark study [14]. Yang et al. subsequently found Tru-cut needles to have a diagnostic yield of 88.9% for mediastinal tumours [15]. The same investigators also pioneered the supraclavicular approach for US-guided biopsies of superior mediastinal tumours [16]. Sawhney et al. reported an even higher sensitivity, as they

were able to diagnose all 25 patients with mediastinal masses by means of a Tru-cut needle [17]. Samad and co-workers reported a more modest yield of 80.5% [18]. Comparable findings were subsequently reported by other investigators [19–21]. Despite the fact that our sample size is on par with these studies, the relatively small numbers limit meaningful statistical comparisons between the various aetiologies. Studies that included more than 40 patients reported a 1–6% complication rate from CNB, with pneumothoraces, haemothoraces and haemoptysis the most common serious complications [14, 15, 18–20].

Although our overall sensitivity is on par with the above-mentioned reports, our study design was unique in that we utilised ROSE to limit CNB to cases where cytology was less likely to provide a definitive diagnosis and thereby potentially limiting complications and cost. This approach has been validated for epithelial carcinomas and tuberculosis, where ROSE has been shown to have a high sensitivity for identifying diagnostic material and suggesting a provisional diagnosis [10–12, 26, 27]. Although cytology may be diagnostic in other types of pathology, further investigations are often required and the value of ROSE is therefore less well defined [28]. We decided upfront to acquire tissue samples for histology in all other diagnoses. As expected, we found that TTFNA with ROSE was superior for epithelial carcinoma and tuberculosis compared to all other diagnoses, which arguably justifies such an approach. We did not perform ROSE of CNB specimens with a touch prep as it would not have aided in the identification of candidates for CNB, would have lengthened the procedure time and potentially jeopardised the core specimens, which are often fragile (unlike sentinel lymph nodes). Moreover, we anticipated that CNB (irrespective of ROSE) would have a high yield based on previous work [10–12, 14–21].

We encountered a number of unexpected findings with regard to the final diagnoses made. We anticipated that tuberculous lymphadenitis may be responsible for a higher percentage of lesions, given the fact that the local incidence of pulmonary tuberculosis is 940 cases per 100,000 population and more than 50% of all new cases of tuberculosis are co-infected with the human immunodeficiency virus [29, 30]. Although thymomas and lymphomas are traditionally considered the most frequent causes of anterosuperior mediastinal mass lesions [1, 31], we found that more than half of our patients had lung cancer, the commonest diagnosis being small cell lung cancer. Approximately 5% of all lung cancers present with mediastinal mass lesions [32, 33]. In fact, 23 of 302 lung cancer patients treated at our institution in the year

preceding our study presented with mediastinal mass lesions (unpublished data). We actively recruited patients with anterosuperior mediastinal mass lesions, irrespective of their respective clinical presentation, and our inclusion criteria did not differ from most published series [14–18, 20]. Historically, however, clinicians have opted for bronchoscopy with transbronchial needle aspirations in the setting of probable lung cancer with central lesions [34], which conceivably introduced a selection bias in most reported series of surgical or minimally invasive biopsies [1–6, 31]. There is unfortunately a paucity of local data on the prevalence of the various aetiologies of anterosuperior mediastinal masses. Although not specifically designed to address this, our data suggest small cell lung cancer to be the commonest cause of anterosuperior mediastinal mass lesions in our population.

A single-session minimally invasive approach has certain limitations and risks not addressed in our study. Albeit exceedingly rare, some case reports implicated needle biopsies of early stage thymoma in seeding into the chest wall [35, 36]. It may therefore be advisable to offer primary surgical resection to patients with a high suspicion of thymoma in order not to breach the capsule.

In conclusion, we found a single-session sequential approach of US-assisted TTFNA with ROSE followed by CNB, where indicated, to have a high diagnostic yield for anterosuperior mediastinal masses. On-site evaluation provided important guidance for the need for CNB, as the yield of US-assisted TTFNA alone was found to be significantly higher in patients with epithelial carcinomas and tuberculosis than all other diagnoses, justifying the routine performance of CNB in the latter group. This approach is safe and offers a less invasive alternative to surgical biopsy.

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Chapter 5

ULTRASOUND-ASSISTED PLEURAL BIOPSIES: A RANDOMISED COMPARISON OF TWO COMMONLY USED BIOPSY DEVICES

> **Koegelenberg CF, Bolliger CT, Theron J, Walzl G, Wright CA, Louw M, Diacon AH. Direct comparison of the diagnostic yield of ultrasound-assisted Abrams and Tru-Cut needle biopsies for pleural tuberculosis. Thorax 2010;65:857-862**

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Direct comparison of the diagnostic yield of ultrasound-assisted Abrams and Tru-Cut needle biopsies for pleural tuberculosis

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ABSTRACT

Background Tuberculous pleuritis remains the commonest cause of exudative effusions in areas with a high prevalence of tuberculosis and histological and/or microbiological confirmation on pleural tissue is the gold standard for its diagnosis. Uncertainty remains regarding the choice of closed pleural biopsy needles.

Objectives This prospective study compared ultrasound-assisted Abrams and Tru-Cut needle biopsies with regard to their diagnostic yield for pleural tuberculosis.

Methods 89 patients (54 men) of mean±SD age 38.7±16.7 years with pleural effusions and a clinical suspicion of tuberculosis were enrolled in the study. Transthoracic ultrasound was performed on all patients, who were then randomly assigned to undergo ≥4 Abrams needle biopsies followed by ≥4 Tru-Cut needle biopsies or vice versa. Medical thoracoscopy was performed on cases with non-diagnostic closed biopsies. Histological and/or microbiological proof of tuberculosis on any pleural specimen was considered the gold standard for pleural tuberculosis.

Results Pleural tuberculosis was diagnosed in 66 patients, alternative diagnoses were established in 20 patients and 3 remained undiagnosed. Pleural biopsy specimens obtained with Abrams needles contained pleural tissue in 81 patients (91.0%) and were diagnostic for tuberculosis in 54 patients (sensitivity 81.8%), whereas Tru-Cut needle biopsy specimens only contained pleural tissue in 70 patients (78.7%, p=0.015) and were diagnostic in 43 patients (sensitivity 65.2%, p=0.022).

Conclusions Ultrasound-assisted pleural biopsies performed with an Abrams needle are more likely to contain pleura and have a significantly higher diagnostic sensitivity for pleural tuberculosis.

INTRODUCTION

Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*[1] and, among communicable diseases, tuberculosis (TB) is the second leading cause of death.[2] Pleural TB remains a common form of extrapulmonary TB, particularly among HIV-positive individuals,[3 4] and it is the most common cause of exudative effusions in areas with a high prevalence of TB.[2 5 6]

Although a presumptive diagnosis of pleural TB is often based on raised levels of adenosine deaminase (ADA) and interferon γ in pleural fluid, actual histological and/or microbiological confirmation of TB pleuritis remains the gold standard.[5 6] Pleural

tissue can be harvested either by means of closed biopsies, thoracoscopy or open surgical biopsies.[5 6] Access to thoracoscopy and open surgical biopsies is limited in many parts of the world and closed biopsies are therefore the preferred initial investigation.[6]

Closed pleural biopsy needles were introduced in the mid-1950s and early 1960s and various types were used, including the Abrams, Cope and Vim-Silverman needles.[7–11] Of these devices, the Abrams needle was consistently shown to have a high yield and became the most widely used device.[11–13] In 1989 Macleod et al described blind cutting needle (Tru-Cut) biopsies as an alternative to Abrams needles in patients who present with large pleural effusions.[14] Around the same time, transthoracic ultrasound (US)-assisted biopsy techniques were pioneered, and the indications were soon expanded to include cutting needle pleural biopsies.[15–18] Focal pleural abnormalities (eg, thickening) and fluid collections could be identified by means of US, and biopsy may be aimed at these areas of interest.[19] Moreover, estimating the size of an associated effusion decreases the risk of visceral pleural lacerations, which is particularly relevant in cases with minimal pleural effusion and where pointed cutting needle biopsy devices are employed.[19]

One small prospective study found a superior diagnostic yield for pleural TB with US-assisted Tru-Cut compared with traditional Abrams needle biopsies.[17] In that study, which was performed in an area with a moderate TB prevalence, only two of 10 Abrams needle biopsies were diagnostic for pleural TB. As most authors have reported diagnostic sensitivities in the order of 50–85% for Abrams needle biopsies,[6 13] uncertainty remains as to which of these closed pleural biopsy techniques is superior for pleural TB.

The aim of this prospective study was to compare US-assisted Abrams needle biopsies with US-assisted Tru-Cut needle biopsies with regard to their diagnostic yield for pleural TB.

METHODS

Study population

All adult patients (≥18 years) referred to the Division of Pulmonology of Tygerberg Academic Hospital with radiological evidence of a pleural effusion and clinical suspicion of pleural TB were potential candidates for this study. Our institution is a 1200-bed academic hospital in Cape Town,

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South Africa. It is one of two academic referral centres in the city and renders a tertiary service to a population of approximately 1.5 million. In 2006 the incidence of pulmonary TB in this population was 940 cases per 100 000.[1]

Patients referred to the division's pleural theatre were screened for indicators of a high clinical suspicion of TB which, for the purposes of the study, included (1) known HIV infection, (2) persistent cough lasting >3 weeks, (3) haemoptysis, (4) weight loss >4 kg (5) intermittent fever >3 weeks and (6) drenching night sweats >2 weeks. Patients were included in the study only if transthoracic US confirmed a pleural effusion of at least 10 mm (as measured from the parietal pleura) and they had at least two clinical indicators of possible TB.

Transthoracic US

A consultant respiratory physician or a senior registrar under supervision performed the sonography (Toshiba Just Vision 200 SSA-320A; Toshiba Medical Systems Corporation, Tochigi-ken, Japan). The preferred patient position for the procedure was the sitting position, with the subject's arms folded across the chest and supported by a bedside table. Surveillance of the dorsolateral thoracic wall was performed by means of a standard 3.75 MHz sector probe. The presence of an effusion was confirmed by standard means.[19] The size of the effusion was documented as follows: minimal (if the echo-free space was confined to the costophrenic angle); small (if the space was greater than the costophrenic angle but still within the range of the area covered with a 3.75 MHz curvilinear probe); moderate (if the space was greater than a one-probe range but within a two-probe range; and large (if the space was larger than a two-probe range).[19] The biopsy site was subsequently identified, with safety being a main determinant. As a rule, the aspirations and biopsies were performed in the midscapular line. For minimal to moderate effusions, the biopsies were taken from the site of maximum effusion as determined by US. In case of a large effusion, the puncture site was chosen to be as low as possible, but not within 25 mm of the diaphragm. All aspirations and biopsies were performed 'freehand' (not under direct US guidance) and patients were requested to remain motionless during the procedures.

Diagnostic thoracentesis

Under sterile technique and local anaesthesia with lignocaine 1%, samples were obtained for pH analysis by means of an on-site blood gas analyser (Bayer Rapidlab 865 Blood Gas Analyzer, Siemens, Midrand, South Africa), chemical analysis, microbiology, cell counts and cytology. The chemical analyses included serum and pleural total protein, albumin, lactate dehydrogenase and pleural fluid ADA levels. Microbiological investigations included routine gram stains and cultures, as well as stains for acid-fast bacilli (Ziehl-Nielsen staining) and TB cultures (MGIT 960 liquid culture system, Becton Dickinson, Sparks, Maryland, USA). We defined a lymphocytic predominant effusion as one with >75% lymphocytes and/or a lymphocyte to neutrophil ratio >0.75.[6]

Closed pleural biopsies

Under sterile technique and local anaesthesia, closed pleural biopsies were subsequently performed on all patients. Patients were randomly assigned (in blocks of six) to undergo either ≥4 Abrams needle biopsies followed by ≥4 Tru-Cut needle biopsies or ≥4 Tru-Cut needle biopsies followed by ≥4 Abrams needle biopsies. These biopsies were performed from the same incision site (5 mm in length) and by experienced clinicians. Abrams

needle biopsies were performed according to standardised guidelines.[20 21] Biopsies were taken with the distal tip of the needle facing up to 45° down in order to avoid laceration of the intercostal vessels. Cutting needle biopsies were performed by means of manually operated 14-gauge Tru-Cut biopsy needles with a specimen notch of 20 mm (Allegiance, Chateaubriand, France) and technically comparable to the way described by McLeod and coworkers (figure 1).[16] Abrams and Tru-Cut needle biopsy specimens were harvested until each technique yielded at least three macroscopically satisfactory specimens for histological evaluation (transported in 4% formalin) and at least one specimen for microbiological investigations (transported in 0.9% saline).

Immediate post-procedure care

The incision site was re-examined by means of US immediately after the procedures for suspected pneumothoraces, and a chest x-ray was obtained if the pre- and post-procedure US findings differed and at the discretion of the attending physician. All patients were observed for at least 1 h before discharge and complications were noted. Patient discomfort was documented, and excessive pain was defined as any pain requiring at least a single dose of parenteral or opiate analgesics. The presence or absence of minor or major haemorrhage as well as iatrogenic pneumothoraces was specifically documented. Major haemorrhage was defined as any haemorrhage that required additional measures above and beyond localised pressure and a single superficial suture.

Further assessment and follow-up

All patients with a non-diagnostic closed biopsy or thoracentesis were referred for medical thoracoscopy. Those who remained undiagnosed following medical thoracoscopy were followed up for a total of 6 months, and the choice of further investigations was guided by the patients' attending chest physicians. These could have included observation, video-assisted thoracoscopy or open surgical procedures. Cases that remained undiagnosed after
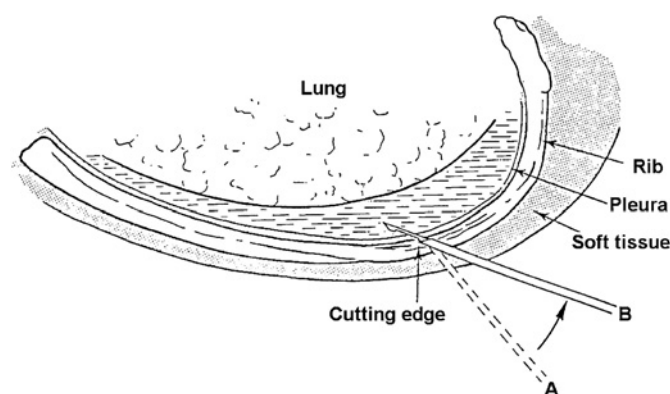

Figure 1 Cross section through an intercostal space showing the position of the open Tru-Cut needle immediately before harvesting a specimen. The Tru-Cut needle is cautiously introduced through an incision at 45° to the skin in the direction of the chosen intercostal space above the lower rib. Adjacent areas of pleura are then sampled. A distinct 'give' indicates entry into the pleural space, which is confirmed by the ease of advancement of the inner stylet. The whole Tru-Cut needle is then angled towards the skin (position A to B), allowing the inner stylet to be advanced along the inner aspect of the thoracic wall and away from the lung. The outer cutting sheath is subsequently advanced over the inner stylet, yielding biopsy samples of up to 2 cm of parietal pleura and intercostal muscle (adapted from McLeod et al[14]).

6 months were deemed 'undiagnosed pleural exudates'. As the negative predicative value of medical thoracoscopy (when combining histology and microbiology) for TB pleuritis is practically 100% and its sensitivity for malignancy, in combination with fluid cytology and closed needle biopsies, is 97%, we decided upfront to retain these patients in the 'non-tuberculous' group for statistical analysis.[6] [22]

Statistical analysis

We expected a diagnostic sensitivity of 80% for both devices based on our own historical data and data from Chang et al.[6] [17] Using the McNemar test for equal proportions, it was estimated that a total sample size of 220 patients was required to prove non-inferiority (difference of less than 10%). We were, however, unsure if the diagnostic sensitivity achieved by Chang et al[17] in a relatively small study population would be reproducible, and given the paucity of data, practical constraints as well as patient safety aspects, it was decided to calculate the diagnostic yield for pleural TB of both needles after 36 months or after the inclusion of 100 patients, whichever came first. At 36 months (with 89 patients included), it became apparent that the yield of the Abrams needle for TB was consistent with the estimate,[6] but that the yield for the Tru-Cut biopsy was clearly lower than anticipated. We terminated the study as the sensitivities for pleural TB differed significantly between the devises and subsequently analysed all the data at this point (McNemar test for equal proportions and χ^2 tests with $p < 0.05$ accepted as significant). Unless stated otherwise, data are displayed as mean±SD. We used standard methods to calculate the sensitivity, specificity, and positive and negative predictive values.[23] For the purposes of the study, we accepted either histology compatible with TB (epithelioid granulomas with central necrosis, with or without acid-fast bacilli) or microbiological proof (pleura yielding a positive culture for M tuberculosis) on any pleural specimen as the gold standard.

RESULTS
Patient characteristics and transthoracic US finding

A total of 89 patients (54 men) of mean±SD age 38.7±16.7 years were enrolled over a 3-year period: 8 had minimal effusions, 19 had small effusions, 36 had moderate effusions and 26 had large effusions. Pleural TB was diagnosed in 66 cases (74.2%; mean±SD age 35.1±15.5 years; 35 men). Of the remaining 23 patients (mean±SD age 49.1±15.9 years; 19 men), 20 (22.5%) had an alternative diagnosis and 3 (3.4%) remained undiagnosed (table 1). The HIV status of 37 patients was known at the time of enrolment: 16/26 (61.5%) of patients who were ultimately diagnosed with pleural TB were HIV positive compared with 4/11 (36.4%) in the group where TB was excluded (p=0.159).

Diagnostic thoracentesis

The pH analysis, biochemistry and microbiological results are summarised in table 2. In patients ultimately diagnosed with pleural TB, 90.9% had a lymphocyte predominant effusion and 89.4% had an ADA >50 IU/l. Combining these parameters yielded a sensitivity of 83.3%, specificity of 95.7%, positive predictive value of 98.2% and negative predictive value of 66.7% for pleural TB (table 3). Seven patients were found to have complicated parapneumonic effusions (with bacterial cultures) and malignant cells were present in five. None of these 12 individuals had histological evidence of pleural TB.

Table 1 Final diagnoses established in all patients (n=89)

Diagnosis	n	%
Pleural tuberculosis	66	74.2
Bronchogenic carcinoma		
Non-small cell lung cancer	4	4.5
Small cell lung cancer	2	2.2
Metastatic adenocarcinoma (other than lung)	3	3.4
Malignant mesothelioma	2	2.2
Sarcoma	1	1.1
Parapneumonic effusion (bacterial)	7	7.9
Sarcoidosis	1	1.1
Undiagnosed pleural exudates	3	3.4

Closed needle biopsies: diagnostic yield

Pleural tissue was present at histology in 91.0% of Abrams needle biopsies and 78.7% of Tru-Cut biopsies (p=0.015, table 4). Abrams needle biopsies had a yield for all diagnoses of 78.7% compared with 62.9% for Tru-Cut needles (p=0.014).

In the 66 patients diagnosed with pleural TB, Abrams needle biopsies provided proof in 81.8%; 77.3% had histological evidence of TB and biopsies from 63.6% were culture positive for M tuberculosis. Tru-Cut needles yielded evidence of pleural TB in 65.2% (p=0.022); 60.6% of patients had histological evidence of TB (p=0.029) and biopsies from 39.4% were culture positive (p<0.001). Two of the 12 cases without a histological diagnosis of TB with Abrams needles were diagnosed on specimens harvested with Tru-Cut needles (a total of 56 patients were thus diagnosed with pleural TB on the basis of closed pleural biopsies).

Malignant pleural effusions were diagnosed in 12 patients. All had diagnostic closed pleural biopsies: Abrams needle biopsies yielded histological confirmation in 10 (83.3%) and Tru-Cut needle biopsies yielded histological confirmation in 8 (66.7%). Two cases not diagnosed with Abrams needles were both diagnosed on specimens obtained with Tru-Cut needles, and the four cases with false negative Tru-Cut biopsies (for malignancies) had positive Abrams needle biopsies. With regard to patients diagnosed with parapneumonic effusions (all with positive gram stains and cultures for bacteria on pleural fluid), acute pleuritis and/or non-specific inflammation were present in six specimens obtained by Abrams needles and five obtained by Tru-Cut needles.

