

**Online Appendix B1      BTS Guideline for Pleural Disease**

**Section B              Investigation of the undiagnosed pleural effusion**

**Question B1          Evidence Review and Protocol**

**B1      What is the diagnostic accuracy of radiology when diagnosing benign pleural disease as a cause of unilateral pleural effusion in adults?**

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## Question Evidence Review

### B1 What is the diagnostic accuracy of radiology when diagnosing benign pleural disease as a cause of unilateral pleural effusion in adults?

#### Background

Radiological tests form a key role in the detection and diagnostic pathway of a unilateral pleural effusion in adults and may include x-ray, computed tomography (CT), thoracic ultrasound, positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI). The diagnostic accuracy of radiological tests for distinguishing benign from malignant disease is addressed in Supplementary Online Appendix D1. This review will focus on the diagnostic accuracy of radiology when investigating unilateral pleural effusions of benign aetiology.

#### Outcomes

Diagnostic accuracy of radiological tests for diagnosing unilateral pleural effusion

#### Evidence Review

The initial literature search identified 43 papers, but data were very limited with most focusing on the differentiation of benign and malignant pleural disease. Papers that did not discriminate between patients with and without a pleural effusion were excluded, but seven papers were deemed relevant to the review<sup>1-7</sup>.

#### *Pleural infection*

The absence of malignant radiological features (circumferential pleural thickening with nodularity involving the mediastinal surface) is suggestive of a benign pleural effusion, but there is overlap in the imaging features of malignancy and infection. On CT, features that are more common in pleural infection (parapneumonic, empyema and tuberculosis (TB)) than malignancy are<sup>1,2</sup>:

- i) Lentiform configuration of pleural fluid
- ii) Visceral pleural thickening ("split pleura sign")
- iii) Hypertrophy of extrapleural fat (>2mm)
- iv) Increased density of the extrapleural fat
- v) Presence of pulmonary consolidation

Poor sensitivity of these features ([Table B1a](#)) highlight the need for diagnostic thoracentesis in unexplained pleural effusions to allow pleural fluid characterisation.<sup>1</sup>

Table B1a: Diagnostic accuracy of chest CT features for pleural infection

CT feature	Sensitivity	Specificity	PPV	NPV
Visceral pleural thickening	0.20	0.98	0.79	0.77
Increased density of extra-pleural fat	0.25	0.91	0.74	0.76
Pulmonary consolidation	0.48	0.90	0.63	0.08

However, it should also be noted that malignancy can co-exist with pleural infection, with synchronous disease processes found in approximately 5% of cases.<sup>3,4</sup> In this context, the presence of a mass involving the extrapleural fat and mediastinal pleural thickening may be markers of co-existent malignancy<sup>4</sup>, but common clinical practice is to perform follow-up imaging for up to two years to exclude occult disease if there are ongoing symptoms or other clinically concerning features.

Tuberculosis pleuritis may mimic malignancy with circumferential pleural thickening >1 cm, involvement of the mediastinal surface and nodularity<sup>2</sup>, but, unlike malignancy, is not associated with chest wall invasion<sup>7</sup>. On

ultrasound, tuberculous effusions tend to be highly complex with internal septations, unlike malignancy, and in lymphocyte-rich pleural effusions, the presence of complex internal septation is reported as predictive of tuberculosis ([Table B1b](#)).<sup>5</sup>

Table B1b: Diagnostic accuracy of chest US features for tuberculosis

CT feature	Sensitivity	Specificity	PPV	NPV
Complex internal septation	0.47	0.96	0.94	0.59

PET-CT data is very limited for the evaluation of pleural infection, but in a meta-analysis of PET-CT for the differentiation of benign and malignant disease, Porcel et al reported that the sensitivity and specificity for identifying malignant effusions were 0.81 and 0.74 respectively. Porcel also noted that around 40% of tuberculous and parapneumonic effusions display avid FDG-PET uptake.<sup>6</sup>

There were no data on the use of MRI in assessment of pleural infection that met inclusion criteria.

#### *Non-infective causes of unilateral pleural effusions*

Pleural effusions due to non-infective inflammatory causes, including rheumatoid arthritis, Dressler syndrome, organising pneumonia, pulmonary emboli and benign asbestos related pleural effusion, are typically bland in appearance on CT, showing mild smooth thickening of the parietal pleura not involving the mediastinum.<sup>1</sup> Chronic inflammatory effusions are commonly associated with the development of pleuroparenchymal bands and subsequently folded lung. In many cases aetiology of pleural effusion may be inferred based on circumstantial findings ([Table B1c](#)).

