Online Appendix B6 BTS Guideline for Pleural Disease

Section B Investigation of the undiagnosed pleural effusion

Question B6 Evidence Review and Protocol

B6 What is the diagnostic accuracy of pleural biopsy in adults with suspected pleural disease?

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Question Evidence Review

B6 What is the diagnostic accuracy of pleural biopsy in adults with suspected pleural disease?

Background

Obtaining pleural tissue is often necessary to achieve definitive diagnosis in patients presenting with pleural effusion and/or thickening. There are a variety of pleural biopsy techniques, and the aim of this review was to assess which biopsy method was most successful in achieving accurate histological diagnosis.

Outcomes

Diagnostic accuracy of pleural biopsy in adults with suspected pleural disease

Evidence Review

The initial literature search identified 86 papers, but large heterogeneity in study methodology and result reporting made meta-analysis impossible. A pragmatic approach was therefore adopted to achieve a structured stepwise narrative approach, focusing on studies where direct comparative data were available. Confirming a diagnosis of malignant pleural disease or pleural infection, specifically tuberculous pleuritis, were both considered. Making a histological diagnosis of non-specific pleuritis (also referred to as other terms such as fibrinous pleurisy and pleural fibrosis) was also considered a genuine and clinically relevant finding when followed-up for at least 12 months.

Awake thoracoscopic pleural biopsy versus video-assisted thoracoscopic pleural biopsy under general anaesthesia ("medical" versus "surgical" thoracoscopic pleural biopsy)

A single retrospective cohort study compared outcomes in 177 patients at a single tertiary thoracic surgical centre who underwent either medical thoracoscopic pleural biopsy using a semi-rigid technique (n = 78) or video-assisted thoracoscopic (VATS) pleural biopsy under general anaesthesia (n = 99). Diagnostic yield, sensitivity and specificity were 94%, 0.85 and 1.00 for medical thoracoscopy and 96%, 0.93 and 0.94 for VATS respectively, with no statistically significant difference (p = 0.59).[1]

Awake ("medical") rigid thoracoscopic pleural biopsy versus awake semi-rigid thoracoscopic pleural biopsy

Three studies compared rigid and semi-rigid thoracoscopy for pleural biopsy and summary of results is shown in Table B6a.[2-4]

Table B6a: Diagnostic yield comparison between awake rigid and awake semi-rigid thoracoscopic pleural biopsy

		Thoracoscopy Diagnostic Yield (patients)		
Study	**Analysis**	**Rigid**	**Semi-rigid**	***p***
Dhooria 2014[2]	Intention-to-treat	97.8% (44/45)	73.3% (33/45)	0.002
Khan 2012[3] *	Intention-to-treat	96.3% (26/27)	92.3% (36/39)	NS
Rozman 2013[4]	Intention-to-treat	90.5% (38/42)	95.2% (40/42)	0.454
Mean ± SD (%)		**94.9 ± 3.9**	**86.9 ± 11.9**	**0.167†**
Dhooria 2014[2]	Biopsy successfully obtained	100.0% (47/47)	94.3% (33/35)	0.180
Rozman 2013[4]	Biopsy successfully obtained	100.0% (38/38)	97.6% (40/41)	NR
Mean ± SD (%)		**100 ± 0.0**	**96.0 ± 2.3**	**0.067†**

* Data limited by retrospective, non-randomised study design and analysis by different operators at two different centres)

† Independent t-test

NR – not reported, NS – not significant

Thoracoscopic pleural biopsy versus image-guided closed pleural biopsy

Four studies prospectively randomised patients to thoracoscopic pleural biopsy or ultrasound-guided closed pleural biopsy[5-8], one study prospectively randomised patients to thoracoscopic pleural biopsy or CT-guided closed pleural biopsy[9], one study involved sequential procedures[10] and the remaining study was a retrospective cohort[11]. A summary of the results is presented in Table B6b and demonstrates a significantly higher definitive diagnosis and diagnostic accuracy with thoracoscopy (p = 0.043 and 0.035 respectively).