Closed pleural biopsies: complications

The procedures were generally well tolerated and no pneumothoraces or major haemorrhages were documented. Two patients required parenteral analgesics; one complained of severe pain following Abrams needle biopsies and one following Tru-Cut biopsies (on both occasions the analgesics were administered following the second procedure). Two women (aged 20 and 22 years) experienced syncope following Abrams needle biopsies, both of whom recovered fully within 60 s (neither required any specific medical intervention). No procedure was abandoned due to complications.

Further assessment and follow-up

Thoracocentesis and closed pleural biopsy established aetiological diagnoses in 75 of the 89 patients. Diagnostic medical thoracoscopies were performed in 14. Aetiological diagnoses were subsequently made in a further 11 patients (10 cases of pleural TB and 1 of sarcoidosis). Three men aged 18, 51 and 63 years, respectively, remained undiagnosed. All were HIV negative, had minimal (n=1) or small (n=2) effusions, and

Table 2 Diagnostic thoracentesis results of tuberculous versus non-tuberculous effusions: continuous and categorical variables

Continuous variables

Variable	Tuberculous effusion (n=66)				Non-tuberculous effusion (n=23)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
pH	7.33	0.11	7.34	0.16	7.31	0.18	7.32	0.15
Lymphocytes (%)	76	23	84	23	47	35	49	77
Neutrophils (%)	13	19	5	17	30	34	39	59
Protein (g/l)	54.2	13.6	56.0	13.5	49.3	15.9	49.5	21.0
Albumin (g/l)	25.3	9.0	26.0	10.5	26.9	10.1	26.5	12.0
LDH (IU/l)	574	900	385	295	1675	2147	1027	1770
ADA (IU/l)	96.9	41.4	96.9	53	49.2	48.4	37.1	40

Categorical variables

Variable	Tuberculous effusion (n=66)		Non-tuberculous effusion (n=23)	
	n	%	n	%
ADA >50 IU/l	59	89.4	6	26.1
Lymphocyte predominant*	60	90.9	9	39.1
ADA >50 IU/l and lymphocyte predominant	55	83.3	1	4.3
Culture positive for bacteria other than *M tuberculosis*	0	0	7	30.4
AFB positive	0	0	0	0
M tuberculosis culture positive	17	25.8	0	0
Cytology positive for malignant cells	0	0	5	21.7

*Lymphocytic predominant effusion: >75% lymphocytes and/or lymphocyte to neutrophil ratio >0.75.
SD, standard deviation; IQR, interquartile range; ADA, adenosine deaminase; AFB, acid-fast bacilli; LDH, lactate dehydrogenase; *M tuberculosis, Mycobacterium tuberculosis*.

specimens obtained during thoracoscopy either showed non-specific pleuritis (n=2) or pleural fibrosis (n=1). A complete radiological recovery was documented in all three cases and all were asymptomatic at 6-month follow-up.

DISCUSSION

To the best of our knowledge, this is the largest prospective and the first randomised study performed to compare US-assisted Abrams needle biopsies with US-assisted Tru-Cut needle biopsies with regard to their diagnostic yield for pleural TB. We enrolled a relatively large population with a moderate to high pretest probability of pleural TB, and randomised patients to undergo either biopsy technique first in order not to disadvantage either needle. Abrams needle biopsies were more likely to contain pleural tissue (p=0.015) and to confirm the diagnosis of TB (p=0.022) than pleural biopsies obtained with Tru-Cut needles.

US-assisted Abrams needle biopsies had an overall diagnostic yield of 81.8% for TB pleuritis in a study population with a high pretest probability for the disease. We previously found medical thoracoscopy to have a diagnostic sensitivity of 100% for pleural TB.[6] The present study establishes US-assisted Abrams needle biopsies as the principal technique for obtaining pleural tissue in patients with suspected TB pleuritis, with medical thoracoscopy being reserved for the small number of cases who are not diagnosed with closed biopsies.

In general, blind Abrams needle biopsies have a yield of 50—85% for TB pleuritis.[6 24—28] Valdés and coworkers reported a diagnostic sensitivity of 79.8% when they analysed the case histories of 254 patients with confirmed pleural TB in a Spanish university hospital.[27] Diacon et al found Abrams needle biopsies to have a diagnostic yield of 79% in patients with undiagnosed exudative pleural effusions who presented to our institution.[6] We specifically enrolled patients with at least a moderate pretest probability of TB, which may account for the relatively high sensitivity. The use of US prior to closed pleural biopsies is currently advocated,[19 29 30] both as a safety measure and to detect localised pleural thickening and other abnormalities.[29 30] Pleural TB is a diffuse disease process,[25] and it can therefore be postulated that the addition of US prior to the Abrams needle biopsies is unlikely to affect the sensitivity. Although we did not specifically employ US to detect localised abnormalities, our findings certainly support this.

Tru-Cut biopsies yielded pleural tissue in 78.7% of patients in the study, with a diagnostic sensitivity of 65.2% for pleural TB and 66.7% for malignancy. Chang et al conducted the only other prospective study that specifically compared the diagnostic yield of US-guided pleural biopsy with a Tru-Cut needle and (blind)

Table 3 Diagnostic accuracy of pleural fluid analysis

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ADA (IU/l)	89.4	73.9	90.8	70.8
Lymphocyte predominance*	90.9	60.9	87.0	70.0
ADA >50 IU/l and lymphocyte predominant	83.3	95.7	98.2	66.7
Mycobacterium tuberculosis culture positive	25.8	100	100	31.9

*Lymphocytic predominant effusion: >75% lymphocytes and/or lymphocyte to neutrophil ratio >0.75.
ADA, adenosine deaminase; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Diagnostic yield of Abrams and Tru-Cut needle biopsies (n=89)

Parameter	Abrams	Tru-Cut	Significance
Pleural tissue present at histology (n=89)	81 (91.0%)	70 (78.7%)	p=0.015
All diagnoses (n=89)	70 (78.7%)	56 (62.9%)	p=0.014
Pleural tuberculosis (n=66)	54 (81.8%)	43 (65.2%)	p=0.022
Histological evidence	51 (77.3%)	40 (60.6%)	p=0.029
AFB positive	29 (43.9%)	25 (37.9%)	p=0.423
Culture positive	42 (63.6%)	26 (39.4%)	p<0.001
Alternative diagnoses (n=23)	16 (69.6%)	13 (56.5%)	p=0.450
Malignancy (n=12)	10 (83.3%)	8 (66.7%)	p=0.683
Benign pathology (n=8)	6 (75.0%)	5 (62.5%)	NA
Undiagnosed exudates (n=3)	0	0	NA

AFB, acid-fast bacilli; NA, not applicable.

pleural biopsy with an Abrams needle.[17] They enrolled 49 patients with unilateral pleural effusions, 24 of whom underwent pleural biopsy with an Abrams needle and 25 underwent US-guided pleural biopsy with a Tru-Cut needle. Only 17 patients had pleural TB. Abrams needle biopsies were diagnostic in 20% (2/10) whereas Tru-Cut needle biopsies were diagnostic in 86% (6/7). The diagnostic yields for malignancies were 44% and 77%, respectively. Four major differences in the studies should be highlighted. We enrolled almost four times as many patients with pleural TB, performed thoracic US before all biopsies, used both biopsy needles in all cases and specifically reported the presence of pleural tissue at histology. Furthermore, we used liquid culture media which have a proven superior yield for the culture of *M tuberculosis*.[31 32]

We encountered a number of unexpected results. All pleural malignancies were diagnosed by means of either the Abrams or Tru-Cut needles, and the combined diagnostic yield was therefore 100%. Although this study was not designed to specifically address this issue, this figure is significantly higher than reported figures.[33] Malignant disease tends to give rise to focal involvement,[25] and the lower thoracic and diaphragmatic parietal pleura are more likely to contain secondary seeding from visceral pleural metastases.[34 35] We aimed to use relatively low (supra-diaphragmatic) biopsy sites, which may partially explain the relatively high yield observed in our study. Moreover, we harvested at least six specimens per patient for histology, and it is known that the yield of closed biopsies increases with increasing number of biopsies.[25] We did not specifically evaluate the role of US in predicting pleural malignancies, as recently reported by Qureshi and coworkers.[36] In their study, US correctly identified 73% of malignant effusions on appearance alone.[36] The yield of US-assisted closed pleural biopsies in experienced hands may be much higher than previously believed and certainly deserves to be studied prospectively.

We found the Abrams needle to have a significantly superior yield for all diagnoses, and our data even suggested a comparable yield for pleural malignancy. Tru-Cut pleural biopsies can safely be performed in the presence of very little pleural fluid and have a diagnostic yield for pleural malignancy that is generally reported to be superior to that of Abrams needle biopsies.[17 19 26 30] Maskell and co-workers previously found CT-guided Tru-Cut pleural biopsies to have a superior sensitivity of 87% for pleural malignancies compared with 47% for unaided Abrams needle biopsies.[33] Local disease prevalence may therefore dictate the choice of biopsy needle, and the Tru-Cut needle may still be the needle of choice in patients with suspected pleural malignancy.

Kitinya *et al* found that the HIV status of a patient impacted on pleural biopsy results.[37] Their data suggested that granulomas were less likely to be observed, whereas pleural tissue from HIV positive patients was more likely to be culture positive. However, in our study population the majority of patients diagnosed with pleural TB by means of closed pleural biopsies had granulomas on histology, and the addition of TB culture only marginally increased the overall diagnostic yield.

Our data confirm previous findings on the very high specificity of an ADA >50 IU/l in the presence of a lymphocyte predominant effusion.[6 38] We found specificity of 95.7% and a positive predictive value of 98.2%. More important was the observation that, in a population with a high pretest probability for TB, pleural TB could be diagnosed in the majority of cases without the need for a pleural biopsy.

After 3 years it became evident that we had to abandon the original non-inferiority design as the sensitivity of the Tru-Cut biopsies was significantly lower than the original estimation at this point. While this certainly could be viewed as a weakness in the original study design, we strongly believe that this had no impact on the conclusion of the study. We collected robust data with complete follow-up. The end points used were dichotomous objective laboratory parameters which are not subject to random variation. Furthermore, the study design was on par with other studies in the field and the achieved sample size was at the higher end of the spectrum.[6 14 17 18 33]

In conclusion, US-assisted pleural biopsies performed with an Abrams needle are more likely to contain pleura and have a significantly higher diagnostic sensitivity for pleural TB. The Abrams needle should be the needle of choice for closed pleural biopsies in the setting of probable tuberculous effusions.

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Chapter 6

DISCUSSION & CONCLUSIONS

Discussion

We investigated the feasibility, diagnostic yield and safety of transthoracic US-assisted biopsy performed by respiratory physicians in various clinical settings relevant to everyday respiratory medicine, and consistently found acceptable to very high diagnostic yields with minimal complications, paving the way for greater utilisation by clinicians.

Study 1

"Drowned lung" is a radiological term often used to describe pulmonary collapse and postobstructive pneumonitis secondary to central tumours [1,2]. In our prospective proof of concept study on the feasibility and utility of US-assisted TTFNA of areas of drowned lung we found that passes at a depth greater than 20 mm from the visceral pleura had a diagnostic sensitivity of 74.2% for malignancy [3]. These passes were also more likely to contain malignant cells than more superficial passes (74.2% vs. 35.5%, p=0.002). Furthermore, we observed no serious complications, thus validating this novel indication for US-assisted TTFNA.

In the spectrum of benign and malignant lesions that abutted the pleura it was previously shown that transthoracic US-assisted FNA with ROSE and CNB had a combined sensitivity of 81% [4,5]. More importantly, this technique had a

sensitivity of 95% for bronchogenic carcinoma and a pneumothorax rate of close to 1% [1]. Yang et al. found that US-guided cutting needle biopsies had a diagnostic yield of 94.6% for subpleural pulmonary tumours [6].

Although the diagnostic yield in our study on US-assisted TTFNA of drowned lung was certainly not on par with these figures, our data provided novel evidence that this application of US-assisted TTFNA may even be useful in cases where the primary tumour does not extend to the chest wall. As the parenchyma of normal aerated lungs is not discernable by means of US and proximal lung tumours were therefore previously not considered amenable to US-assisted transthoracic FNA [3].

Bronchoscopy has an overall sensitivity of 88-95% for malignancy in the setting of centrally located lesions with secondary collapse [7,8]. It allows for the inspection of central airways, the evaluation for therapeutic airway management and the acquisition of histological samples that allow for superior subtyping and immunohistochemistry [7]. Furthermore, mediastinal nodal staging by means of transbronchial needle aspirations has important implications for staging and the management of lung cancer [9,10]. It therefore has to be emphasised that our study was purely a proof of concept study, designed to explore the feasibility of US-assisted transthoracic FNA in a novel setting, and was not designed to compare US-assisted transthoracic FNA with bronchoscopy (or CT-guided FNA), nor to define which patient may be best suited for a particular procedure.

Notwithstanding these important considerations, US-assisted TTFNA of drowned lung was shown to have an acceptable diagnostic yield, particularly when deep passes are performed and our findings suggest that it may be utilised in specific circumstances, which may include patients who are considered high risk for bronchoscopy, those who refuse to undergo bronchoscopy and in those patients where a preceding bronchoscopy was non-diagnostic. Moreover, it may be viewed as an acceptable alternative when endoscopic mediastinal staging is not relevant or when bronchoscopy is unavailable. Only future randomised studies will, however, be able to specifically delineate the subgroup of patients with drowned lung in whom a bronchoscopy may be considered superfluous.

Study 2

We performed the largest single-centre study on US-assisted TTFNA with ROSE and CNB in the setting of SVC syndrome ever reported, and were able to accurately diagnose 96% of all patients who presented with an SVC syndrome with an associated mass lesion that either abutted or infiltrated the chest wall [11]. A single-session approach was utilised, with CNB performed in all cases where a provisional on-site diagnosis of malignant epithelial neoplasm of the lung could not be established, and in 57.1% of patients with malignant epithelial neoplasms of the lung. In this pre-selected group, CNB had a diagnostic yield of 87.5%. No pneumothoraces or major haemorrhage was caused, and mild haemorrhage occurred in 4% of needle aspirations and 18.8% of biopsies. These findings were comparable to case series not limited to SVC syndrome [4,5].

Most authorities still consider cervical mediastinoscopy and anterior mediastinotomy as the gold standard for establishing a diagnosis in patients with SVC syndrome secondary to anterior mediastinal mass lesions [12,13]. These procedures have a diagnostic yield of almost 100%, but many patients suffer a major complication [12,13]. Furthermore, patients need to be able to withstand a general anaesthetic and lie in a supine position. Our results suggested that US-assisted TTFNA and CNB may be viewed as the primary investigation in this setting, given the speed, low cost, safety and sensitivity of these minimally invasive techniques [11]. In fact, we were able to diagnose 96% percent of patients after a single visit, a yield that is comparable to mediastinoscopy [12,13].

US-assisted TTFNA with rapid on-site evaluation and CNB performed by a clinician therefore have a high diagnostic yield and are safe in the setting of SVC syndrome with an associated mass lesion that abuts the chest wall. Study 2 validated the single-session approach, and confirmed that US-assisted TTFNA (with ROSE) should be the initial investigation of choice in suspected bronchogenic carcinoma, whereas both TTFNA and CNB need to be performed in all other cases.

Study 3

Incorporating the knowledge gained in the study 2, we continued to refine and validate our novel single-session sequential approach specifically in patients with

anterosuperior mediastinal masses. In our one-year prospective study we assessed the yield and safety of US-assisted TTFNA with ROSE followed by CNB performed by physicians [14]. US-assisted TTFNA with ROSE was performed on 45 consecutive patients, immediately followed by CNB where a provisional diagnosis of epithelial carcinoma or probable tuberculosis (necrotising and/or granulomatous inflammation) could not be established. TTFNA alone was deemed adequate by means of ROSE in 60%. CNB could be performed in 17 of the remaining 18 cases. An accurate cytological diagnosis was made in 73.3%, and was more likely to be diagnostic in epithelial carcinoma and tuberculosis than all other pathology (p<0.001). CNB yielded a diagnosis in 88.2%. Overall 93.3% of patients were diagnosed by the single-session approach. We observed no pneumothorax or major haemorrhage [14].

CT scanning is indicated in practically all cases of mediastinal masses [12,13,15-17] and tissue is generally harvested by means of mediastinoscopy, mediastinotomy or related surgical procedures [12,13,16-18]. Although the diagnostic yield of such an approach exceeds 90%, surgical biopsies carry a complication rate of up to 5% [12,13,16-18]. Moreover, these procedures usually need to be performed in theatre under general anaesthesia and require significant expertise and resources [12,13,16].

US-assisted biopsy of mediastinal masses is admittedly not a novel technique. Saito and co-workers described it two decades ago when they reported a

diagnostic yield of 87% for malignant tumours and 67% for benign masses [19]. Despite these promising findings, US-assisted biopsies have as yet failed to gain popularity amongst clinicians, possibly because subsequent investigators generally utilised only CNB [6,20] and were almost exclusively specialist interventional radiologists [21-25]. Studies that included more than 40 patients reported a 1-6% complication rate from CNB, with pneumothoraces, haemothoraces and haemoptysis the most common serious complications [19,20,22-24].

Although our overall sensitivity was on par with previous reports [6,19-25], our study design was unique in that ROSE was utilised to limit CNB to cases where cytology was less likely to provide a definitive diagnosis and thereby potentially limiting complications and cost. This approach has been validated for epithelial carcinomas and tuberculosis, where ROSE has been shown to have a high sensitivity for identifying diagnostic material and suggesting a provisional diagnosis [3,4,26,27]. Although cytology may be diagnostic in other types of pathology, further investigations are often required and the value of ROSE is therefore less well defined [28]. We decided upfront to acquire tissue samples for histology in all other diagnoses. As expected, we found that TTFNA with ROSE was superior for epithelial carcinoma and tuberculosis compared to all other diagnoses, which justified this approach. Albeit exceedingly rare, some case reports implicated needle biopsies of early stage thymoma in seeding into the chest wall [29,30]. It may therefore be advisable to offer primary surgical

resection to patients with a high suspicion of thymoma in order not to breach the capsule.

A single-session sequential approach of US-assisted TTFNA with ROSE followed by CNB, where indicated, therefore has a high diagnostic yield for anterosuperior mediastinal masses. On-site evaluation provided important guidance for the need for CNB, as the yield of US-assisted TTFNA alone was found to be significantly higher in patients with epithelial carcinomas and tuberculosis than all other diagnoses, justifying the routine performance of CNB in the latter group. This approach is safe and offers a less invasive alternative to surgical biopsy.

Study 4

In the largest prospective and the first randomised study performed to compare US-assisted Abrams needle biopsies with US-assisted Tru-Cut needle biopsies with regard to their diagnostic yield for pleural TB, we enrolled 89 patients with a moderate to high pre-test probability of pleural TB, and randomised patients to undergo either biopsy technique first. Pleural biopsy specimens obtained with Abrams needles contained pleural tissue in 91.0% of patients and were diagnostic for tuberculosis in 81.8%, whereas Tru-Cut needle biopsy specimens only contained pleural tissue in 78.7% (p=0.015) and were diagnostic in 65.2% (p=0.022) [31].

We found US-assisted Abrams needle biopsies to have an overall diagnostic yield of 81.8% for TB pleuritis in a study population with a high pre-test probability for the disease. Medical thoracoscopy has a diagnostic sensitivity of 100% for pleural TB, but is not widely available [32]. Study 4 established US-assisted Abrams needle biopsies as the principle technique to obtain pleural tissue in patients with suspected TB pleuritis, with medical thoracoscopy being reserved for the minority of cases that escape diagnosis by means of closed biopsies.