Table B1c: Ancillary imaging observations potentially linked to the aetiology of a unilateral pleural effusion

Aetiology	Examples of ancillary findings
Benign asbestos pleural effusion	Calcified pleural plaques may be present
Cardiac dysfunction	Usually bilateral; cardiomegaly; pericardial effusion
Post-cardiac surgery	Temporal relationship with surgery; usually left sided
Traumatic	Rib fractures; signs of active bleeding on CT; high density on CT in the acute phase
Abdominopelvic pathology	Signs of cirrhosis; adnexal mass

#### **Evidence statements**

CT features such as lentiform pleural collection, enhancement of the visceral pleura, adjacent hypertrophied extrapleural fat of increased density and an absence of malignant features may suggest pleural infection over malignancy (**Ungraded**)

Tuberculosis may mimic malignancy on imaging (**Ungraded**)

Malignancy may co-exist with pleural infection (**Ungraded**)

In the context of pleural infection, PET-CT is not a useful test to identify pleural malignancy (**Ungraded**)

Assessment of extrathoracic structures on imaging may provide clues to underlying aetiology (**Ungraded**)

#### **Recommendations**

There is not enough evidence to make any recommendations.

## Good Practice Points

- ✓ Imaging findings of a unilateral pleural effusion should be interpreted in the context of clinical history and knowledge of pleural fluid characteristics
- ✓ CT follow-up should be considered for patients presenting with pleural infection to exclude occult malignancy if there are ongoing symptoms, or other clinically concerning features
- ✓ PET-CT should not be used in the assessment of pleural infection

## Research Recommendation

- Further research is needed to characterise the radiological features of individual non-malignant causes of pleural effusion to improve radiological assessment of non-malignant pleural effusions

## Risk of bias summary

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Arenas-Jimenez 2000	+	+	+	?	+	+	+
Chen 2006	-	+	+	?	+	?	+

  

<span style="color: red;">-</span> High	<span style="color: yellow;">?</span> Unclear	<span style="color: green;">+</span> Low
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## References

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2. Yilmaz U, Polat G, Sahin N, Soy O, Gulay U. CT in differential diagnosis of benign and malignant pleural disease. *Monaldi Archives for Chest Disease - Pulmonary Series.* 2005;63(1):17-22.
3. Hallifax R, Haris M, Corcoran JP, et al. Role of CT in assessing pleural malignancy prior to thoracoscopy. *Thorax.* 2015;70(2):192-193.
4. Lee HY, Goo JM, Lee HJ, Lee CH, Chun EJ, Im JG. The value of computed tomography for predicting empyema-associated malignancy. *J Comput Assist Tomogr.* 2006;30(3):453-459.
5. Chen HJ, Hsu WH, Tu CY, et al. Sonographic septation in lymphocyte-rich exudative pleural effusions: a useful diagnostic predictor for tuberculosis. *J Ultrasound Med.* 2006;25(7):857-863.
6. Porcel JM, Hernandez P, Martinez-Alonso M, Bielsa S, Salud A. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. *Chest.* 2015;147(2):502-512.
7. Bugalho A, Ferreira D, Dias SS, et al. The diagnostic value of transthoracic ultrasonographic features in predicting malignancy in undiagnosed pleural effusions: a prospective observational study. *Respiration.* 2014;87(4):270-278.

## Question Protocol

Field	Content
Review Question	What is the diagnostic accuracy of radiology when diagnosing unilateral pleural effusion in adults?
Type of review question	Diagnostic accuracy
Objective of the review	Will cover the relative diagnostic accuracy of radiological techniques in the diagnosis of common pleural pathologies (ultrasound, CT, PET and MRI for the diagnosis of malignant, infectious and benign pleural disease).
Eligibility criteria – population / disease / condition / issue / domain	Adults with unilateral pleural effusion 18+
Eligibility criteria – index test(s)	US PET CT MRI
Eligibility criteria – gold standard	Clinico-pathological final diagnosis
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients only
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but <b>DO NOT</b> use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	None

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	<p>RevMan5      Meta-analysis data input. Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.</p> <p>MetaDTA      Data meta-analyses</p> <p>Gradepro      Quality of evidence assessment / Recommendations</p>
Information sources – databases and dates	MEDLINE, Embase, PubMed, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews  1966 - present
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in ' <i>BTS Guideline Process Handbook - Diagnostic Accuracy</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	<p>If 3 or more relevant studies:</p> <p>RevMan5 for forest plots, summary ROC plot</p> <p>MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot</p> <p>(follow instructions in '<i>BTS Guideline Process Handbook - Diagnostic Accuracy</i>')</p>
Meta-bias assessment – publication bias, selective reporting bias	<p>GRADEpro      Diagnostic accuracy quality of evidence assessment for each index test</p> <p>(follow instructions in '<i>BTS Guideline Process Handbook - Diagnostic Accuracy</i>')</p>
Rationale / context – what is known	CT has a reasonable diagnostic sensitivity and specificity for the diagnosis of malignant and infectious disease. Ultrasound has a reasonable diagnostic accuracy for malignant disease. PET has higher diagnostic yield than CT alone