Table B6b: Summary of studies comparing thoracoscopic pleural biopsy and image-guided closed pleural biopsy

	Thoracoscopic pleural biopsy		**Image-guided closed pleural biopsy**		
Study	**Method**	**Results**	**Method**	**Results**	***p***
		Definitive diagnosis		*Definitive diagnosis*	
Zhou 2018[5]	Semi-rigid	84/98 patients (85.7%)	US (direct vision) 18G core needle	81/98 patients (82.7%)	NS
Salim 2018[6]	Rigid	43/45 patients (95.6%)	US (assisted) Abrams needle	39/45 patients (86.7%)	NS
Mohamed 2014[7]	Rigid	17/20 patients (85%)	US (direct vision) Abrams needle	15/20 patients (75%)	NS
Mohamed 2013[8]	Rigid	20/20 patients (100%)	US (direct vision) core needle	18/20 patients (90%)	NS
Metintas 2010[9] *	Rigid	48/51 patients (94.1%)	CT (assisted) Abrams needle	42/48 patients (87.5%)	NS
Mean ± SD (%)		**92.1 ± 6.5**		**84.4 ± 5.9**	**0.043‡**
		Diagnostic yield		*Diagnostic yield*	
Agmy 2014[10]	Semi-rigid	93/96 cases (96.9%)	US (direct vision) biopsy forceps	84/96 cases (87.5%)	0.030
Sobhy 2017[11] †	Rigid	58/61 cases (95.1%)	US (direct vision) core needle	26/32 cases (81.3%)	NS
Mean ± SD (%)		**96.0 ± 1.3**		**84.4 ± 4.4**	**0.035‡**

* Evaluated histological results for malignant or tuberculous pleuritis only; other pathology was considered indeterminate

† Reported outcomes for 39 patients undergoing thoracoscopic biopsy alone, 10 patients undergoing image-guided biopsy alone and 22 patients who underwent both procedures

‡ Independent t-test

NS – not significant

Thoracoscopic pleural biopsy versus blind closed pleural biopsy

Six studies compared thoracoscopy with blind closed pleural biopsy. In three studies patients had both procedures sequentially[12-14]; in two studies patients were randomised to thoracoscopic or blind closed pleural biopsy[15,16] and one was a retrospective cohort study[17]. The results are summarised in Table B6c, with 5/6 studies demonstrating a significantly higher definitive diagnosis and diagnostic yield with thoracoscopy (p = 0.007 and 0.030 respectively).

Table B6c: Summary of studies comparing thoracoscopic and blind closed pleural biopsy

	Thoracoscopic pleural biopsy		Blind closed pleural biopsy		
Study	**Method**	**Results**	**Method**	**Results**	***p***
		Definitive diagnosis		*Definitive diagnosis*	
Chen 2018[12]	Semi-rigid*	84/92 patients (91.3%)	Abrams needle	25/92 patients (27.1%)	<0.001
Mishra 2016[13] †	Rigid	36/46 patients (78.3%)	Copes needle	10/46 patients (21.7%)	<0.001
Mean ± SD (%)		**84.8 ± 9.2**		**24.2 ± 3.8**	**0.007‡**
		Sensitivity/Specificity		*Sensitivity/Specificity*	
McLean 1998[14]	Semi-rigid	0.81 / 1.00 for malignant disease	Abrams needle	0.62 / 1.00 for malignant disease	NS
		Diagnostic yield		*Diagnostic yield*	
Haridas 2014[15]	Rigid	25/29 cases (86.2%)	Abrams needle	18/29 cases (62.1%)	0.036
Son 2014[16]	Needle ("mini")	29/31 cases (93.5%)	Abrams needle	20/36 cases (55.6%)	<0.001
Maturu 2015[17]	Rigid (182) & semi-rigid (66)	231/248 cases (93.2%)	Abrams (50) & core needle (34)	71/84 cases (84.5%)	0.020
Mean ± SD (%)		**91.0 ± 4.1**		**67.4 ± 15.2**	**0.030‡**

* Results reported for both flexible forceps biopsy and cryoprobe biopsy via the semi-rigid thoracoscope; the results for the former (more widely used) technique are presented here

† Histological results reported for malignant or tuberculous pleuritis only; other pathology was considered indeterminate (10/46, 21.7% cases)

‡ Independent t-test

NS – not significant

CT-guided closed pleural biopsy versus ultrasound-guided closed pleural biopsy

Two studies compared CT-guided closed pleural biopsy against ultrasound-guided closed pleural biopsy and a summary of the results is shown in Table B6d.[18,19]

Closed pleural biopsy using core needle versus Abrams needle

A single randomised trial in suspected tuberculous pleuritis patients compared diagnostic yield, randomising patients to the order in which they underwent both ultrasound-assisted Abrams biopsies and 14-gauge core needle biopsies.[20] Ultrasound was used to identify the optimal pleural sampling site and biopsies were performed without direct image guidance. Diagnostic yield was higher using Abrams than core needle (Abrams 91.0% (81/89), core needle 78.7% (70/89), $p = 0.015$), but the data may be limited by the focus on suspected tuberculous pleuritis rather than undiagnosed pleural disease.