An interesting and unexpected finding in this study was the fact that we were able to diagnose all malignant effusions by means of either the Abrams or Tru-cut needles. Although this study was not designed to specifically address this issue, this figure is significantly higher than reported figures [33,34]. Malignant disease tends to give rise to focal involvement [34], and the lower thoracic and diaphragmatic parietal pleura are more likely to contain secondary seeding from visceral pleural metastases [33,34]. We aimed to utilise relatively low (supra-diaphragmatic) biopsy sites, which may partially explain the relatively high yield observed in our study. Moreover, we harvested at total of at least six specimens for histology per patient, and it is known that the yield of closed biopsies increases with increasing number of biopsies [35]. We did not specifically evaluate the role of US in predicting pleural malignancies, as reported by Qureshi and co-workers [36]. In their study, US correctly identified 73% of malignant effusions on appearance alone [36]. The yield of US-assisted closed pleural

biopsies for pleural malignancy may be much higher than previously believed and certainly deserves to be studied prospectively.

US-assisted pleural biopsies performed with an Abrams needle are therefore more likely to contain pleura and have a significantly higher diagnostic sensitivity for pleural TB. Abrams needle should be the needle of choice for closed pleural biopsies in the setting of probable tuberculous effusions.

General Comments

As a central theme, US-assisted biopsy performed by clinicians was shown to be feasible in the settings described, very safe and to have diagnostic yields comparable to more conventional techniques (ranging from bronchoscopy to surgical biopsies, as discussed above). The four studies expanded the evidence base for the greater utilisation of US-assisted biopsy by chest physicians, not only a novel setting (drowned lung), but also in combination with ROSE in a structured single-session approach in the settings of SVC syndrome with an associated mass lesion that abutted the chest wall and anterosuperior mediastinal masses. Furthermore, with regards to US-assisted pleural biopsy, the Abrams needle was shown to have a superior yield for pleural tuberculosis, although a combination of Abrams and Trucut needle biopsies was found to have an overall diagnostic yield for pleural malignancy never before recorded in the literature.

Modern US units are mobile, cheap and available in practically all secondary and tertiary, as well as many primary healthcare facilities, even in the developing world [37-42]. All the US-assisted biopsy techniques described in this dissertation can be performed by a single operator with no sedation and minimal monitoring, potentially outside of theatre [37,38]. Furthermore, the consumables (transmission gel, local anaesthetic, needles and syringes) are relatively cheap [37-40]. These practical consideration need to be emphasised when comparing the yield of US-assisted with marginally superior conventional techniques that are invariably performed in theatre under general anaesthesia or conscious sedation and that require significant expertise and resources [38].

Transthoracic US is still not utilised to its full potential by chest physicians, both in the developed and developing world [37-40]. We validated the use of US-assisted biopsy by clinicians in various settings, all of which are common in resource poor settings. We showed that specialised services including radiology and cardiothoracic surgery were only required in a minority of patients studied in all four sub-studies. In fact, in studies 2 and 3 we found US-assisted procedures to have comparable yields to conventional invasive investigations. At our institution the current average waiting period for CT-guided biopsy and mediastinoscopy is 6 weeks. The implementation of the protocols described has already expedited the definitive treatment of many patients, as practically all procedures are performed within 5 days. Additionally, and as discussed above, the direct cost-lowering implications are potentially considerable. Moreover, less

utilisation of overburdened specialist radiology and thoracic surgery services may lead to an increased efficiency in our institution as well as other facilities that operate under the same constraints.

The diagnostic algorithms and techniques developed in this thesis were developed with the resource limited health care system in mind. We validated the use of US-assisted FNA of drowned lung, potentially negating the need for bronchoscopy in up to two thirds of patients. Using a novel single-session approach of US-assisted FNA with ROSE followed where indicated by CNB, we were able to reduce the need for surgical biopsy to less than 10% of patients with SVC syndrome (with masses amenable to US-assisted FNA) and anterosuperior mediastinal masses. Furthermore, we showed that US-assisted Abrams needle biopsy is not only superior to Tru-cut needle biopsy in the setting of probable TB pleuritis, but could potentially lessen the need for thoracoscopy to less than 20% of cases not diagnosed on pleural fluid analysis.

Although our research should be of particular interest to physicians practicing in resource poor health care settings, our findings could potentially also impact on the way respiratory medicine is practiced in the first world. Given the diagnostic yield, safety profile and rapidity of the techniques described, as well as the fact that no radiological or surgical input is initially required, it seems logical to offer these minimally invasive techniques to patient as first line investigations, and to reserve surgical biopsies for non-diagnostic cases [11,14].

Recently there have been renewed calls for formal instruction of basic transthoracic ultrasound skills to all respiratory physicians in training, and for some form of certification in basic competence in ultrasonography [43-46]. The studies contained in this dissertation add to an ever growing evidence base, and certainly echo these sentiments.

We concentrated on US in the hands of the clinician, but it seems plausible that the US-assisted diagnostic techniques in the hands of interventional radiologist may have an equal or even higher yield. Although CT-guided biopsy has a marginally superior diagnostic yield in general [47], interventional radiologists should be encouraged to utilise this modality, particularly where a biopsy needs to be performed outside of a radiology unit or when CT services are compromised in any way.

The boundaries of the applications of transthoracic US have yet to be defined and several unanswered questions remain. Our study on US-assisted TTFNA of drowned lung was, for example, purely a proof of concept study designed to explore the feasibility of US-assisted TFNA in a novel setting, and not designed to compare US-assisted TFNA with bronchoscopy (or CT-guided FNA), nor to define which patient may be best suited for a particular procedure. Only future randomised studies will specifically be able to delineate the subgroup of patients with drowned lung in whom a bronchoscopy may be considered superfluous. The

single session approach used to investigate patients with SVC syndrome and anterior mediastinal masses needs validation in other settings.

Although we were able to show that Abrams needles were more likely to contain pleura and be diagnostic for pleural TB, it remains to be elucidated if these findings could be extrapolated to malignant diseases. Clearly there is a need for further studies in the field.

US-assisted biopsy is conceivably a cheaper alterative to traditional surgical biopsy. Yet, very little data exist on the actual cost-effectiveness of US-assisted biopsy as a modality and on where this modality should be strategically positioned in the greater field of imaging. Future studies are certainly indicated to address this question and how US-assisted biopsy can be optimally incorporated into the field of medical imaging and specifically interventional radiology.

The author of this dissertation is currently involved in numerous studies (in various phases of development) in the field of transthoracic US, including a study on the diagnostic yield of US-assisted closed pleural biopsy for pleural malignancy, the sensitivity of transthoracic ultrasound to detect pulmonary collapse in an intensive care setting, a study on the role of on-site US findings in the decision to drain parapneumonic effusions, and a study on liquid based cytological evaluation of TTFNA specimens.

Conclusions and Reflective Assessment of Contribution

Several theoretical contributions to current literature were made. A novel indication for US-assisted biopsy, TTFNA of drowned lung was described; this technique was shown to be safe and to have an acceptable diagnostic yield, particularly when deep passes are performed. US-assisted TTFNA with ROSE and CNB performed by a clinician was found to have a high diagnostic yield comparable to surgical biopsies and were safe in the settings of SVC syndrome with an associated mass lesion that abutted the chest wall and anterosuperior mediastinal masses. On-site evaluation provided important guidance for the need for CNB, as the yield of US-assisted TTFNA alone was found to be significantly higher in patients with epithelial carcinomas and tuberculosis than all other diagnoses, justifying the routine performance of CNB in the latter group. Finally, we were able to show that the US-assisted pleural biopsy performed with an Abrams needle is more likely to contain pleura and have a significantly higher diagnostic sensitivity for pleural tuberculosis than biopsy performed by means of Tru-cut needles.

The major methodological contribution of this thesis was validation of US-assisted biopsy in a novel setting (drowned lung), as well as the prospective validation of a single session approach in two challenging clinical settings, that of SVC syndrome and anterosuperior mediastinal masses. Furthermore, we found that the Abrams needle should be the needle of choice for closed pleural biopsies in the setting of probable tuberculous effusions.

The empirical contribution of this thesis is significant. The diagnostic algorithms and concepts described in this thesis have been developed specifically for health care systems with limited resources. Moreover, we consistently found that US-assisted biopsy performed by clinicians in the various settings had diagnostic yields comparable to surgical or CT-guided biopsy, therefore limiting the need for these special investigations that require significant expertise and cost. This body of work should pave the way for greater use of US-assisted biopsy as a first line investigation, reserving surgical biopsy for the undiagnosed cases, even in non-resourced constrained settings.

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Appendix A

SUPPLEMENTARY PUBLICATIONS

➤ **von Groote-Bidlingmaier F, Koegelenberg CF, Bolliger CT. Transthoracic Ultrasound. ERS Handbook. Sheffield, European Respiratory Society, 2010, pp 138-142**

➤ **von Groote-Bidlingmaier F, Koegelenberg CF. Ultrasound in Pulmonary Medicine. The Buyers' Guide to Respiratory Care Products. Sheffield, European Respiratory Society, 2010, pp 69-77**

➤ **Koegelenberg CFN, Diacon AH, Bolliger CT. Parapneumonic pleural effusion and empyema. Respiration 2008;75:241-250**

➤ **Koegelenberg CFN, Diacon AH. Ultrasound-Assisted Pleural Biopsies. Int Pleural Newsletter 2010;8(2):8-9**

➤ **Koegelenberg CFN, Diacon AH. Pleural Biopsy for Patients with Suspected Malignant Effusions. Int Pleural Newsletter 2008;6(2):8-9**

➤ **Koegelenberg CFN, Diacon AH. Diagnosis of TB Pleural Effusions. Int Pleural Newsletter 2007;5(2):6-7**

TRANSTHORACIC ULTRASOUND

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Transthoracic ultrasonography can be performed with the most basic ultrasound (US) equipment. It is used for the investigation of chest wall abnormalities, pleural thickening and pleural tumours, and the qualitative and quantitative description of pleural effusions. Lung tumours, pulmonary consolidations and other parenchymal pulmonary processes abutting the pleura can also be visualised. Furthermore, US is ideal to guide thoracentesis, drainage of effusions and other thoracic interventions. US is particularly useful in intensive care units where radiographic equipment is unavailable.

Advantages of thoracic US include its mobility, dynamic properties, lack of radiation and low cost.

The ultrasonographic appearance of the normal thorax and the most common pathologies are reviewed in this chapter.

General technical aspects and appearance of the normal thorax

A low-frequency probe (*e.g.* 3.5 MHz) is routinely used for screening purposes, while detailed assessment of an abnormal chest wall or pleura can be performed with a high-frequency probe (*e.g.* 8 MHz).

Superficial muscles and fascia planes appear as a series of echogenic layers during the initial surveillance of a normal chest. Curvilinear structures on transverse scans, associated with posterior acoustic shadowing represent the ribs.

The visceral and parietal pleura normally appear as one highly echogenic line. Movement of the lung with the respiratory cycle in relation to the chest wall on real-time US is called the "lung sliding" sign. Its presence is strong evidence against a pneumothorax.

US cannot visualise normal aerated lung tissue. The large change in acoustic impedance at the pleura–lung interface, however, causes horizontal artefacts that are seen as a series of echogenic parallel lines equidistant from one another below the pleura. These bright but formless lines are known as reverberation artefacts (fig. 1).

Chest wall pathology

Soft-tissue masses, such as abscesses, lipomas and a variety of other lesions, can be detected by US. These lesions are mostly benign, but variable echogenicity and nonspecific US findings make differentiation between various aetiologies difficult. Supraclavicular and axillary lymph nodes are usually accessible, and US may even help to distinguish benign from malignant lymph nodes. Hypoechoic masses disrupting the normal structure of a

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Key points

- Transthoracic US can be used to investigate chest wall abnormalities, pleural thickening and pleural tumours, and to describe pleural effusions.

- Advantages of the technique include its mobility, dynamic properties, lack of radiation and low cost.
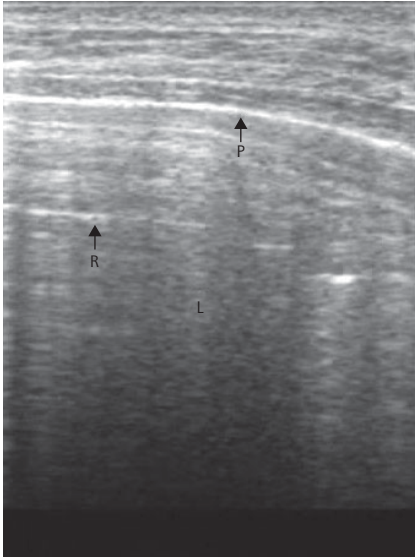

Figure 1. The typical appearance of a normal chest on ultrasound (US). A transverse view through the intercostal space is shown. The chest wall is visualised as multiple layers of echogenicity representing muscles and fascia. The visceral and parietal pleura appear as an echogenic bright line (two distinct lines sliding during respiration are visible on real-time US). Reverberation artefacts beneath the pleural lines imply an underlying air-filled lung. P: pleura; L: lung; R: reverberation artefact.

rib may represent bony metastases and can be seen on US.

Pleural pathology

Transthoracic US is most commonly used to investigate pleural effusions, and is more sensitive than decubitus radiographs at demonstrating minimal or loculated effusions. The US appearance of a pleural effusion depends on its nature and chronicity. Four appearances based on the internal echogenicity are recognised: anechoic; complex but nonseptated; complex and septated; and homogenously echogenic. Transudates are invariably anechoic, unseptated and free flowing, whereas complex, septated or echogenic effusions are usually exudates. Malignant effusions are frequently anechoic. The atelectatic lung inside a large effusion may appear as a tongue-like structure within the effusion. Inflammatory effusions are often associated with strands of echogenic material and septations that show more or less mobility with respiration and the cardiac cycle (fig. 2).

The volume of a pleural effusion can be estimated using the following classification: minimal, if the echo-free space is confined to the costophrenic angle; small, if the space is greater than the costophrenic angle but still within the range of the area covered with a 3.5 MHz curvilinear probe; moderate, if the space is greater than a one-probe range but within a two-probe range; and large, if the space is bigger than a two-probe range.

Both small effusions and pleural thickening may appear as hypoechoic on US, so differentiation might be difficult. An important sign in favour of an effusion is mobility on real-time US.

Metastatic pleural tumours and malignant mesothelioma can be visualised as polypoid pleural nodules or irregular sheet like pleural thickening. They are often associated with large pleural effusions. Benign pleural tumours are rare.

QURESHI *et al.* found that pleural thickening >1 cm, pleural nodularity and diaphragmatic thickening >7 mm were highly suggestive of malignant disease. In their study, US correctly identified 73% of malignant effusions.

The absence of normal lung sliding, the loss of comet-tail artefacts and exaggerated horizontal reverberation artefacts are reliable signs for the presence of a pneumothorax.

Pulmonary pathology

A lung tumour abutting the pleura will be detectable by US (fig. 3). In most cases these tumours present as a hypoechoic mass with posterior acoustic enhancement (fig. 4).

Visceral pleura or chest wall involvement is important for staging of malignant lung tumours. Loss of movement of a visualised
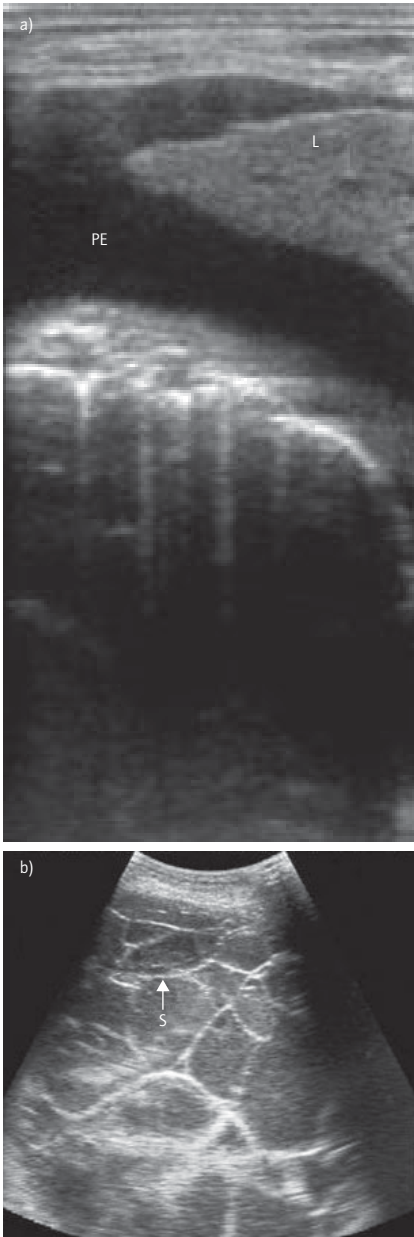
tumour with respiration suggests infiltration beyond the parietal pleura.

US can detect pneumonic consolidations provided they have contact with the pleura. Non-infective causes of consolidations with similar appearance on US include pulmonary infarction, haemorrhage and bronchoalveolar carcinoma.

A hypoechoic lesion with a well-defined or irregular wall abutting the pleura might represent a lung abscess. The centre of the abscess is most often anechoic, but may reveal septations and internal echoes.

Conclusion

The value of US for chest physicians is firmly established. Basic thoracic ultrasonography is an elegant and inexpensive investigation that extends the physicians' diagnostic and interventional potential at the bedside in peripheral lung, pleural, and chest wall disease.

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Figure 2. Example of an anechoic pleural effusion is shown on the left. It presents as an echo-free space between the visceral and parietal pleura. Compressive atelectasis of the lung may be seen as a tongue-like structure in a large effusion. Note the
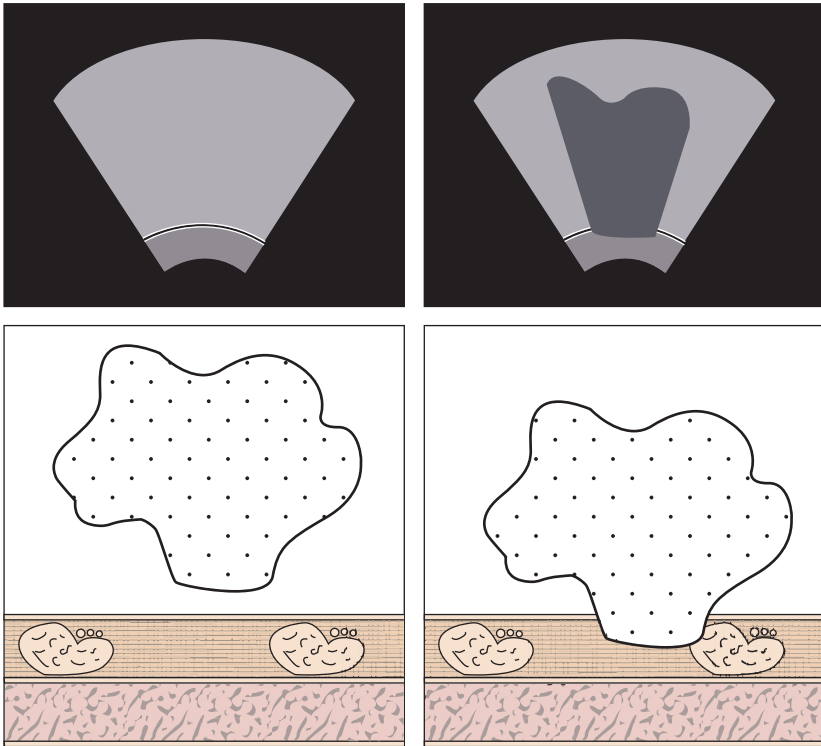
Figure 3. A peripheral pulmonary lesion is shown schematically without (top) and with (bottom) pleural contact. Only the lesion with pleural contact is visible on ultrasound. Reproduced from DIACON et al. (2005), with permission from the publisher.
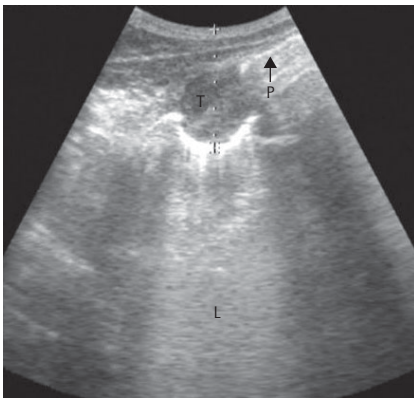

Figure 4. A sonographic image showing a solid lung lesion with posterior echo enhancement. Note that the tumour is abutting the pleura and is therefore visible on ultrasound. P: pleura; L: lung; T: tumour.

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ULTRASOUND IN PULMONARY MEDICINE

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Although diagnostic ultrasonography was pioneered as early as the 1940s, many modern-day respiratory physicians still underestimate its usefulness and growing number of applications. Interest in ultrasound (US) as an aid to the clinician has been revived in recent years; this article will review transthoracic and endobronchial US.

TRANSTHORACIC ULTRASOUND

Transthoracic US can be performed by means of the most basic US equipment and its mobility allows use in the endoscopy theatre, intensive care unit (ICU) and emergency room. Other important advantages of transthoracic US are the ability to produce dynamic images in a noninvasive manner, the lack of radiation and its relatively low cost [1–6].

General technical aspects and principles

Although US images are not as reproducible as computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET)/CT images, a major advantage of US is the ability to create dynamic real-time images. The quality of the images is dependent on the skills of the operator, on the positioning of the probe and respiratory movement. The dynamic properties are not only highly valuable in characterising pathologies but also in guiding interventions with real-time images.

Most US devices come equipped with a low frequency curvilinear transducer probe (2–5 MHz) and a high-frequency linear transducer probe (7.5–10 MHz). Doppler and colour-flow echo are not required for routine pleural or pulmonary examination. Higher frequency gives better resolution closer to the probe, but at the cost of lower penetration. The lower frequency probe is therefore suitable for initial screening of superficial and deeper structures, while the high frequency probe is used for refined assessment of an abnormal chest wall or pleural area.

The three most important controls on a standard US are "depth", "gain" and "freeze". The depth function is a zoom that defines what portion of the scanned image is displayed. Obese subjects or patients with a large effusion require a depth setting of up to 12 cm. The gain is a measure that determines the brightness of the image. The freeze function allows for the capturing of still images for documentation and measurements.

The optimal patient position for scanning is of great importance. Access to the chest can be achieved *via* the abdomen, intercostal spaces or the supraclavicular fossae. It is imperative to review relevant chest radiographs and CT scans prior to performing an US. The posterior chest is best scanned with the patient in the sitting position. The lateral and anterior chest wall can be scanned in either the lateral decubitus or supine position. Maximum visualisation is achieved by examining along the intercostal spaces. Elevating the arm above the head increases the intercostal space distance and facilitates scanning. A patient can fold the arms across the chest in order to displace the scapulae when surveying the upper posterior thorax. An apical ▶

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approach is used with superior sulcus pathology.

Applications

Chest wall pathology

A variety of chest wall lesions, mostly soft tissue masses, such as abscesses and lipomas, can be detected by US. Most of these lesions are benign but nonspecific US findings make differentiation between various aetiologies difficult [1, 4]. Bony metastases may present as hypoechoic masses disrupting the normal rib structure [7].

Pleural pathology

The most common application of transthoracic US is the investigation of pleural effusions, as it is more sensitive than decubitus chest radiographs, especially in small and loculated effusions [8]. The appearance of a pleural effusion on US depends on its nature and chronicity. Four appearances based on the internal echogenicity have been described and are recognised: anechoic; complex but nonseptated; complex and septated; and homogenously echogenic. Transudates are invariably anechoic, unseptated and free flowing, whereas complex, septated or echogenic effusions are usually exudates [9, 10]. Malignant effusions are frequently anechoic, while inflammatory effusions are often associated with strands of echogenic material and septations which show more or less mobility with respiration and the cardiac cycle (fig. 1).

Differentiation between small effusions and pleural thickening might be challenging, as both may appear hypoechoic on US. An important feature in favour of an effusion is mobility on real-time US.

Metastatic pleural tumours and malignant mesothelioma can be visualised as polypoid pleural nodules or irregular sheet-like pleural thickening [11], often
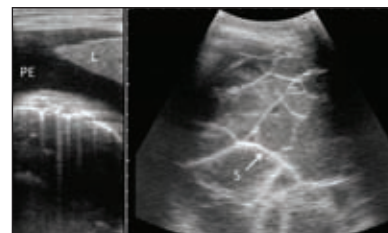

Figure 1. Example of an anechoic pleural effusion is shown on the left. It presents as an echo-free space between the visceral and parietal pleura. Compressive atelectasis of the lung may be seen as a tongue-like structure. Note the difference to the effusion on the right which is classified as complex septated. Multiple septa form many compartments in the same effusion. PE: pleural effusion; L: lung; S: septum.

associated with large pleural effusions. In a recent study, QURESHI et al. [12] were able to identify 73% of malignant effusions on appearance alone. They found that pleural thickening >10 mm, pleural nodularity and diaphragmatic thickening >7 mm were highly suggestive of malignant disease.

The loss of comet-tail artefacts, exaggerated horizontal reverberation artefacts and the absence of normal lung sliding are reliable signs for the presence of a pneumothorax [13].

Pulmonary pathology

Lung tumours are detectable by US provided they abut the pleura or the chest wall (fig. 2). In most cases, these tumours present as a hypoechoic mass with posterior acoustic enhancement (fig. 3) [3]. Chest wall infiltration has obvious implications for the staging of lung cancer and is suspected when the movement of a visualised tumour with respiration is lost.

Pneumonic consolidations with contact to the pleura can be detected by US. Noninfective causes of consolidations with similar appearance on US include pulmonary infarction, haemorrhage and bronchoalveolar carcinoma. A hypoechoic lesion with a well-
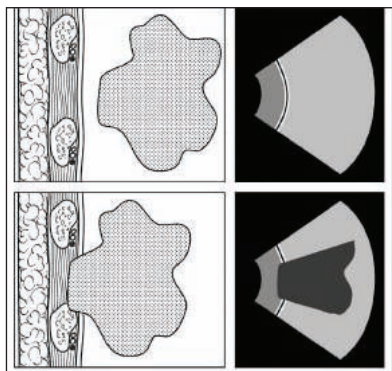
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Figure 2. A peripheral pulmonary lesion is shown schematically without (top) and with (bottom) pleural contact. Only the lesion with pleural contact is visible on ultrasound (from [3] with kind permission).

Figure 3. A sonographic image showing a solid lung lesion with posterior echo enhancement. Note that the tumour is abutting the pleura and is therefore visible on ultrasound. The distance to the distal tumour end is measured. P: pleura; L: lung; T: tumour.

defined or irregular wall abutting the pleura may represent a lung abscess [14]. The centre of the abscess is most often anechoic but may reveal septations and internal echoes.

Interventions

Compared with blind procedures, US-guided procedures have an increased success rate and are safer [1]. Specific probes for real-time guidance of fine needle aspirations (FNA) or biopsies are available but many experienced physicians prefer the 'freehand' technique. Following adequate patient positioning, the

intended site of needle insertion is identified under US and marked, while the direction, the depth of interest and the safety range for the procedure are memorised. Movement should be avoided at all cost; it may even be necessary to ask the patient to hold their breath for the duration of the aspiration or biopsy.

Pleural fluid aspiration under US guidance can have a success rate as high as 97% [15] and even small fluid accumulations can be identified, the most accessible site chosen and the aspiration performed using the 'freehand' technique.

Intercostal drains can be inserted more safely after determination of the insertion site by means of US. In an ICU setting and with complicated parapneumonic effusions this becomes particularly relevant. US may also guide further decisions regarding the need for interventions in addition to drainage and antibiotics [16]. A recent survey carried out in the UK highlighted the dangers of blind pleural procedures: 67 out of 101 trusts reported at least one serious complication from intercostal drainage. In all, 47 cases of serious lung or chest wall injuries with eight deaths and six cases of intercostal chest drain placement on the wrong side were described [17]

Closed pleural biopsies can only be performed unaided in sizeable effusions. Recent studies have re-emphasised the importance of transthoracic US as a guide to pleural procedures, both with regards to safety and diagnostic yield [1]. In a recent prospective randomised study, we found that US-assisted Abrams needle biopsy specimens were more likely to contain pleural tissue than specimens obtained by means of US-assisted Tru-cut biopsies (91.0 *versus* 78.7%) [18].

Peripheral lung tumours can safely be assessed by US-guided FNA or ▶

cutting biopsy provided they either abut or invade the pleura or the chest wall. Those procedures can be performed by nonradiologists under local anaesthesia and have a high diagnostic yield [19]. The risk of pneumothorax is low as no aerated lung tissue needs to be transversed. A study by DIACON *et al.* [19] showed that transthoracic FNA and closed needle biopsies corresponded well in the diagnosis of epithelial lung carcinoma. US-assisted 'free-hand' closed needle biopsies of tumours abutting the chest wall had a sensitivity of 85.5%. US can even be used to guide biopsies of the mediastinum and peripheral lung in the setting of superior vena cava syndrome [20].

US-assisted FNA can also be helpful in defining the aetiology of pulmonary consolidation. YANG *et al.* [21] found that US-assisted biopsies of pulmonary consolidations were diagnostic in 93% of cases. Lung abscesses could be demonstrated by means of US in 94% of patients with radiologically confirmed lung abscesses. More than 90% of aspirates yielded a positive culture, whereas less than 10% of patients had positive blood cultures [22].

Ultrasound of the neck

The most common indication for US evaluation of the neck is staging of lung cancer including US-assisted biopsy of suspicious lymph nodes. US has been shown to be superior to CT in the detection of metastases of lung cancer in the neck and should be included early in the diagnostic work up [23]. US was able to avoid bronchoscopy in about 15% of patients with lung cancer where neck metastases were detected by US. Nonmalignant conditions, such as sarcoidosis and tuberculosis, can also be diagnosed.

ENDOBRONCHIAL US

Endobronchial US (EBUS) has revolutionised bronchoscopy. It allows the endoscopist to evaluate the mediastinum and lungs beyond the endoluminal surface. Peribronchial structures and peripheral lung lesions become visible. The gastroenterologists HAGENMÜLLER and CLASSEN [24] were the first to report on the use of endoscopic (oesophageal) US endoscopic ultrasound scan (EUS) in 1980. The endobronchial use of this technology lagged by 10 yrs; the first report by Hürther and Hanrath [25] on the endobronchial use of US was only published in 1990. Most research has been conducted in Germany and Japan, from where landmark publications by BECKER [26] and KURIMOTO *et al.* [27] came. Two forms of EBUS systems with specific transducers and different applications are currently commercially available, namely the "linear" and "radial" EBUS transducers.

The development of a dedicated EBUS- transbronchial needle aspiration (TBNA) bronchoscope with a convex US probe in 2005 made needle aspirations under real-time US possible [28].

Radial EBUS

Radial EBUS probes generally have a 20 MHz rotating transducer that can be inserted through the working channels of flexible bronchoscopes. Radial miniature probes are available in different sizes and can be used with balloon sheaths to assess central peribronchial structures in the proximal airways or without balloon sheaths to identify peripheral lung lesions. Two different types of miniprobes are mostly used: a 20 MHz probe (UM-BS20-26R; Olympus, Tokyo, Japan) is used with an inflatable balloon for the assessment of the central airways (fig. 4). By inflating the balloon and filling it with sterile water, coupling of the transducer with the bronchial mucosa is made easier. The probe is inserted through the working channel of a standard therapeutic bronchoscope (2.8 mm) and produces a 360° image

perpendicular to the insertion access of the probe (fig. 5). Another miniature radial probe (UM-S20-17S; Olympus) has a maximum insertion tube diameter of 1.8 mm and can be inserted through the 2.0 mm working channel of a standard flexible bronchoscope. For sampling of peripheral lesions, the radial probe is covered by a guide sheath also called 'extended working channel' (fig. 6) and brought to the area of interest. As the lesion is identified the probe is pulled back, leaving the guide sheath in place and a biopsy tool is advanced to obtain specimens.

In a large-scale prospective study, EBUS-guided transbronchial biopsy has been shown to significantly increase the diagnostic yield in lesions <3 cm and <2 cm [29]. In patients with fluoroscopy-invisible solitary pulmonary nodules, 89% of lesions were identified by EBUS [30]. EBUS can also distinguish between benign and malignant lesions. A classification system has been reported, dividing lesions into three categories according to their US appearance. 92% of type I lesions were benign, whereas 99% of type II and III lesions were malignant [31]. Although radial EBUS provides detailed information about the location and the nature of a peripheral lesion, biopsies are not real-time.

Complications of EBUS guided transbronchial biopsies are rare and do not differ significantly from those of regular transbronchial biopsies [30, 32]. Complications, such as minor bleeding and pneumothorax, are therefore rather attributed to the biopsy itself and ▶

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Figure 4. A radial endobronchial ultrasound miniprobe (UM-BS20-26R, Olympus, Japan) is shown inside the working channel of a standard bronchoscope. For improved coupling with the bronchial mucosa in the central airways the balloon can be inflated.
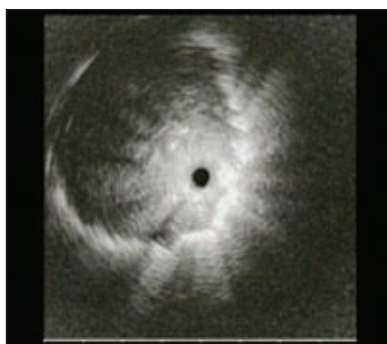

Figure 5. Endosonographic image of a peripheral lung lesion. Note the 360° view of the radial probe.

Figure 6. Radial miniprobe (UM-S20-17S, Olympus, Japan) inside the guide sheath. Once a peripheral lesion is located by endobronchial ultrasound the probe is retracted and the guide sheath left in place.

not to the EBUS procedure. Even without fluoroscopic guidance, EBUS-guided transbronchial biopsies appear to be safe and effective [33, 34].

Linear EBUS

Linear EBUS technology is used with a dedicated EBUS bronchoscope and enables real-time TBNA (fig. 7). The latest addition to the range of instruments (BF-UC180F, Olympus) has an insertion tube outer diameter of 6.3 mm, making oral intubation preferable. It contains an electronic curved linear array transducer (5–12 MHz) with a penetration depth of 50 mm, which also supports Power Doppler functions. The angle of view is 80° in a 35° forward oblique direction and the US view is parallel to the long axis of the bronchoscope. A balloon filled with sterile water can be inflated to improve coupling with the bronchial wall if needed. US image and bronchoscopic image can be viewed side by side and the US image can be frozen for measurement of the target lesion. For a full inspection of the airways, a standard flexible bronchoscope might be required due to the size of the EBUS bronchoscope.

Real-time TBNA using a 22G needle through the 2.2 mm working channel can be performed, once the target lesion is identified (fig. 8). With exception of American Thoracic Society lymph node stations 5, 6, 8 and 9, all mediastinal stations are reachable by EBUS-TBNA. Real-time EBUS-TBNA has a higher diagnostic yield in mediastinal lymph node staging than blind TBNA and may be comparable in sensitivity to cervical mediastinoscopy [35, 36]. Even in the absence of rapid on-site cytology evaluation, high diagnostic yields up to 100% have been reported for real-time EBUS-TBNA. The fairly high false-negative rate makes further investigations such as mediastinoscopy necessary for negative results.

Accurate staging of non-small cell lung cancer is of utmost importance, as it not only determines the patient's prognosis but has important implication with regards to the therapy. In the absence of ▶

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Figure 7. The tip of a dedicated endobronchial ultrasound transbronchial needle asperation bronchoscope (BF-UC180F, Olympus, Japan) is shown in this image. A needle is advanced through the working channel of the endoscope for real-time TBNA.

Figure 8. Endosonographic image of real-time lymph node transbronchial needle asperation. Note the needle (N) as it is advanced into the lymph node (LN).

distant metastasis, mediastinal involvement often determines operability. Noninvasive techniques (i.e. CT, PET-CT, and MRI) have been improved over time, but most abnormal findings on imagery still require confirmation with histology or cytology. EBUS-TBNA has proven to be a minimally invasive, safe and accurate procedure. In the largest study, HERTH and co-workers [37] showed a sensitivity of 94% and a specificity of 100% in 502 patients [37]. The same authors reported unexpected mediastinal metastases in 17% of 119 lymph nodes in patients with a radiologically normal mediastinum [38]. Even in the radiologically normal and PET-normal mediastinum, a 9% prevalence of mediastinal metastases was detected by EBUS-TBNA [39]. Combination of endoscopic US (EUS) with EBUS

represents a sampling method that may replace mediastinoscopy, since all mediastinal lymph node stations become accessible [35, 40].

CONCLUSIONS

The value of both transthoracic and EBUS for clinicians is firmly established. Basic thoracic US is an inexpensive investigation that extends the physicians' diagnostic and interventional potential in peripheral lung, pleural and chest wall disease. It can potentially replace CT-guided fine-needle biopsies of all lesions involving the pleura and chest wall, as well as lung masses or consolidations abutting the pleura.

EBUS provides an accurate and safe means of evaluating a variety of pulmonary conditions. It has a high diagnostic rate in mediastinal lymph node staging, and radial EBUS can facilitate identification of more peripheral lung lesions.

All academic institutions should have a basic training program in transthoracic and endobronchial US in place in order to ensure that all aspiring chest physicians are familiar with the basic aspects.

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Respiration

Parapneumonic Pleural Effusion and Empyema

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Key Words

Parapneumonic pleural effusion · Empyema · Fibrinolytics · Thoracoscopy · Thoracotomy · Thoracostomy

Abstract

At least 40% of all patients with pneumonia will have an associated pleural effusion, although a minority will require an intervention for a complicated parapneumonic effusion or empyema. All patients require medical management with antibiotics. Empyema and large or loculated effusions need to be formally drained, as well as parapneumonic effusions with a pH <7.20, glucose <3.4 mmol/l (60 mg/dl) or positive microbial stain and/or culture. Drainage is most frequently achieved with tube thoracostomy. The use of fibrinolytics remains controversial, although evidence suggests a role for the early use in complicated, loculated parapneumonic effusions and empyema, particularly in poor surgical candidates and in centres with inadequate surgical facilities. Early thoracoscopy is an alternative to thrombolytics, although its role is even less well defined than fibrinolytics. Local expertise and availability are likely to dictate the initial choice between tube thoracostomy (with or without fibrinolytics) and thoracoscopy. Open surgical intervention is sometimes required to control pleural sepsis or to restore chest mechanics. This review gives an overview of parapneumonic effusion and empyema, focusing on recent developments and controversies.

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Previous articles in this series: 1. Froudarakis ME: Diagnostic work-up of pleural effusions. *Respiration* 2008;75:4–13.   2. Jantz MA, Antony VB: Pathophysiology of the pleura. *Respiration* 2008;75: 121–133.

Introduction and Definitions

At least 40% of all patients diagnosed with pneumonia will have an associated pleural effusion, although the minority of these will require active intervention [1, 2]. A parapneumonic pleural effusion refers to any effusion secondary to pneumonia or lung abscess [1]. It becomes 'complicated' when an invasive procedure is necessary for its resolution, or if bacteria can be cultured from the effusion [1]. Empyema is a term derived from the Greek verb *empyein* ('to suppurate') and literally refers to frank pus in the pleural space. Parapneumonic effusion and empyema remain important medical conditions associated with significant morbidity and mortality [2]. It is estimated that in the United States alone, pleural infections have an incidence of 60,000 per year and a mortality of approximately 15% [3, 4]. Yet, controversy remains regarding the management and specifically the role of fibrinolytic therapy.

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Epidemiology and Risk Factors

Complicated parapneumonic effusions and empyema are more common at both extremes of age [2, 3]. At least two thirds of patients will have an identifiable risk factor at presentation [2], which may include immunosuppressive states (most frequently HIV infection, diabetes mellitus and malnutrition), alcohol or intravenous drug abuse, bronchial aspiration, poor dental hygiene, gastrooesophageal reflux, and chronic parenchymal lung disease [3, 4]. Microbial virulence and idiosyncrasies of the immune system are often also implicated, principally in individuals with no apparent predisposition.