Table B6d: Diagnostic accuracy of CT-guided closed pleural biopsy versus US-guided closed pleural biopsy

	CT-guided closed pleural biopsy		US-guided closed pleural biopsy		
Study	**Method**	**Results**	**Method**	**Results**	***p***
		Diagnostic accuracy		*Diagnostic accuracy*	
Metintas 2016[18] *	Abrams needle	61/74 patients (82.4%)	16G core needle	48/72 patients (66.7%)	0.029
Sivakumar 2016[19] †	Core needle	22/29 patients (75.9%)	Abrams needle	49/63 patients (77.8%)	NS
Mean ± SD (%)		**79.2 ± 4.6**		**72.3 ± 7.8**	**0.198‡**

* Neither procedure performed under real-time visualisation – CT or ultrasound used to identify/characterise the anatomical site for pleural sampling and the needle biopsy performed afterwards without the use of direct imaging observation

† CT-guided core needle biopsy performed under direct imaging observation; US-guided closed pleural biopsy performed using ultrasound to identify/characterise pleural sampling site as described above

‡ Independent t-test

CT – computed tomography; NS – not significant; US – ultrasound

Image-guided closed pleural biopsy versus blind closed pleural biopsy

A final three studies compared image-guided closed pleural biopsy against blind closed pleural biopsy and a summary of the data are presented in Table B6e.[21-23]

Table B6e: Summary of studies comparing image-guided closed pleural biopsy and blind closed pleural biopsy

	Image-guided closed pleural biopsy		Blind closed pleural biopsy		
Study	**Method**	**Results**	**Method**	**Results**	***p***
		Definitive diagnosis		*Definitive diagnosis*	
Rezk 2015[21] *	CT-guided 16G core needle	14/16 patients (87.5%)	Abrams needle	6/15 patients (40.0%)	0.009
		Sensitivity/Specificity		*Sensitivity/Specificity*	
Maskell 2003[22] †	CT-guided 18G core needle	0.87 / 1.00 for malignant disease	Abrams needle	0.47 / 1.00 for malignant disease	0.02
Chang 1991[23]	US-guided 16G core needle	0.70 / 1.00 for malignant disease	Abrams needle	0.44 / 1.00 for malignant disease	NR
Chang 1991[23]	US-guided 16G core needle	0.86 / 1.00 for tuberculous pleuritis	Abrams needle	0.20 / 1.00 for tuberculous pleuritis	<0.05

* Cytology-positive malignant pleural effusion patients

† Cytology-negative suspected malignant pleural effusion

NR – not reported

Evidence statements

There is insufficient evidence to determine the diagnostic test performance comparing awake thoracoscopic pleural biopsy and video-assisted thoracoscopic pleural biopsy under general anaesthesia (**Ungraded**)

There is no difference in diagnostic yield when using rigid thoracoscopy or semi-rigid thoracoscopy to obtain a pleural biopsy (**Ungraded**)

Definitive diagnosis is more likely with thoracoscopic pleural biopsy when compared to image-guided closed pleural biopsy (**Ungraded**)

Diagnostic accuracy appears to be higher with thoracoscopic pleural biopsy when compared to image-guided closed pleural biopsy (**Ungraded**)

Definitive diagnosis is more likely with thoracoscopic pleural biopsy when compared to blind closed pleural biopsy (**Ungraded**)

Diagnostic yield appears to be higher with thoracoscopic pleural biopsy when compared to blind closed pleural biopsy (**Ungraded**)

There is no difference in diagnostic accuracy between CT-guided closed pleural biopsy and ultrasound-guided closed pleural biopsy (**Ungraded**)

Image-guided closed pleural biopsy may increase definitive diagnosis and diagnostic accuracy when compared to blind closed pleural biopsy (for malignant disease and tuberculous pleuritis) (**Ungraded**)