Pathogenesis

Although pleural infection may occur as a primary event, most cases of pleural sepsis are secondary to pneumonias, lung abscesses or infective exacerbations of bronchiectasis. It should be noted that the associated pulmonary consolidation may be minimal [2]. Other identifiable causes include thoracic surgery, diagnostic procedures involving the pleural space, trauma, oesophageal rupture, transdiaphragmatic spread and rarely bronchial obstruction [5]. Primary pleural infections are presumably most often due to the haematogenous spread of organisms from gingival and upper respiratory tract infections (with cultures yielding oropharyngeal flora and anaerobes) [2, 6] or due to *Mycobacterium tuberculosis* [7].

The development of a parapneumonic effusion occurs in three clinically relevant stages that represent a continuous spectrum [1, 8]. A rapid influx of exudative fluid into the pleural space is observed in up to 40% of patients with pneumonia and heralds the first or exudative stage [1, 2]. The accumulation of fluid is thought to be a direct result of increased pulmonary interstitial fluid traversing the pleura to enter the pleural space [1] and an increase in vascular permeability secondary to pro-inflammatory cytokines [2, 9], e.g. interleukin-8 and tumour necrosis factor-α. During this stage pleural fluid culture is negative for bacteria, fluid pH is >7.20, the glucose level is within the normal range and lactate dehydrogenase remains <3 times the upper limit of normal [1, 2]. Most patents with uncomplicated parapneumonic effusions will respond to antibiotics alone and drainage is generally not required [1, 2, 10].

Untreated exudative effusions may develop into fibrinopurulent effusions. This second stage is characterized by positive microbial cultures. Ongoing phagocytosis and cell lysis result in fluid that most frequently has a pH of <7.20, a lactate dehydrogenase >3 times the upper limit and a low glucose [1, 2, 10]. Rarely, fibrinopurulent effusions can have a pH in the normal or even in the alkaline range. This phenomenon is limited to a few pathogens (e.g. *Proteus* spp.) with enzymatic activity that can elevate fluid pH, for instance by cleaving urea into ammonia [11]. During the fibrinopurulent stage the pleural space becomes increasingly infected. Loculations may develop and closed or open drainage becomes necessary – the point in time where an effusion is referred to as 'complicated'. A critical characteristic of the fibrinopurulent stage of pleural sepsis is the disturbance of the physiological equilibrium between clotting and fibrinolysis within the pleural space [2, 12]. Several mediators for the activation of the coagulation cascade and inhibition of fibrinolysis have been suggested: TNF-α, for example, has been shown to stimulate the release of plasminogen activator inhibitors from pleural mesothelial cells. Aleman et al. [13] were able to show increased levels of plasminogen activator inhibitor-2 and depressed levels of tissue plasminogen activator (tPA) during complicated pleural sepsis. Although the exact mechanisms behind the procoagulate state still need to be elucidated, its effects are well-known: pleural surfaces coated with fibrin and fibrin strands with secondary adhesions and loculations, all complicating pleural fluid drainage.

The third and final stage of pleural infection is the organizing phase [1, 2]. Fibroblasts grow into the pleural space from both the visceral and parietal pleura. This eventually results in a thick pleural peel, which restricts chest mechanics and often necessitates a surgical decortication to address restrictive impairment. Recent research on animal models has suggested a cardinal role for transforming growth factor-β_1 as a fibrogenic cytokine in the development of pleural fibrosis [14].

Bacteriology

The reported bacteriology of pleural sepsis varies significantly between community-acquired and nosocomial infections [2]. Maskell et al. [15] reported the large prospective MIST 1 trial (Multicenter Intrapleural Sepsis Trial 1) in 2005. Their study included 430 subjects across 52 centres in the United Kingdom. Of these, 232 (54%) had positive pleural cultures. The *Streptococcus milleri* group was the most common pathogen (29%), followed by staphylococci (21%) and *Streptococcus pneumoniae* (16%). Anaerobes were isolated in 15%. Other isolates in-
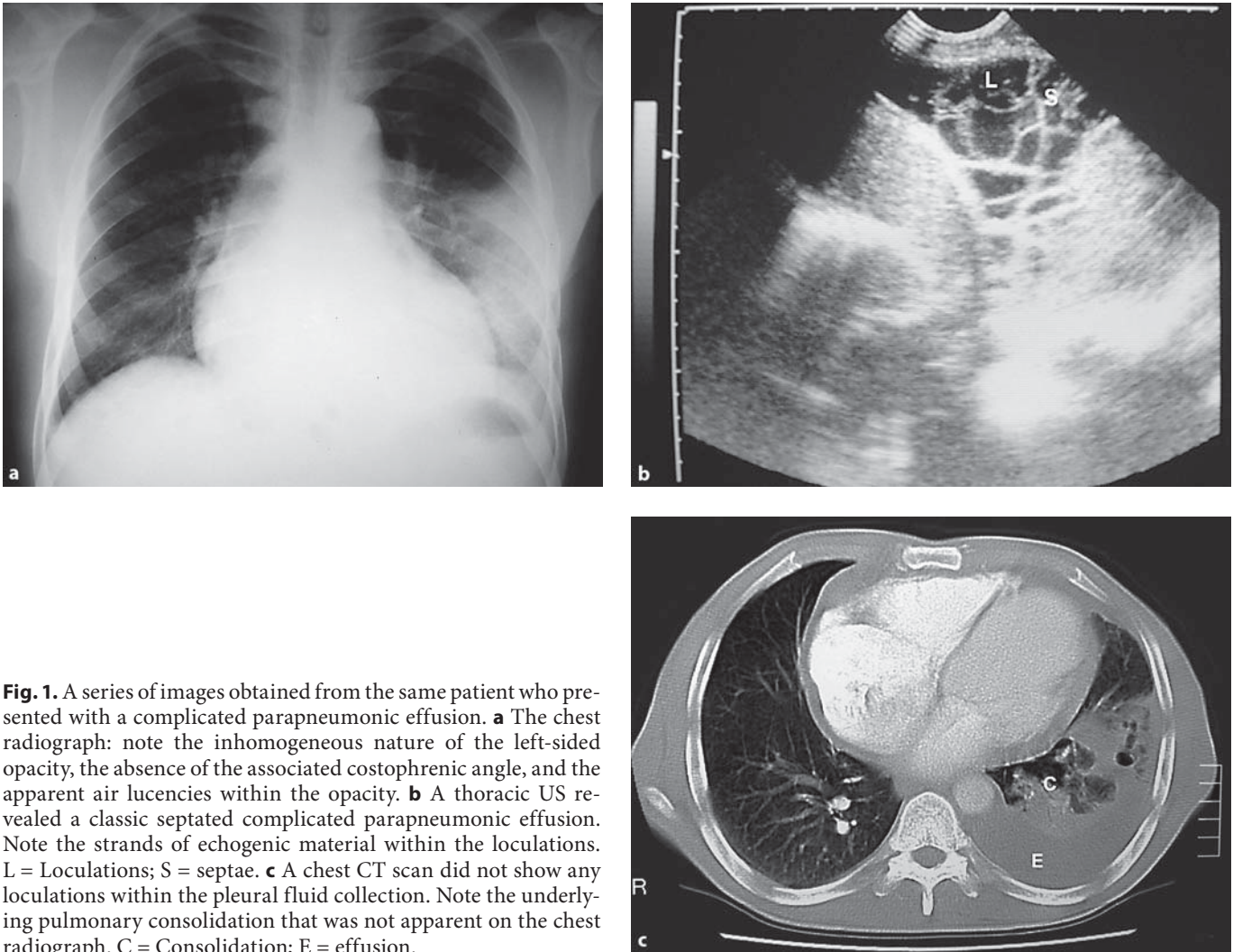
Fig. 1. A series of images obtained from the same patient who presented with a complicated parapneumonic effusion. **a** The chest radiograph: note the inhomogeneous nature of the left-sided opacity, the absence of the associated costophrenic angle, and the apparent air lucencies within the opacity. **b** A thoracic US revealed a classic septated complicated parapneumonic effusion. Note the strands of echogenic material within the loculations. L = Loculations; S = septae. **c** A chest CT scan did not show any loculations within the pleural fluid collection. Note the underlying pulmonary consolidation that was not apparent on the chest radiograph. C = Consolidation; E = effusion.

cluded other streptococci, *Haemophilus influenzae*, enterobacteria, *M. tuberculosis*, and *Nocardia*. The same investigators previously reported that nosocomial pleural infections were most commonly caused by methicillin-resistant *Staphylococcus aureus* (27%), other staphylococci (22%) and enterobacteria (20%) [16].

monia' picture with pleuritic chest pain, fever spikes and a failure to improve on apparently adequate antibiotic therapy. Elderly individuals, immunocompromised patients and those with anaerobic infections can have a more indolent course, and may present with weight loss, cough, unexplained fever and anaemia [1].

Clinical Presentation

The presenting symptoms of complicated parapneumonic effusions and empyema can vary significantly and can be dominated by the preceding infective process. Immunocompetent patients with aerobic infections tend to be more acutely ill, and the clinical presentation is similar to pneumonia. This is followed by a 'non-resolving pneu-

Diagnosis

Imaging
The chest radiograph usually shows a small to moderate pleural effusion with or without parenchymal infiltrates (fig. 1a). There may be evidence of loculations and air-fluid levels. Longstanding empyema may sometimes cause isolated rounded pleural opacities, which may be

confused with malignant pathology. It was once considered standard practice to request a lateral decubitus radiograph on all patients with suspected pleural sepsis and to use the lateral thickness of the effusions on these films to guide the decision on the need for a thoracentesis [1, 2]. Light et al. [17] showed that pleural effusions less than 1 cm thick on these radiographs resolved with antibiotic therapy alone and did not require pleural aspiration thoracentesis. Thoracic ultrasound (US), however, is an attractive alternative to a lateral decubitus film, as it can very accurately measure the extent of pleural effusions and yields significantly more information regarding the state of the pleural space [18, 19].

The routine use of thoracic US in patients with suspected pleural sepsis should be encouraged. US is particularly helpful in determining the nature of localized or diffuse pleural opacities, and is more sensitive than decubitus expiratory films in identifying small or loculated effusions [18, 19]. Complicated parapneumonic effusions are associated with floating strands of echogenic material which shows mobility with the respiration cycle and denotes advancing stage and chronicity. Complicated effusions may be subdivided into either septated or nonseptated effusions (fig. 1b). The presence of septae is clinically relevant: Chen et al. [20] demonstrated that patients with septated effusions needed longer chest tube drainage, longer hospital care, and were more likely to require fibrinolytic therapy or surgery compared with those with unseptated effusions. Tu et al. [21] confirmed these findings in medical intensive care unit patients. Empyema with high viscosity may cause a strongly echogenic effusion that can be mistaken for a solid pleural lesion. A change in shape during respiratory excursion and the presence of movable strands or echo densities are signs in favour of empyema [22]. Furthermore, thoracic US is invaluable in guiding pleural aspirations and drainage and is superior to chest radiographs at identifying the optimal site for diagnostic thoracentesis [23]. The success rate of US-guided thoracentesis can be as high as 97%. US guidance also decreases the risk of complications following pleural procedures [24].

A thoracic computed tomography (CT) scan may be indicated to better delineate pulmonary and pleural anatomy, particularly if there is a suspicion of an alternative diagnosis (e.g. bronchogenic carcinoma) or prior to surgical intervention [25]. It should be appreciated that loculations within a collection are best appreciated on US, and often not seen on a chest CT scan (fig. 1c). However, collections in interlobar spaces and those adherent to the paramediastinal pleura may escape detection by US and
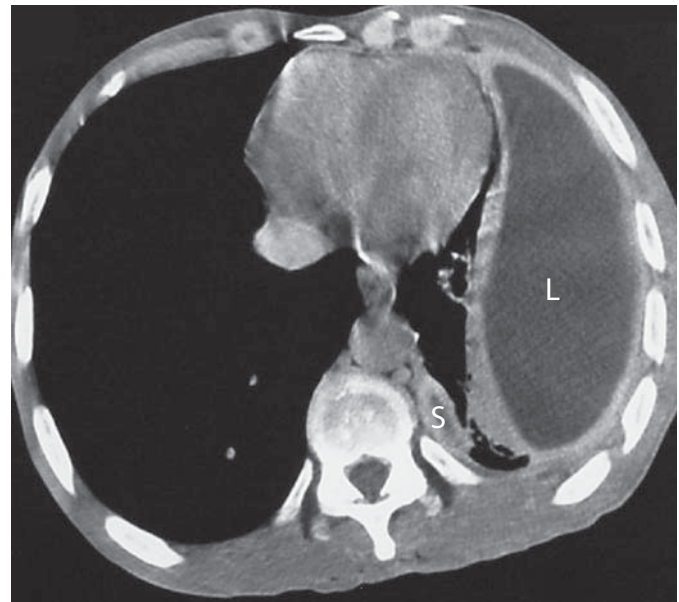

Fig. 2. A CT scan of a patient with empyema showing marked pleural thickening with enhancement, as well as volume loss of the left hemithorax (L, large collection). Also note the second, much smaller, left paravertebral pleural collection (S).

may only be visible on a CT scan (fig. 2: the small paravertebral collection will not be detected on ultrasound). Thickening of the parietal pleura (fig. 2) on a contrasted CT scan is suggestive of empyema [26] and thus an indication for thoracentesis, even in the presence of relatively small pleural collections.

Diagnostic Thoracentesis

All but small (<10 mm on US or lateral decubitus radiograph), free-flowing parapneumonic effusions should be aspirated for diagnostic purposes [27]. Apart from the routine chemistry, cytology and cell count analysis fluid should be sent off for a Gram stain and culture, and pleural fluid pH should be measured by means of a blood gas machine (not a pH meter or an indicator strip) [1]. A positive result from either the Gram stain or culture, or a pH of <7.20 is associated with a worse outcome and indicates the need for drainage [27, 28]. If the pleural fluid pH is unavailable, the pleural fluid glucose may serve as a surrogate. A glucose level >3.4 mmol/l (60 mg/dl) is associated with a better prognosis [1]. Pleural fluid adenosine deaminase is usually elevated in bacterial parapneumonic effusions and empyema, which are neutrophilic in nature. In the setting of a lymphocytic effusion, however, an elevated pleural adenosine deaminase is highly suggestive of a tuberculous effusion, even in low prevalence areas [25, 29, 30].

Table 1. Risk of poor outcome in patients with parapneumonic effusions and empyema

Category	Pleural space anatomy		Pleural fluid chemistry		Pleural fluid bacteriology	Risk of poor outcome	Drainage
1	Minimal, free-flowing effusion (<10 mm)	and	pH unknown	and	Gram stain and culture results unknown	very low	no
2	Small to moderate free-flowing effusion (≥10 mm and <½ hemithorax)	and	pH ≥7.20	and	negative Gram stain and culture	low	no
3	Large, free-flowing effusion (≥½ hemithorax), or loculated effusion, or effusion with thickened parietal pleura	or	pH <7.20	or	positive Gram stain and/or culture	moderate	yes
4	Empyema				pus	high	yes

Adapted from the American College of Chest Physicians' consensus statement on the Medical and Surgical Treatment of Parapneumonic Effusions [27]. Note that the presence of frank pus indicates need for drainage irrespective of pH.

Management

Principles

The treatment options for parapneumonic effusions range from non-invasive antibiotic therapy and observation, to semi-invasive techniques such as therapeutic aspiration, tube thoracostomy and intrapleural fibrinolytics, to invasive interventions such as thoracoscopy, thoracotomy or open drainage [1]. In practical terms, however, the initial evaluation should focus on three critical questions, namely: (1) Should the pleural space be drained? (2) How should the pleural space be drained? (3) Should fibrinolytics be instilled? Table 1 is adapted from the American College of Chest Physicians' (ACCP) consensus statement that categorizes parapneumonic effusions according to the need for drainage [25]. It is important to realize that the pleural space anatomy (best visualized by means of US), pleural fluid appearance and smell, as well as pleural pH are often the only useful criteria for initial decision making, as all other laboratory tests need time for processing. Frank pus on aspiration, large effusions greater than half of one hemithorax, effusions with loculations (see fig. 2), or fluid with a pH <7.20 all herald the need for immediate drainage. Further indications include a positive Gram stain, a positive microbial culture and pleural fluid glucose of <3.4 mmol/l (60 mg/dl).

Antibiotics

The initial antibiotic cover of patients with parapneumonic effusions is generally dictated by treatment guidelines for pneumonia, and is altered according to blood and pleural fluid microbial cultures and antibiotic sensitivities. Empirical anaerobic antibiotic cover is generally advised [2], as there may be an anaerobic co-infection which is generally not as amenable to culture as aerobes. Choices in community-acquired empyema include intravenous amoxycillin with clavulanic acid or a combination of a second generation cephalosporin (e.g. cefuroxime) and metronidazole [31]. Clindamycin monotherapy is an effective alternative for patients with a β-lactam allergy. Patients with nosocomial empyema need adequate Gram-negative cover. Possible choices include carbapenems, antipseudomonal penicillins (e.g. piperacillin/tazobactam), or third or fourth generation cephalosporins (e.g. ceftazidime, cefepime) with metronidazole [31]. Vancomycin, linezolid or alternatives may have to be added for suspected or proven methicillin-resistant *S. aureus* infections. Aminoglycosides demonstrate poor pleural penetration and reduced efficacy in acidic environments and should thus be avoided [32].

Observation

ACCP category 1 (table 1) effusions may be observed without a diagnostic aspiration, as the risk of a complicated course is remote [11]. All other cases require at least a diagnostic pleural aspiration before this decision can be made: only category 2 effusions may be observed without formal drainage. There should be no delay in draining category 3 and 4 effusions, as a free-flowing effusion may become loculated in a matter of 1 day.

Therapeutic Thoracentesis

A once-off US-guided therapeutic thoracentesis is an initial treatment option for moderately sized effusions involving less than one hemithorax, in the absence of empyema or a pH <7.20. It may serve as both diagnostic and, if no re-accumulation occurs, definitive management. Recurrent therapeutic pleural aspirations for empyema or complicated parapneumonic effusions have been largely abandoned, although Simmers et al. [23] showed that they were able to successfully treat 24 of 29 patients with parapneumonic effusions by means of alternate day US-guided pleural aspirations. Major disadvantages of this technique seem to be the high number of necessary aspirations and the long hospital stay, as a mean of 7.7 aspirations in 31 days was needed in their study.

Tube Thoracostomy

Indications for chest tube drainage include empyema, complicated parapneumonic effusions (pH <7.20, loculations or positive bacteriological investigations) and large effusions (more than half of a hemithorax involved) [27]. This is most commonly achieved by a standard (24–28 french) intercostal chest drain that is positioned in the dependent part of a free-flowing pleural effusion (most often the posterior costophrenic recess). Insertions are best guided by US, as thickened parietal pleura, adhesions or loculations often complicate insertion. Common sense suggests that smaller bore drains are likely to fail in the presence of pus with a high viscosity. However, some prospective studies have found that 8- to 12-french pigtail catheters or 10- to 14-french catheters inserted with the Seldinger technique under US or CT guidance were at least as effective as larger catheters inserted without imaging [33–35]. However, the positioning of the catheter tips with guidance is likely to be superior compared to blind insertion, irrespective of drain size. Most of these studies also employed a strict rinsing schedule (often several times a day), which might be difficult to sustain in everyday clinical practice. Moreover, a very recent study found a failure rate of 19% with small-bore catheters and concluded that the threshold for using fibrinolytics and large-bore catheters should be low in empyema [36].

Thrombolytics

Complicated parapneumonic effusions and empyemas are characterized by a procoagulant state within the pleural space which results in the progressive development of dense layers of fibrin and loculations. It therefore seems highly plausible that intrapleural fibrinolytics given early in the fibronopurulent phase should prevent loculations and promote pleural drainage. In fact, Tillett and Sherry [37] described the use of streptokinase and streptodornase for this very indication as early as 1949. Unjustified fears of systemic side effects and a paucity of controlled clinical trials have unfortunately delayed the compilation of an evidence base for the use of this modality for many years.

Numerous case series and controlled trials have shown that intrapleural fibrinolysis is safe, increases drainage and improves radiological appearance. A randomized controlled study by Davies et al. [38] established that systemic fibrinolysis or bleeding complications did not occur with streptokinase, and that patients who were given intrapleural streptokinase drained significantly more pleural fluid both during the days of treatment (n = 24; mean 391 vs. 124 ml, p < 0.001) and overall. Patients who received fibrinolytics also showed greater improvement on the chest radiograph at discharge.

Bouros et al. [39] demonstrated that urokinase was a safe intrapleural fibrinolytic. The same group showed that streptokinase and urokinase were clinically and radiologically equally effective as intrapleural fibrinolytics [40], and that intrapleural urokinase decreased the duration of hospitalization, duration of pleural drainage and time to defervescence. Furthermore, Bouros et al. [41] were able to show that urokinase's effect in empyema was through the lysis of pleural adhesions, rather than the volume effect of instilled urokinase and saline.

Lim and Chin [42] evaluated the efficacy of three different treatment protocols, namely simple chest tube drainage, adjunctive intrapleural streptokinase, and an aggressive empirical approach incorporating streptokinase and early surgical drainage in patients with pleural empyema and high-risk parapneumonic effusions. In this non-randomized, prospective, controlled series they found that the average duration of hospital stay and mortality in both the streptokinase and early surgical drainage group was significantly shorter than with tube drainage alone. The authors concluded that an empirical treatment strategy which combines adjunctive intrapleural fibrinolysis with early surgical intervention resulted in shorter hospital stays and possible reduced mortality in patients with pleural sepsis.

The most meaningful clinical endpoint, that of the necessity for surgical intervention, was only recently addressed in randomized controlled studies. Tuncozgur et al. [43] found a significantly lower decortication rate (60 vs. 29.1%, p < 0.01) and shorter duration of hospitalization (14 vs. 21 days, p < 0.01) with urokinase than with

placebo. A single-centre, randomized, placebo-controlled study by Diacon et al. [44] used structured clinical protocols for inclusion and evaluation and demonstrated that intrapleural streptokinase resulted in faster resolution of infection, reduced need for surgery (13.6 vs. 45.5%, p = 0.018) and improved clinical outcome in patients with loculated parapneumonic effusions and empyema.

The largest prospective double-blind controlled study on the role of intrapleural streptokinase for pleural infection was published in 2005 (MIST 1) [15]. In this study 454 patients with pleural pus, pleural sepsis with a pH <7.2 or bacterial invasion of the pleural space were randomly assigned to receive streptokinase or placebo. The patients included were older than in most other studies (average age 60 years) and had a high prevalence of comorbidities. The MIST 1 study could not substantiate the role of streptokinase in pleural infections: There was no difference in mortality, need for surgery, radiographic outcome or length of hospitalization. The design and execution of this study, however, were criticized [45–47]. The lack of image-based selection criteria meant that patients with pleural sepsis were included irrespective of presence, quantity and quality of loculations. Questions were raised about the reproducibility of clinical management decisions taken across 52 study centres, many of which lacked on-site surgical expertise and contributed only small numbers of patients. The study permitted small-bore chest tubes, but did not report on pleural drainage volumes, which casts doubt on the efficacy of the drainage techniques used. Furthermore, owing to the decentralized and blinded design streptokinase/placebo was shipped to the study centres after randomization causing delays in the initiation of treatment. The value of mortality as an endpoint was also questioned, as patients with serious concomitant illnesses that made survival beyond 3 months unlikely were excluded from the study. The 3-month mortality after hospitalization for pneumonia among middle-aged and older patients is more closely associated with the fact that an episode of pneumonia often identifies a fragile underlying health status than with the severity of the acute episode of pneumonia itself [45]. Intrapleural streptokinase may therefore not have been given a fair chance to improve the short-term mortality [45]. These deficiencies do not invalidate this large randomized trial, but concerns remain about the validity of its results with regards to younger, more severely ill patients and in different health care settings.

The most recent and second largest prospective study was conducted by Misthos et al. [48]. In their study patients were randomized to a group managed solely with tube thoracostomy or a group treated with a combination of tube thoracostomy and streptokinase instillation (no placebo control). They found that tube thoracostomy was successful in 67.1% of cases, whereas the installation of streptokinase led to a favourable outcome in 87.7% (p < 0.05) and significantly shortened hospital stay. The mortality rate was also significantly lower in the fibrinolytic group, and streptokinase was found to decrease the rate of surgical interventions and the length of hospital stay.

Tokuda et al. [49] published a meta-analysis of all the major placebo-controlled studies on intrapleural fibrinolysis prior to publication of the study by Misthos et al. Albeit they were able to demonstrate a trend towards improved survival and a decreased need for surgical interventions, the differences failed to become statistically significant.

Clinical trials on the efficacy of recombinant tPA and DNase are currently being performed. An interesting ex vivo observation by Light et al. [50] was that DNase combined with streptokinase (known as Varidase) was superior to either streptokinase or urokinase at liquefying empyemic pleural material obtained from rabbits. It was postulated that the streptodornase (DNase) was necessary for the liquefaction of the deoxyribose nucleoproteins, which make up a sizable proportion of the solid sediment of purulent exudates.

In conclusion, current evidence suggests that intrapleural fibrinolytics cannot be recommended as the standard treatment of parapneumonic effusion and empyema. There seems to be a place for fibrinolytics in the early management of loculated (complicated) parapneumonic effusions and empyema, particularly in young, acutely ill patients, poor surgical candidates and in centres where surgical facilities are limited. Streptokinase and urokinase are presumably equally effective and safe. The efficacy of tPA and DNase still needs to be established. The suggested dosages of the current fibrinolytics in use are summarized in table 2.

Thoracoscopy

Thoracoscopy remains a treatment option for the patient with an incompletely drained loculated parapneumonic effusion, provided that it is performed early in the disease and that the pleural anatomy is defined by means of either US or CT scan [51, 52]. Loculations can be broken down, the visible pleural space completely drained,

Table 2. Intrapleural fibrinolytics – practical use

Fibrinolytic	Dose	Instillation[1]	Duration
Streptokinase	250,000 IU	100–200 ml saline	daily for up to 7 days (until drainage <100 ml/day)
Urokinase[2]	100,000 IU	100 ml saline	daily for up to 3 days
tPA	10–25 mg	100 ml saline	twice daily for up to 3 days

[1] Drain should be clamped for approximately 2 h following installation of fibrinolytics.
[2] Urokinase is no longer universally available.
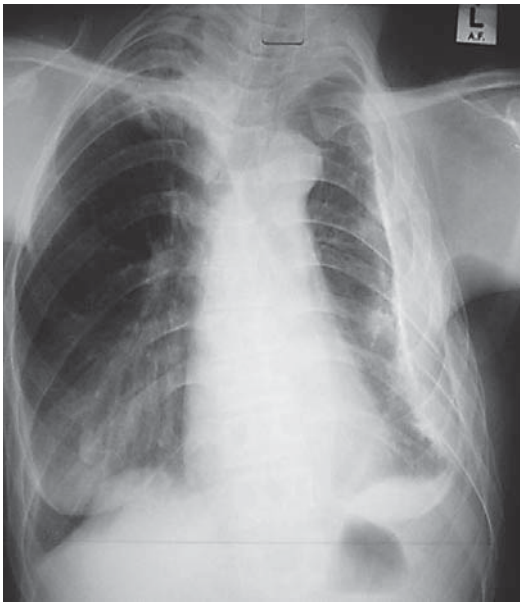
Fig. 3. A chest radiograph showing the long-term sequelae of empyema. Note the formation of a thick pleural peel with volume loss and incarceration of the left lung causing restrictive impairment.

and an intercostal chest tube can be optimally placed [1]. Furthermore, visual inspection of the pleura may guide decisions regarding the need for an open surgical procedure [1].

The exact point where thoracoscopy becomes useful in the management of pleural sepsis remains unclear and is even less well defined than the role of fibrinolytics. Several small retrospective and unblinded prospective studies suggest that thoracoscopy is superior to fibrinolysis [51–54], with the need for thoracotomy or thoracostomy almost halved [53]. At least one study performed on a paediatric population, however, found urokinase to be more cost-effective than routine thoracoscopy [55]. Practically

all prospective studies on the role of thoracoscopy [51, 53–55] utilized video-assisted thoracoscopy (VATS), as opposed to medical thoracoscopy. Current evidence does not allow a clear choice between the modalities, and local expertise is likely to dictate the preferred method.

Surgical Management

Open surgery may be required at various stages of the evolution of complicated parapneumonic effusions or empyema. The aim of a procedure in the subacute phase is usually to control sepsis, whereas a procedure in the chronic phase aims to restore chest mechanics by removing a restrictive fibrotic peel encasing the lung (fig. 3).

The main indications for open surgical drainage are failure of medical management to control sepsis in the acute stages of pleural sepsis and failure of tube thoracostomy or thoracoscopy to yield reexpansion of the lung [1, 56]. Thoracotomy with drainage and subsequent closure of the chest with one or more drains left in situ is the standard procedure. Thoracostomy involves incision through the chest wall with rib resection, which produces a stoma with continuous drainage of the chest cavity. In addition, one or more chest tubes can be inserted through the opening, and irrigated daily. The chest tubes can gradually be retracted until complete removal, a process that takes 2–3 months to complete. Drainage from the thoracostomy or from the tubes (cut off close to the skin) can be collected in a colostomy bag. A different approach involves packing the empyema cavity with gauze. A more complex procedure may be performed when the tract between the pleural cavity and the surface of the chest is lined with a skin and muscle flap following rib resection [1]. Drainage is thus achieved without chest tubes with gradual obliteration of the empyema cavity [57].

Decortication is a major surgical intervention that entails the excision of all fibrous tissue from the pleura, with or without the evacuation of associated pus and debris

from the pleural cavity, in order to permit lung reexpansion [58]. It remains a procedure with significant morbidity and a reported mortality of up to 10% [59]. As pleural thickening may resolve over time, decortication is best deferred for up to 6 months [60].

Conclusions: Suggested Management of Parapneumonic Effusions and Empyema

All patients with parapneumonic pleural effusions and empyema require early and adequate antibiotic treatment. Thoracic US should be performed on patients with suspected parapneumonic effusion that is not clearly visualized on a routine postero-anterior chest radiograph. Small, unseptated and free-flowing effusions may be observed, but all other effusions warrant an urgent diagnostic thoracentesis. Sterile effusions with a pH ≥7.20 may be observed on antibiotic cover. Empyema and large or loculated effusions need to be drained, as well as parapneumonic effusions with a pH <7.20, glucose <3.4 mmol/l or positive microbial stain and/or culture.

An US-guided therapeutic thoracentesis is an elegant initial treatment option for uncomplicated effusions of moderate size, in the absence of empyema or a pH <7.20, loculations or positive bacteriological investigations. It may serve both as a diagnostic and, if no reaccumulation occurs, definitive procedure. The US evaluation of the pleural cavity will also guide further management. Large bore tube thoracostomy is the treatment option of choice for patients with empyema. Parapneumonic effusions that recur following a single aspiration or cases at high risk should be drained by means of either standard or small-bore intercostal drains.

The use of fibrinolytics remains controversial, although evidence suggests a role for the early use in complicated, loculated parapneumonic effusions and empyema, particularly in young, acutely ill patients, poor surgical candidates and in centres with inadequate surgical facilities. Early thoracoscopy is an alternative to thrombolytics. Local expertise and availability will to a certain extent dictate the initial choice between tube thoracostomy with fibrinolytics or thoracoscopy, although thoracoscopy may also be performed following fibrinolytics if complete drainage is not achieved.

An open surgical drainage procedure will be required for complete drainage where tube thoracostomy or thoracoscopy with associated medical management fails to control pleural sepsis. A surgical decortication may be needed to remove a thick pleural peal and to restore chest mechanics, but this procedure is best deferred for at least 6 months.
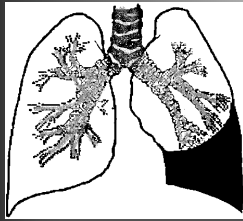
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Pleural Ultrasonography

Diagnosis of Malignant Pleural Effusion using Thoracic Ultrasound

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The most common cause of unilateral pleural effusions in the UK and USA is malignancy, with an estimated 250,000 new cases of malignant pleural effusions diagnosed annually[1]. The gold standard imaging modality for patients with suspected malignant effusion is thoracic contrast-enhanced computed tomography (CECT) scanning. CECT is both a specific and a sensitive test for differentiating benign and malignant pleural disease[2].

Recently, an emerging role for thoracic ultrasound (TUS) in the investigation of malignant pleural effusion has been demonstrated. TUS is a quick, relatively inexpensive investigation, which is increasingly being performed by chest physicians. TUS is recognized as an accurate and reliable technique for pleural fluid detection, assessment of fluid characteristics and for guiding pleural intervention[3].

More recently, TUS has been shown to be a valuable clinical tool in the diagnosis of malignant pleural effusion. Studies have evaluated high frequency real-time sonography in determining the nature of pleural effusions: appearances consistent with a high suspicion of malignancy include pleural thickening of more than 1 cm and the detection of pleural nodules[4], but the sonographic fluid characteristics themselves are non-specific[5].

The accuracy of TUS in the diagnosis of suspected malignant pleural effusion has been shown to be comparable to that of CECT[6]. In the study by Qureshi *et al*. TUS correctly diagnosed malignant pleural effusion with an overall sensitivity of 79%, specificity of 100%, positive predictive value (PPV) of 100% and negative predictive value of 73%. Good inter-observer agreement between TUS operators was also demonstrated[6]. This study used previously reported CECT morphological criteria for the diagnosis of malignant pleural disease[2] and applied them to TUS. These included: 1) diaphragmatic and parietal pleural nodule or nodules; 2) pleural thickening >1 cm (*below*); and 3) hepatic metastasis.

By employing a threshold value for parietal pleural thickening of >1 cm as suggestive of malignancy, TUS had a specificity of 95% and a PPV of 93% for
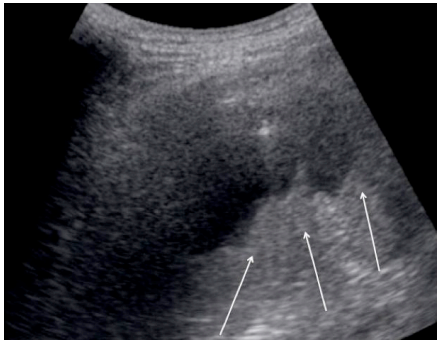
distinguishing malignant from benign disease[6]. The appearance of nodular pleural thickening on TUS was also associated with malignant pleural effusions and demonstrated a specificity of 100% and a PPV of 100%[6]. The TUS echotexture of malignant pleural thickening appeared to be non-specific, and was hypoechoic, hyperechoic or isoechoic relative to the intercostal muscles. In contrast, TUS echotexture of benign pleural thickening was most often hypoechoic.

As well as the recognized CECT criteria, additional TUS morphological features were also shown to be associated with malignant pleural effusions, namely, visceral pleural thickening, diaphragmatic nodularity and thickness >7 mm (Table). In contrast, diaphragmatic thickening <5 mm and readily resolved normal diaphragmatic appearances, with all five layers clearly seen, were suggestive of benign disease[6].

In summary, there are now defined TUS morphological features enabling the differentiation between benign and malignant pleural effusions. With its low cost and ready availability, TUS should be performed initially in the investigation of patients with pleural effusion of unknown etiology, with CECT being reserved for patients requiring further investigation.

TUS morphological feature	Malignant pleural effusion	Benign pleural effusion
Parietal pleural thickening	>1 cm Non-specific echotexture	<1 cm Hypoechoic echotexture
Pleural nodularity/irregularity	Present	Absent
Visceral pleural thickening	Present	Absent
Diaphragmatic thickening	>7 mm	<7 mm
Diaphragmatic nodularity	Present	Absent
Hepatic metastasis	Present	Absent

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Ultrasound Guided Thoracentesis

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Approximately 1.5 million persons are found to have pleural effusions each year in the USA. Over the last several years, the use of portable, point of care ultrasound has greatly enhanced the evaluation and management of patients with pleural disease. Ultrasonography has been found to be more sensitive than chest X-ray for the detection of pleural fluid, can predict the need for more invasive pleural intervention and has been associated with a significant reduction in pneumothorax rates, when used to guide thoracentesis. Though there is a learning curve associated with the use of thoracic ultrasound (TUS), it is relatively short and should consist of both didactics as well as hands-on training[1,2].

Examination of the pleural space with ultrasound is best performed with a convex array 3.5 – 5MHz probe. This frequency range provides both excellent resolution and penetration. In the absence of pleural fluid, identification of the hyperechoic visceral and parietal pleurae can be difficult. However, when it is

present, evaluation of the pleural space, visceral and parietal pleura and even the lung becomes possible. Movement of the lung with respiration produces a 'sliding' or 'gliding' sign, and this dynamic movement identifies the visceral pleura and lung parenchyma. Diaphragmatic movement can also be visualized in real-time, and is a key reference point when starting to perform TUS examination of the pleural space.

Several studies have found that ultrasound can be helpful in identifying exudative pleural fluid. Complex effusions (either septated or non-septated) or homogenously echoic effusions are always exudates. The converse, however, may not be true. Though transudates are almost always anechoic, anechoic fluid can be transudative or exudative.

Thoracentesis is typically thought to be a relatively safe procedure with few complications. The incidence of pneumothorax, however, has been reported to be as high as 20-39%. Though there are no blinded randomized trials comparing ultrasound *vs* physical exam guided thoracentesis, several studies have associated ultrasound use with lower complications. Procedural factors that have been shown to reduce the rate of pneumothorax include performance by experienced personnel[3] as well as the use of ultrasound[4,5]. Diacon's group found that, even in the hands of trained pulmonologists, the use of ultrasound increased the accuracy in site selection by 26%, and decreased the number of near misses (i.e. the number of potentially dangerous needle insertion sites) by 15% when compared to fluid localization by physical exam and chest radiography[6]. In a recent meta-analysis of 6,605 thoracenteses, Gordon *et al.* found that the use of ultrasound was associated with a 50% reduction in the risk of pneumothorax, using historical controls for comparative analysis[3]. In Mayo's study of critically ill patients receiving mechanical ventilation, the rate of pneumothorax using ultrasound-guided thoracentesis was 1.3%.

TUS has also been shown to be an excellent tool to both rule-out and in pneumothorax and is increasingly being used to evaluate lung parenchyma as well. Its use is quickly becoming the standard of care for procedural guidance in the pleural space.

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Ultrasound-Assisted Pleural Biopsies

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Recent studies have reemphasised the importance of transthoracic ultrasound (TUS) as a guide to pleural procedures, both with regards to safety and diagnostic yield. TUS is an ideal aid to the clinician, given its mobility, low cost, lack of irradiation, and short examination time. TUS is superior to chest radiography for the visualisation of pleural effusions. Moreover, the volume of fluid, the presence of septations, pleural thickening and pleural-based tumours can be accurately assessed.

Closed pleural biopsies were introduced in the late 1950s, and the Abrams, Cope or Vim-Silverman needles were used blindly for many decades. Unaided closed biopsies have a modest yield for malignancy, on the order of 60%. Tru-cut needle pleural biopsies were first performed in the 1980s, initially without TUS assistance. Maskell *et al.* showed that CT-guided Tru-cut pleural biopsies were superior for pleural malignancies compared to unaided Abrams needle biopsies (diagnostic yields 87% and 47% respectively)[1]. Chang *et al.* previously found the diagnostic yield of TUS-guided Tru-cut pleural biopsy to be as high as 87% for all pleural pathologies (77% for malignancies)[2]. For malignant mesothelioma our research has shown that this figure may be as high as 100%[3].