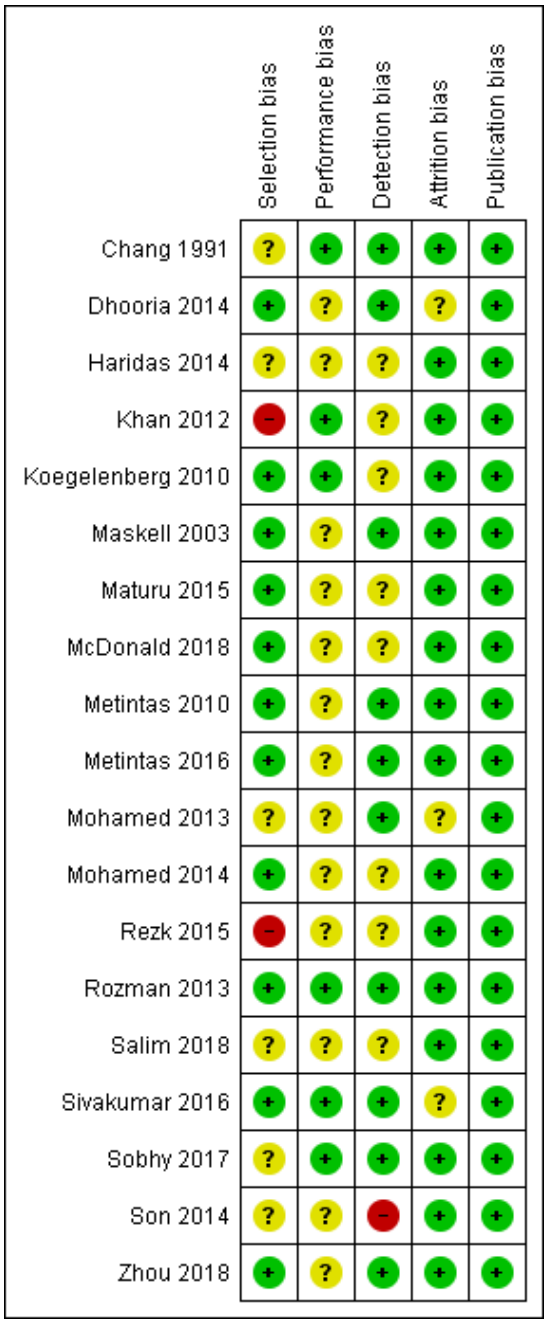
Recommendations

- Thoracoscopic or image-guided pleural biopsy may be used depending upon the clinical indication and local availability of techniques (including need for control of pleural fluid) (**Strong** – by consensus)
- Blind (non-image guided) pleural biopsies should not be conducted (**Strong** – by consensus)

Research Recommendation

- Further research is needed into comparing rigid versus semi-rigid thoracoscopy to determine if one technique is superior to the other in terms of diagnostic accuracy of pleural biopsy and other clinical outcomes
- Research is needed into the role of tools such as cryobiopsy, narrow band imaging and confocal laser endomicroscopy as adjuncts to standard thoracoscopic pleural biopsies
- Further research is needed into the role of image-guided closed pleural biopsy in the diagnostic pathway for patients with suspected pleural disease, particularly its use as a front-line test alongside diagnostic thoracentesis for individuals with identifiable pleural thickening or nodularity on imaging studies

Risk of bias summary



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Question Protocol

Field	Content
Review Question	What is the diagnostic accuracy of pleural biopsy in adults with suspected pleural disease?
Type of review question	Diagnostic accuracy
Objective of the review	Assess the evidence for the use of pleural biopsies in the diagnosis of common pleural conditions, specifically malignancy, TB, infection
Eligibility criteria – population / disease / condition / issue / domain	Adults with unilateral pleural effusion 18+
Eligibility criteria – index test(s)	Pleural biopsy
Eligibility criteria – gold standard	Clinico-pathology
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
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 **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Blind or guided Surgeon or physician Rigid or semi-rigid thoracoscopy
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)	RevMan5	Meta-analysis data input. Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.
	MetaDTA	Data meta-analyses
	Gradepro	Quality of evidence assessment / Recommendations
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 '*BTS Guideline Process Handbook - Diagnostic Accuracy'*)	
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plot MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in '*BTS Guideline Process Handbook - Diagnostic Accuracy'*)	
Meta-bias assessment – publication bias, selective reporting bias	GRADEpro	Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in '*BTS Guideline Process Handbook - Diagnostic Accuracy'*)
Rationale / context – what is known	Pleural biopsy has a higher sensitivity than fluid alone for the diagnosis of malignancy and TB	