In a recent prospective randomized study it was found that TUS-assisted Abrams needle biopsy specimens were more likely to contain pleural tissue than specimens obtained by means of TUS-assisted Tru-cut biopsies (91% *vs* 78.7%, *p*=0.015)[4]. Furthermore, Abrams needle biopsies had a significantly superior yield for pleural tuberculosis compared to Tru-cut needle biopsies (81.8% *vs.* 65.2%, *p*=0.022), but not compared to previously reported figures for blind Abrams needle biopsies. The distribution of granulomatous inflammation in pleural tuberculosis is uniform over the pleura and visual aids, therefore, seem to offer little advantage

beyond increased safety. Interestingly, and contrary to previous reports, the respective yield for both needle types for pleural malignancies was comparable and relatively high, with TUS-assisted Abrams needle being diagnostic in 83.3%[4]. One possible explanation for this may have been the selection of low biopsy sites utilised, as the lower thoracic parietal pleura is more likely to contain secondary spread from visceral pleural metastases. Such an approach is possible with TUS assistance, but not with digital percussion as a guide. Moreover, malignant disease tends to give rise to more focal pleural involvement which may be visible on high frequency TUS (see article by Matin and Gleeson in this issue).

Apart from increasing diagnostic sensitivity, TUS very likely lowers the procedure-related risk. A recent survey carried out in the UK highlighted the dangers of blind pleural procedures: 67 of 101 trusts reported at least one serious complication from intercostal drainage (ICD)[5]. In all, 47 cases of serious lung or chest wall injuries with 8 deaths and 6 cases of ICD placement on the wrong side were described. Although similar multicenter data for unaided closed pleural biopsies does not exist, it seems plausible that similar complications can occur. Such incidents could be avoided by means of TUS assistance[6].

In conclusion, we believe that closed pleural biopsies should routinely be performed under TUS guidance, as it is likely to increase the yield for malignancies and to decrease the risk of complications.

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Competence in Pleural Ultrasonography

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Ultrasonography has emerged as 123 important modality in the management of pleural diseases over the past decade. Routine use of ultrasonography for thoracentesis, pleural biopsy, placement of chest tubes and chronic indwelling pleural catheters lower the procedure risk and improves diagnostic accuracy. Reducing complications and improving diagnostic accuracy of pleura-related procedures have been the impetus' to mandate the routine use of ultrasound as the standard of care. However, formal training in the use of ultrasound has been adopted in a limited number of pulmonary/critical care programs in the United States.

The Critical Care Network of the American College of Chest Physicians and La Société de Réanimation de Langue Francaise collaborated in the development of a consensus statement on competence in critical care ultrasonography[1]. Pleural ultrasonography was identified as one of the core areas in this statement. The proposed standard establishes the training goals needed for the non-radiologist to acquire competencies in pleural ultrasonography and is applicable outside the ICU environment.

The clinician must demonstrate competences in five areas according to the consensus document by: 1) having an understanding of basic ultrasound physics and how images are created through the interaction of sound waves and tissue; 2) demonstrating knowledge of the machine controls and transducer manipulation since they are personally conducting the exam; 3) being able to distinguish normal from abnormal ultrasound anatomy; 4) being able to interpret acquired images and know the limitations of ultrasonography pertinent to the examination conducted; and 5) being able to recognize when an examination is beyond the technical capabilities of either the device or themselves.

The elements required for mastery of pleural ultrasonography include: 1) identifying safe puncture sites and knowing how far to insert needles to avoid inadvertent penetration into lungs or other organs and vasculature; 2) identifying and characterizing pleural effusion echogenicity patterns such as anechoic, complex non-septate, complex septate, and homogenously complex; 3) identifying pleural effusion boundaries; 4) identifying the dynamic findings of pleural fluid, such as lung flaps, swirling

debris, and respirophasic shape changes; 5) identifying the liver, spleen, ascites, kidneys, heart, pericardium, aorta, and inferior vena cava; 6) providing a semi-quantitative assessment of pleural fluid volume; 7) identifying pleural-based masses and thickening; and 8) recognizing the technical limitations to image acquisition in the presence of subcutaneous emphysema, hemothorax, and echo-dense empyemas[1].

In our institution, new-trainees to our fellowship program spend the first week reviewing the basic ultrasound operations, understanding ultrasound probe manipulation, identifying landmarks above and below the diaphragm, and watching a 45-minute real-time video showing normal and abnormal pleural pathology. Image acquisition, transducer manipulation, and image interpretation is taught at bedside. In summary, competence can be easily obtained by those who are non-radiologically trained if a systematic approach is adopted.

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PLEURAL IMAGES

Pleural Metastases

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Case 1. An 80-year-old-man was hospitalized after a lung mass with an associated left pleural effusion was detected on a chest radiograph that was done to evaluate new-onset dyspnea on exertion. He had a 60-pack-year history of cigarette smoking. Thoracentesis yielded bloody fluid and analysis showed: erythrocyte count 250,000/µL, leukocytes 800/µL with 79% lymphocytes, total protein 3.9 g/dL, lactate dehydrogenase (LDH) 461 U/L, glucose 135 mg/dL, pH 7.44, adenosine deaminase (ADA) 18.4 U/L and positive cytology for an undifferentiated carcinoma. Immunoreactivity for thyroid transcription factor 1

(TTF-1) was negative in a cell block preparation of pleural fluid.

Both chest ultrasound and CT scanning revealed a moderate effusion along with multiple parietal pleural nodules (*below*) consistent with metastases. The CT images also indicated mediastinal lymph node and liver involvement from a primary lung tumor. Additional diagnostic maneuvers were considered unnecessary. The patient died two weeks later.
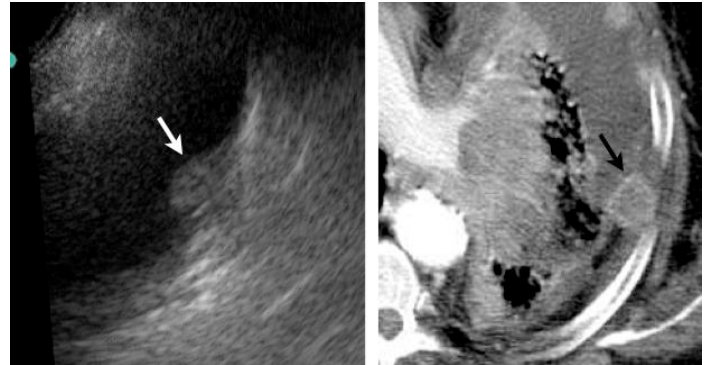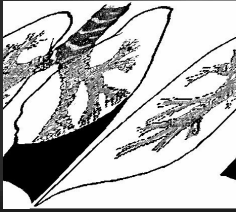

Case 2. An 89-year-old man was evaluated for a 3-month history of left scrotal swelling, growing lump in the upper back chest wall and progressive dyspnea. Chest ultrasound and CT exhibited parietal pleural thickening and effusion (*below*). Pleural fluid analyses showed: erythrocyte count 1010/µL, leukocytes 280/µL (99% lymphocytes), total protein 4 g/dL, LDH 636 U/L, glucose 117 mg/dL, pH 7.6, ADA 40.2 U/L, and negative cytological examination.
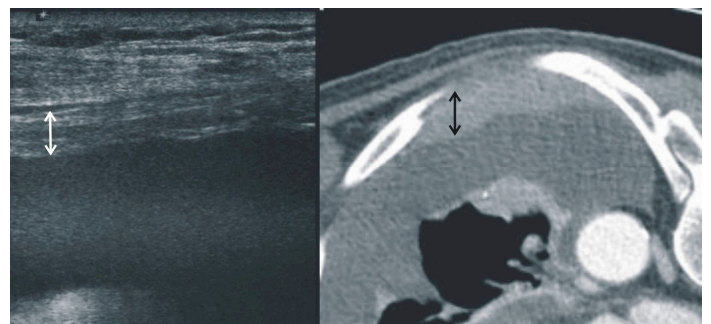
Biopsies of the parietal pleura (Tru-cut CT-guided), testicular mass and bone marrow were diagnostic of a diffuse large B-cell lymphoma. Staging also demonstrated chest wall, myocardial and abdominal lymph node involvement. The patient is currently receiving treatment with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).

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Malignant Pleural Diseases
Guest editor: Dr Ioannis Kalomenidis

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Pleuro-peritoneal Shunt for Malignant Pleural Effusions

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The prognosis of patients who have a malignant pleural effusion (MPE) is poor, with a median survival of 4 months[1]. The presence of a malignant effusion significantly impairs quality of life due to dyspnea (96%), pain (57%) and cough (44%)[2]. The management remains controversial for recurrent MPE in the presence of a trapped lung that fails to completely re-expand after drainage of the effusion.

The pleuro-peritoneal shunt allows continuous drainage of pleural fluid into the peritoneal cavity. This allows the lung to expand to its maximal possible extent and the mediastinum to shift back towards the affected side, thus improving dyspnea. Pleuro-peritoneal shunts are more commonly used for intractable aseptic MPE, when a trapped lung is present. The shunt has also been used for the treatment of chylothorax in both adults and children.

The pleuro-peritoneal shunt (see figure, courtesy of Cardinal Health, Inc.) is made of silicone and consists of a double-valved pumping chamber with a catheter at either end. These peritoneal and pleural catheters are both fenestrated to facilitate drainage.

Operative technique. The shunt is normally inserted under general anesthesia with the patient in a supine position or with the operative side slightly

elevated. We perform bronchoscopy to exclude endobronchial obstruction. Thoracoscopic assessment is then performed. If the lung is trapped, we proceed with shunt insertion. The VATS port site is extended to 4-5 cm in length and a subcutaneous pocket is created in a position to allow fixation of the pumping chamber over a rib for ease of palpation and compression. The shorter of the two catheters is inserted into the pleural space. Fluid should be left in the pleural space or normal saline instilled to allow flushing of the shunt in the early post-operative period. A separate 3-4cm transverse, sub-costal incision is made and purse-string sutures are placed in either the posterior rectus sheath or transversalis fascia and the peritoneum.

We then verify, visually and digitally, that the peritoneal space is free of adhesions. The peritoneal catheter is passed through the pocket and tunneled to the sub-costal incision using long Robert's forceps. The catheter is then passed through the purse-strings into the peritoneal cavity. The pumping chamber is secured within the pocket using non-absorbable sutures. It is then primed by pressing until fluid flows though from the pleural cavity.

In the next 24 hours the pumping chamber is pressed 25-30 times every 3 to 4 hours. After the first day the patient is encouraged to press the chamber for 5 to 10 minutes, three to four times a day. Regular pumping of the shunt reduces the likelihood of occlusion. Port-site radiotherapy is considered after recovery from surgery[3]. The intra-operative use of a single VATS port limits the radiation field.

Results. Over a 15 year period, 360 patients with a MPE were treated in our unit, 160 (44%) of which had a trapped lung at operation and underwent pleuro-peritoneal shunt insertion. Good palliation was achieved in 95% of patients[4]. There were no operative deaths, although three patients died in hospital from progressive respiratory failure. Twelve patients (8.5%) developed shunt occlusion requiring revision or replacement (we prefer the latter). 4% of the shunts had to be removed because of infection and one patient developed tumor seeding along the tract. Peritoneal seeding was not a problem, even in longer term survivors (>6 years in one case). The patients' relatively short life expectancy means that any peritoneal seeding that develops is unlikely to impact significantly on their quality of life.

Pleuro-peritoneal shunts have been used in many cancers, including breast carcinoma (36%), malignant mesothelioma (23%) and lung carcinomas (22%).

Discussion. The majority of patients with MPEs suffer from dyspnea. In most cases, dyspnea can be relieved or improved by talc pleurodesis if the lung re-expands, or by pleuro-peritoneal shunt insertion if it remains trapped. Other treatment modalities include the use of a permanent indwelling catheter, decortication or pleurectomy. The former has been associated with infection and empyema, and also has the drawback of external tubing and requiring training of the patient or carer. Decortication and pleurectomy are more major surgical procedures unsuitable for palliative purposes.

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Prophylactic Drain Site Radiotherapy for Mesothelioma: Does it Make Sense?

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Diagnosis of pleural mesothelioma can be made by cytology of pleural effusion, closed pleural biopsy or video-assisted thoracoscopy. Many patients require repeated drainage of effusions and both the original and subsequent drain sites are at risk of subcutaneous tumor growth from direct seeding outwards from the pleural surface. Estimates of the incidence of tumor seeding ranged from 5 to 48%[1-4]. Prophylactic radiotherapy to drain sites has been offered by an increasing number of centers over recent years[2] to reduce the incidence of tumor seeding based on the premise that such tumor deposits are common, painful and resistant to treatment.

The table at the end of the article lists seven published series addressing this topic of which only three are randomised controlled trials. The Boutin trial, based on which prophylactic radiotherapy was first promoted, was published in 1995[1]. None of the 20 patients treated with prophylactic radiotherapy developed drain site metastasis whereas 8/20 (40%) who did not receive radiotherapy had tumor seeding. The radiotherapy delivered was 21 Gy in three fractions on consecutive days. In those patients who did develop subcutaneous tumour deposits, the mean interval between intervention and appearance of nodule was 6 months (range 1-13). This study

stimulated other investigators to publish retrospective case series. A Dutch Belgian survey in 2002 found that prophylactic irradiation of intervention sites was offered in 32 of 38 responding centers (84%)[2].

In Glasgow, having adopted the Boutin regimen, we observed that in spite of prophylactic radiotherapy some patients still developed subcutaneous tumor. We also noted that for many patients these nodules were not symptomatic and in those who did have discomfort, further radiotherapy appeared to be effective in reducing the size and tenderness of the mass. We designed a study to assess the efficacy of radiotherapy in preventing tumor seeding and to determine if tumor nodules were painful or troublesome to patients[3]. Patients (n=61) were randomised to immediate drain site radiotherapy 21 Gy in three fractions given within 21 days of intervention, or to best supportive care, and followed up for 12 months. Subcutaneous tumor deposits developed in 10 patients: 7/31 (23%) in the treated arm and 3/30 (10%) in the best supportive care arm p<0.05). Median time to development of subcutaneous tumor was six months. The one other published RCT by Bydder[4] randomised 43 patients with 58 drain sites between single fraction (10 Gy) prophylactic radiotherapy and no treatment. The rate of subcutaneous tumor development was 7% in the radiotherapy arm compared to 10% in the control arm. Given the short survival of patients with mesothelioma and that subcutaneous tumor deposits may take months to develop and may not cause symptoms, prophylactic radiotherapy is not justified.

Published series on radiotherapy to mesothelioma drain sites

Year	First author	design	Patients (nr)	RT Mets	no RT Mets
1995	*Boutin*	RCT	40	**0%**	**40%**
1995	*Low*	RS	20	**0%**	**NA**
2004	*Bydder*	RCT	43	**7%**	**10%**
2004	*Cellerin*	RS	33	**22%**	**48%**
2005	*Pinto*	RS	85	**NA***	**0%**
2006	*West*	RS	37	**5%**	**NA**
2007	*O'Rourke*	RCT	61	**23%**	**10%**

RCT= randomized controlled trial; RS=retrospective series; mets = metastasis*. All patients in this trial received chemotherapy but no drain site radiotherapy

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4. Bydder S, et al. Br J Cancer 2004; 91:9-10.

Pleural Biopsy for Patients with Suspected Malignant Effusions

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Malignant pleural effusions (MPE) result from infiltration of the pleura by malignant cells[1]. Cytological examination of pleural fluid is diagnostic in 60-90%, depending on the volume and frequency of aspirations. Pleural biopsy offers excellent specificity, but sensitivity varies among different methods and whether or not an image-guided procedure is performed.

Closed pleural biopsy needles with either Abrams (guillotine) or Cope (hook) devices were developed over 50 years ago. Yields of >90% have been reported in pleural tuberculosis (TB). Malignant pleural disease is less homogeneously distributed over the pleura than TB, which predisposes blind biopsies to sampling errors. Furthermore, only 70-90% of all pleural biopsy specimens contain pleural tissue. It is therefore no surprise that unguided pleural biopsies are only diagnostic in approximately half of all MPEs[2]. Among patient with negative cytology for malignant disease only an additional 7% will have diagnostic unguided biopsies[1].

Utilizing imaging to assist pleural biopsy increases the diagnostic yield, particularly if a pleural based tumor or focal nodular pleural thickening can be identified. Ultrasound (US)-assisted Tru-cut needle biopsies have higher sensitivity and specificity in the diagnosis of pleural malignancy than unaided biopsies. Diacon *et al*[3] found that US-assisted cutting needle biopsy (CNB) had 85% sensitivity for malignant neoplasms in general and 100% for mesothelioma in tumors over 2cm in diameter[3]. The same authors showed that the less traumatic US-assisted transthoracic fine needle aspiration (TTFNA) with rapid on-site evaluation was diagnostic in 87% of cases while avoiding the increased risk of bleeding with CNB in the vicinity of intercostals arteries[4]. Compared to CNB, US-guided TTFNA had a superior yield for bronchial carcinoma whereas CNB was superior in the minority of cases with non-carcinomatous tumors and non-malignant lesions. CT-guided pleural biopsies with CNB have the highest diagnostic yield and can be performed in lesions as small as 5mm. Maskell *et al* reported a

sensitivity of 87% in patients with suspected MPEs but negative pleural fluid cytology[5].

A suspected MPE that remains undiagnosed on cytology and transthoracic biopsy is an indication for either medical thoracoscopy or video-assisted thoracoscopic surgery (VATS). Local expertise and availability often dictate the choice between the procedures. Both allow for wide inspection of the pleura and harvesting large biopsy specimens which results in sensitivities of >90% in MPE[1]. Medical thoracoscopy is usually performed under local anesthesia and conscious sedation, whereas VATS requires general anesthesia, which can put patients with impaired pulmonary reserve at increased risk. Semi-rigid pleuroscopy was recently introduced[6]. The technique is similar to medical thoracoscopy, but uses devices derived from bronchoscopes, which should make medical thoracoscopy more affordable and technically accessible to practicing interventional pulmonologists. Recent studies have reported sensitivities of 62-90% for MPE.

In conclusion, patients with a suspected MPE and negative cytology should undergo transthoracic pleural biopsy, preferably using US or CT guidance. Patients who remain undiagnosed should be referred for medical thoracoscopy, and if non-diagnostic or unavailable, VATS. Very rarely open surgical biopsy may be required.

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Mesothelin for Diagnosis of Mesothelioma: **Enough evidence for clinical use?**

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Malignant mesothelioma (MM) is a cancer with poor survival, mainly induced by past asbestos exposure. MM incidence is rising in many countries worldwide. The possible use of serum or pleural fluid proteins to establish an early diagnosis or assess response to treatment and disease progression has been recently evaluated. Finding a biomarker for these purposes is extremely challenging, given the biologic features of MM, and the need to differentiate MM from benign pleural diseases and metastatic pleural malignancies[1].

Mesothelin is a glycoprotein expressed on the cell surface of normal mesothelial cells and highly overexpressed in mesothelioma and various carcinomas. Soluble mesothelin (SM) or soluble mesothelin-related peptides, have emerged as a promising biomarker for MM. SM levels were significantly increased in serum and in pleural effusion of patients with MM compared to healthy asbestos-exposed subjects or patients with benign pleural lesions or pleural metastasis. Serum and pleural fluid SM showed excellent sensitivity (70-80%) and specificity (80-100%) as diagnostic markers for MM[1-3]. However, SM does not capture sarcomatoid (and some of the biphasic) mesotheliomas which hampers its use as a sole diagnostic (or screening) marker. Combining osteopontin or CA125 with SM was not helpful towards this goal[4, 5].

It has been suggested that elevated serum SM in asbestos-exposed subjects may predict the development of MM long before it becomes clinically apparent, reflecting the presence of yet undetectable small foci of MM. It could be thus suggested that invasive diagnostic methods should be used in subjects with pleural abnormalities and high SMRP levels to exclude mesothelioma or metastatic malignancies though such a strategy requires validation by prospective trials. Presently mesothelioma cannot meet the essential criteria for cancer screening programs: there is no validated screening tool or effective cure for MM, and no evidence that early detection alters outcome. However, detecting mesothelioma years before its clinical presentation may allow the investigation of new treatment modalities in early-stage patients. Studies assessing SM alone or combined with other potential biomarkers for MM diagnosis or screening are underway.

Serum SM levels were higher in patients with larger tumor load[2]. Preliminary data suggested that serum SMRP may be helpful in monitoring patient response to therapy. In those who underwent tumor debulking surgery for peritoneal MM (or ovarian carcinomas), serum SMRP levels decrease dramatically within days. Our (unpublished) data from patients subjected to chemotherapy or gene therapy support this hypothesis. Reports on SM value as a prognostic marker in patients with MM are discordant[2, 4].

In conclusion, there is not enough evidence yet to justify clinical applications of serum or pleural fluid SM determination in all MM patients. SM alone has probably insufficient specificity and sensitivity for MM screening, but may help clinicians in the diagnosis of epithelioid MM. In the meantime, histopathologic diagnosis should remain the "gold standard" given the important therapeutic and medical-legal implications of mesothelioma. SM may be also used to assess MM patients' outcome and response to treatment, but this needs to be tested in prospective studies.

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CASE REPORT

Epithelioid Hemangioendothelioma/ Angiosarcoma of the Pleura

Epitheliod hemangioendothelioma (EHE)-angiosarcoma, first described in 1975[1], is a rare malignant tumor of vascular origin usually arising in bone, liver, soft tissue, or lung but rarely the pleura[2]. We describe a case of EHE with bilateral pleural, lung and bone manifestations.

A 71 years old asbestos-exposed ex-smoker was evaluated for persistent low back pain and a left-sided pleural effusion. The pleural fluid was a serosanguinous, lymphocytic (lymphocytes 75% of total leukocytes) exudate with a low ADA level (22 IU/L). Blood tests showed anemia (Hct 31%), raised serum CA125 (2135 U/ml) and ESR (105). Bone scintigraphy revealed increased osteoblastic activity
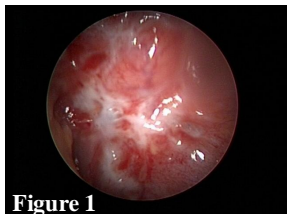

Figure 1

of the vertebral body of T12. Medical thoracoscopy on the left pleural cavity revealed diffuse irregular thickening of visceral and parietal pleura and scarce white nodules on the parietal pleura (figure 1).

Histologic studies failed to establish a specific diagnosis. Cytology revealed clusters of atypical cells with hyperchromatic nuclei and well visible nucleolus. Immunostaining was negative for keratin 5/6, 7, 20, TTF1, calretinin, thrombomodulin, PAS/AB and Perls. No staining for vascular markers were performed.
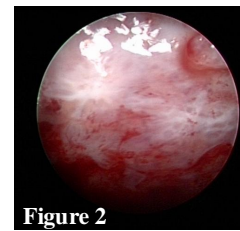

Figure 2

Two months later the patient developed bilateral pleural effusions together with multiple pulmonary nodules. Thoracoscopy was performed again, this time on the right side, and revealed diffuse white-gray nodules and plaques on the parietal pleura (figure 2).

Figure 3

The pleural biopsies showed thickening with large epithelial-like malignant cells with abundant eosinophilic cytoplasm and large nuclei with discrete nucleolus, moderate cellular atypia and rare mitotic figures (figure 3).
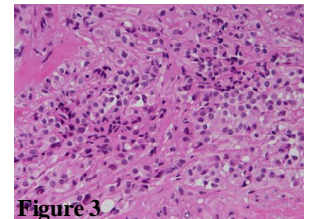
The tumor cells were surrounded by cellular fibrous stroma. Intense mesothelial hyperplasia was observed. Tumor cells were positive for CD31, factor VIII, CEA and vimentin confirming the diagnosis of EHE/pleural angiosarcoma. The patient received four courses of carboplatin/etoposide, and had an initial partial response before he deteriorated and died 12 months after diagnosis.

Pleural angiosarcoma is a multi-organ, aggressive malignancy that is difficult to characterize. Prognosis is poor, though sensitivity to cisplatin/etoposide has been reported[3,4]. High suspicion and thorough pathologic investigation are needed for its diagnosis. Malignant cells are cytokeratin negative but vimentin positive. Immunoreactivity to CD31, CD34 and factor VIII is further diagnostic.

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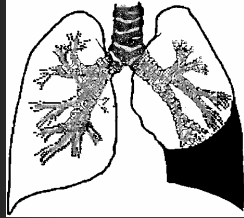
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The 2008 Congress of the International Mesothelioma Interest Group will be held in Amsterdam from Sept 25th to 27th. For details, see **www.imig.org**.

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Diagnosis of TB Pleural Effusions

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Tuberculous (TB) pleural effusions may occur at any age, reach any size and be uni- or bilateral. Patients present with fever, night sweats, weight loss, cough, chest pain and dyspnea varying in severity with the size of the effusion. The diagnosis is straightforward when typical radiographic changes hint at parenchymal TB or when expectorated sputum is found positive for acid fast bacilli. A recent study from Brazil[1] demonstrated that the yield of induced sputum in patients with pleural TB but without spontaneous sputum production was as high as 52%.

Although some cases might be self-limiting, pleural TB should be diagnosed and treated expeditiously as a high proportion of untreated patients will eventually develop more serious manifestations of TB. An array of special investigations exists, the diagnostic value and cost-effectiveness of which are greatly dependent on the local prevalence of TB and hence the pre-test probability. The pleural aspirate is frequently a non-malodorous, clear, straw-colored exudate with a pH of 7.2-7.4. It is rarely turbid or hemorrhagic. The fluid is rich in proteins and tends to clot if not injected into a heparinized container. Microscopy reveals inflammatory cells with lymphocytic predominance. Polymorphonuclear cells may predominate in very early exudates. The presence of >5% mesothelial cells is unusual in TB pleuritis. Microscopy and culture are often negative due to the paucibacillary nature of the disease.

Pleural fluid surrogate markers are in widespread use in countries with a high prevalence of TB. Pleural adenosine deaminase activity (ADA) is a simple,

cheap and robust colorimetric test. A range of cut-off values has been suggested depending on the prevalence of the disease. ADA levels of >40 IU have a sensitivity of 96-100% and specificity of 89-97% for TB in effusions with a lymphocytic predominance[2,3]. ADA levels in non-tuberculous lymphocytic effusions seldom exceed this cutoff, which makes ADA a valuable screening tool in regions with a low TB incidence[3,4]. Although the determination of ADA isoenzymes may increase the specificity, this is infrequently performed.

Pleural interferon-gamma (IFN-γ) is technically more demanding and more expensive than ADA. In a study from India using a cutoff of 138pg/ml, IFN-γ had a sensitivity of 90% and specificity of 97% for pleural TB[5]. In contrast to ADA, IFN-γ does not yield false positive results in empyema or parapneumonic effusions. Combining ADA with the equally cheap cell count and restricting its application to lymphocytic effusions nullifies this apparent advantage. PCR and nucleic acid based techniques have disappointingly low sensitivities. This might be due to the presence of inhibitors in the pleural fluid or to intracellular sequestration of mycobacteria, which makes the target proteins less accessible for amplification.

The gold standard for the diagnosis of pleural TB remains histological evidence of granulomatous pleural inflammation combined with the finding of mycobacteria on microscopy or culture. Material for histology can be obtained with closed pleural biopsy. Published results vary greatly, but if at least six specimens are harvested a yield of up to 87% can be expected in experienced hands[6]. The problem of sampling errors can be overcome by taking biopsies under vision during thoracoscopy, which has a sensitivity and specificity of close to 100% but is not universally available[2].

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If you have any comment on the Newsletter or interesting cases of pleural disease, contact:
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Epidemiology & Drug Resistance

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Pleural TB should be considered in any patient with a lymphocyte predominant exudative pleural effusion[1-3]. The diagnostic approach is debated[1,2], particularly with the advent of new pleural fluid measurements including ADA, IFN-γ, nucleic acid amplification, tuberculous proteins and antibodies, and lysozyme levels[3]. Such measurements may obviate the need for a pleural biopsy (closed biopsy or by video-assisted thoracoscopic surgery) to identify pleural granulomas, culture the TB organism, and obtain antimicrobial sensitivity studies. A central weakness of the use of pleural fluid measurements alone to diagnose pleural TB is their failure to provide antimicrobial sensitivity data. Culture confirmation and drug-susceptibility testing remains a mainstay of the United States Centers for Disease Control and Prevention (CDC)[4].

Knowledge of the epidemiology and antimicrobial resistance pattern of pleural TB can aid its diagnosis and treatment. The most comprehensive epidemiological analysis of pleural TB in U.S.A. utilized the CDC TB database[5] (full report[6]). From 1993 to 2003, 7,549 pleural and 156,779 pulmonary TB cases were analyzed. The annual proportion of pleural TB was relatively stable (median 3.6%) compared to pulmonary TB which steadily decreased (mean decrease 0.9% / year), p=0.001. Pleural TB occurred significantly more often proportionally than pulmonary TB (30.4% *vs* 23.3%, p=0.001) among persons ≥65 years old and significantly less often among children <15 years (pleural 1.8%, pulmonary 6.1%, p<0.001). Pleural TB patients (63.4%) were slightly more often born in the US than pulmonary TB patients (61.0%). Among foreign-born persons with TB, more than twice as many patients with pleural TB (9.4%) than pulmonary TB (4.4%) reported being born in India. Among 25-44 year olds, persons with pleural TB (11.7%) were significantly less likely to report positive HIV test results than those with pulmonary TB (20.0%), p=0.0009.[5]

Drug resistance patterns of pleural TB generally reflected those of pulmonary TB. However, isolates from pleural TB patients were less often resistant to

at least isoniazid (6.0% *vs* 7.8%, p<0.01) and to at least one first-line TB drug (9.9% *vs* 11.9%, p<0.01) compared with pulmonary cases. Not surprisingly, rates of drug resistance were higher among foreign-born than among US-born persons. Approximately twice as many foreign-born pleural patients as US-born pleural patients had isolates resistant to at least isoniazid (8.7% *vs* 4.6%, p<0.01) and at least one first-line drug (14.2% *vs* 7.6%, p<0.01)[5,6].

Such information for patients in U.S.A. may alter physician diagnostic and treatment habits for suspected pleural TB. For example, clinicians should pursue a tissue diagnosis by pleural biopsy with accompanying culture and sensitivity data in foreign-born patients suspected of pleural TB given concerns for drug resistance. Conversely, given the similarity of drug resistance patterns of pleural and pulmonary TB, for US-born patients from areas with low drug-resistance rates for pulmonary TB, diagnosis and treatment of pleural TB based solely upon pleural fluid measurements seems reasonable. Similar epidemiological information from other countries could assist in the management of pleural TB.

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Management of TB Pleural Effusions

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TB pleural effusion generally arises from the rupture of a sub-visceral pleural focus of disease within the lung parenchyma into the pleural space, followed by the development of a delayed-type hypersensitivity (immunological) reaction to the mycobacterial antigens[1]. The involvement of elaborated cytokines leads to clinical symptoms like malaise, fever, and pleuritic pain, as well as the pathological appearance of an exudative pleural effusion due to increased vascular permeability.

The chemotherapy of TB pleural effusion does not differ basically from that used for pulmonary tuberculosis[1]. Standard short-course treatment is usually successful. The Cochrane review analyzed randomized and quasi-randomized clinical trials evaluating the role of systemic corticosteroids as adjunctive therapy in patients diagnosed with TB pleural effusion[2]. However, it has only furnished the conclusion of insufficient evidence to know whether corticosteroids are effective in TB pleural effusion, the alluded immunological mechanism in its pathogenesis notwithstanding.

Lately, there has been some preliminary suggestion on the possible utility of percentage changes in pleural cytokine level[3], and perhaps even radiographic area of effusion[4] after two weeks of therapy in predicting the extent of residual pleural adhesion. From these two studies, the rate of resolution of pleural inflammation appears to be more important than the intensity of inflammation initially in determining the residual pleural scarring. Thus, some patients with pleural TB may be intrinsically more prone to develop subsequent scarring than others. If such findings can be further confirmed, they might usefully enable selecting a more "homogeneous" population of subjects with tuberculous pleural effusion for evaluation of the therapeutic benefit of anti-inflammatory interventions. Hopefully, a more informative answer regarding the efficacy of such treatment strategies would be obtained eventually. At present, given the potential side effects of corticosteroids, I would contemplate the selective use of such adjunctive therapy in patients with TB pleuritis on a case-by-case basis, in the absence of a contraindicating co-morbidity. Perhaps, steroids can help in some patients with significant symptoms (like fever) and very sizeable radiographic effusion after 1-2 weeks of anti-TB chemotherapy.

Aside from very early reports of the equivocal efficacy of intrapleural steroid therapy in managing TB pleuritis which were not further pursued, there has been a recently reported study regarding the possible efficacy of intrapleural urokinase in reducing subsequent pleural adhesion among subjects with loculated TB effusion[5].

Finally, TB empyema representing an extreme form of tuberculous pleural effusion with pus recovered from the pleural cavity generally necessitates surgical drainage (thoracostomy or

decortication) as an adjunctive therapy to improve patient outcome[6]. In this setting, the accumulated thick pus and its encapsulation by chronic inflammatory tissue might pose a significant barrier to the penetration of anti-TB drugs, thus increasing the risk of treatment failure and even emergence of drug resistance. In the rare occasions of functionally incapacitating fibrin-trapped lung or overt fibrothorax that results from tuberculous pleural effusion, recourse to decortication as an adjunct to chemotherapy may also be required.
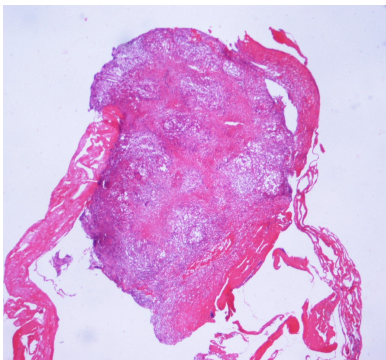
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IMAGES OF THE PLEURA

Blind needle biopsy of pleura is the most commonly used method in the diagnosis of TB pleurisy. Demonstration of granuloma in the biopsy specimen from parietal pleura suggests TB pleuritis. It should be kept in mind that other disorders such as fungal diseases, sarcoidosis, tularemia and rheumatoid pleuritis may also produce granulomatous pleuritis. However, >95% of patients with granulomatous pleuritis have TB.

Histologically, coalescent granulomas are present, composed of epithelioid cells surrounded by a zone of fibroblasts and lymphocytes that usually contains Langhans giant cells (fig). Some necrosis (caseation) may be present in the centers of these tubercles, the amount of which depend on the sensitization of the patient and the virulence of the organism.

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Genetic Predisposition to Pleural Infection

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The importance of an individual's genetic background in determining their susceptibility to many infectious diseases is now well established[1]. Studies have highlighted the genetic basis of susceptibility to respiratory infections, such as tuberculosis and invasive pneumococcal disease[1,2,3]. Research into the role of host genetics in susceptibility to pleural infection has been neglected until recently, however, reflecting the considerable difficulty in assembling large collections of DNA samples from individuals with this phenotype. The UK Multicenter Intrapleural Streptokinase Trial-1 (MIST-1) study generated samples from patients with well-documented pleural infection[4], and work in Oxford utilizing this sample collection has recently identified the first susceptibility locus for Gram-positive pleural infection, a gene called *PTPN22*[5].

PTPN22 is of considerable interest because it has emerged as the leading genetic risk factor for autoimmunity outside the major histocompatibility complex region. The gene encodes the lymphoid protein tyrosine phosphatase LYP, which inhibits T-cell signaling by dephosphorylating and inactivating T-cell-receptor-associated kinases and their substrates[6]. A naturally occurring variant (polymorphism) within the *PTPN22* gene results in a substitution of arginine to tryptophan at codon 620 of the protein and exerts an effect on LYP function, with the tryptophan variant associated with an increase in phosphatase activity in T cells. In keeping with such a functional effect leading to down-regulation of immune responses, the tryptophan variant appears to confer increased susceptibility to both Gram-positive pleural infection and invasive pneumococcal disease (primarily pneumococcal bacteremia and meningitis): odds ratios for the development of invasive bacterial disease were just over 1.5 in heterozygote individuals carrying a single copy of the tryptophan variant, and over 5 in homozygote individuals with two copies of the tryptophan mutant[5]. As samples from non-invasive pneumonia were not available for study, it was not possible to further define the action of *PTPN22* within the overall pathogenesis of pleural infection.

As with other infectious diseases, the development of pleural infection in a particular individual is likely to reflect a combination of multiple acquired and genetic risk factors. Many additional genes besides *PTPN22* are likely to influence the development of pleural infection, and indeed other recent work suggests that common polymorphisms within genes encoding the innate immune signaling 'Toll-like receptors' may also affect susceptibility to both pneumococcal empyema as well as other manifestations of invasive pneumococcal disease (Chapman SJ, unpublished). An increased knowledge of the genes involved in empyema development may eventually lead to novel therapeutic targets for pleural infection. Furthermore, the identification of any genetic predictors of outcome may perhaps be combined with clinical predictors, leading to a more complete prognostic model and ultimately more effective, individually-targeted treatment.

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CASE REPORT

Primary Spontaneous Hemopneumothorax

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A 28 year-old Chinese smoker presented at the Emergency Department for left-sided chest pain of 4 hours. There was no history of trauma. His younger brother has had a spontaneous pneumothorax. He was afebrile, hemodynamically stable and has no marfanoid features. A chest radiograph showed a small apical left pneumothorax. He was kept under observation and given supplemental oxygen. A repeat x-ray (below) taken 6hrs later showed no change.

He was admitted to hospital and treated conservatively. Two days later, his hemoglobin level fell from 16.5 to 13.5g/dL, and a repeat chest film showed a large effusion in addition to the known left pneumothorax. A 20-F chest tube was inserted and drained 1.1L of frank blood. Urgent video-assisted thoracoscopic surgical evacuation of blood clots, hemostasis, pleurectomy, bullectomy and pleurodesis was performed.

Discussion: This case highlights the insidious development of a primary spontaneous hemopneumothorax (PSH-P) over 2 days in a patient who initially presented with a small innocuous pneumothorax. The Ohmori Criteria[1]: draining ≥400ml of blood on initial chest tube insertion in the presence of a pneumothorax is used to facilitate diagnosing a PSH-P.
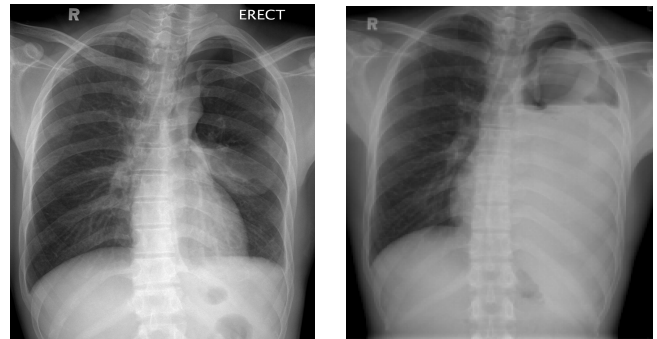
CXR at 6 hr (left) and the 2nd day after admission

Hwong et al[2] found that 10% of their PSH-P cases had admission chest radiographs showing only a pneumothorax with no apparent pleural fluid, as was in our patient. Up to 12%[3] of admission for spontaneous pneumothorax may potentially develop into PSH-P. Eight out of 16 patients (50%) who were referred for surgical management of PSH-P from 2002 to 2006 at our hospital had an occult presentation. So far, only the male gender has been found to confer higher associations with PSH-P[4] over PSP.

PSH-P is potentially life-threatening due to unopposed bleeding into the thoracic cavity and, as this case has illustrated, can be occult in nature and develop after hospitalization. While surgical treatment is well established, this warrants vigilance in considering the possibility of PSH-P in all cases of PSP. For patients bearing clinical indices of suspicion, adequate venous access, cross-matching of blood and close monitoring should be performed.

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