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ORIGINAL PAPER

Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease—a systematic review and cost analysis

C. Sharp[1,2], M. McCabe[3], H. Adamali[2] and A.R. Medford[2]

From the [1]Academic Respiratory Group, University of Bristol, Bristol, UK, [2]North Bristol Lung Centre, Southmead Hospital, Bristol, UK and [3]Research Department, University of Cambridge Local Examinations Syndicate, University of Cambridge, Cambridge, UK

Address correspondence to Dr A. Medford, North Bristol Lung Centre, Southmead Hospital, Bristol BS10 5NB, UK. email: andrew.medford@nbt.nhs.uk

Summary

Background: Histological diagnosis by surgical lung biopsy for interstitial lung disease (ILD) is currently limited. Transbronchial cryobiopsy via flexible bronchoscope may this for more patients. The relative costs, diagnostic yields and safety of this approach and more traditional approaches have not been determined.
Objectives: To perform a systematic review and meta-analysis of transbronchial cryobiopsy, forceps transbronchial biopsy and video assisted (VATS) surgical lung biopsy assessing their relative diagnostic yields and safety. To perform a cost analysis to demonstrate any savings through change to the newer technique.
Methods: We performed a systematic review of the literature using MEDLINE and EMBASE for all original articles on the diagnostic yield and safety of transbronchial cryobiopsy, forceps transbronchial biopsy and VATS-biopsy in ILD up to February 2016. Data were extracted on yield and complication rates, in addition to study characteristics. Theoretical cost analysis was performed from local institution financial data, 2015–16 reimbursement tariffs and results of the systematic review.
Results: A meta-analysis of 11 investigations for transbronchial cryobiopsy, 11 for forceps transbronchial biopsy and 24 for VATS-biopsy revealed diagnostic yields of 84.4% (75.9–91.4%), 64.3% (52.6–75.1%) and 91.1% (84.9–95.7%), respectively. Pneumothorax occurred in 10% (5.4–16.1%) of transbronchial cryobiopsy procedures, moderate bleeding in 20.99% (5.6–42.8%), with three deaths reported. Surgical mortality was 2.3% (1.3–3.6%). Cost analysis demonstrated potential savings of £210 per patient in the first year and £647 in subsequent years.
Conclusions: Transbronchial cryobiopsy represents a potentially cost-saving approach to improve histological diagnosis in ILD, however is accompanied by a significant risk of moderate bleeding.

Introduction

Fibrosing interstitial lung diseases (ILD) are diagnosed by a multidisciplinary synthesis of clinical, radiological and histological features, as advised by national and international guidelines.[1–4] While invasive procedures are only considered where a confident diagnosis cannot be made using only information from clinical and radiological assessment, these are sometimes required.

Current guidelines advise against the use of forceps transbronchial biopsy in the diagnosis of ILD, advocating surgical lung biopsy where histological diagnosis is required.[2–4] While the advent of video-assisted thoracoscopic surgical biopsy

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(VATS) has made surgical lung biopsy much safer, it is still associated with significant complications. Frail patients may be unable to undergo VATS-biopsy, thus making confident diagnosis and clinical decision making more challenging.

The use of bronchoscopic cryoprobes was initially developed for the treatment of central airway obstruction.[5] Subsequently, cryoadhesion was introduced for endobronchial biopsy[6,7] and cryorecanalization of central airway obstruction. More recently, cryoadhesion has been investigated for transbronchial lung biopsy following the observation of improved preservation of histological architecture and larger specimens compared to conventional endo- and trans-bronchial biopsies.[8,9]

The conduct of this procedure has varied; it can be performed by respiratory physicians or thoracic surgeons with skills in interventional bronchoscopy, in an endoscopy suite with or without fluoroscopic guidance. It has been conducted under both conscious sedation and general anaesthesia, with or without an anaesthetist present. This variation in conduct of cryobiopsy has led to calls for procedural standardisation.[8]

The cryoprobe makes use of the Joule–Thomson effect through which rapid decompression of a gas from high pressure (45 bar) lowers temperature significantly.[10] Cryobiopsy systems use nitrous oxide to cool the tip of a cryoprobe to −80–89°C, resulting in tissue adherence to the probe during the freezing process. This technique allows the retrieval of larger biopsy specimens; however, it does have an increased risk of both bleeding and pneumothorax.[10] A recent study by Tomassetti et al[11] examined the influence on diagnostic confidence in a multidisciplinary (MDT) meeting of transbronchial cryobiopsy as compared to VATS biopsy; however, there has been no previous comparative meta-analysis of the literature for these procedures.

The cost effectiveness of transbronchial cryobiopsy for diagnosis of ILD has not yet been formally evaluated. Appropriate reimbursement tariffs need to be adopted in healthcare systems operating by payment by results (PbR) in order to adequately account for the increased resources required for this procedure compared to standard bronchoscopy with forceps transbronchial biopsy. The uptake of this procedure is likely to reduce costs associated with VATS-biopsy, however it is unclear from the literature how many surgical procedures may be avoided.

A further consideration is the accuracy of coding of procedures for calculation of PbR tariffs. This has been observed to be poor in other areas of interventional pulmonology, including thoracoscopy[12] and endobronchial ultrasound guided transbronchial needle aspiration.[13] Physician involvement significantly improves the accuracy of this coding and this will need to be appreciated in accurate cost analysis for any novel procedure introduced under analogous healthcare systems.

Our aims in this work were to conduct a systematic review of the literature for the use of forceps transbronchial biopsy, VATS-biopsy and transbronchial cryobiopsy in the histological diagnosis of patients with ILD. We have also conducted a theoretical cost analysis for the introduction of transbronchial cryobiopsy in an ILD service.

Materials and Methods

Systematic review data sources and searches

Any observational study examining forceps transbronchial biopsy, transbronchial cryobiopsy or VATS-biopsy in the diagnosis of ILD in adults over the age of 18 years was included in the review. Studies were excluded if they did not include patients with ILD. The outcome measures determined prior to conducting the review were, for all procedures, diagnostic yield and procedure-related mortality. For forceps transbronchial biopsy and transbronchial cryobiopsy, pneumothorax and bleeding rates and post-procedure admissions were also examined. For bleeding, classification of severity was based on that described in British Thoracic Society guidelines;[14] moderate bleeding was that requiring endobronchial cold saline or adrenaline, severe bleeding required endobronchial blockers or surgical intervention.

Electronic searches were performed in MEDLINE (1950–Feb 2016) and EMBASE (Feb 1980–Dec 2016). No language restrictions were applied. The search strategies are detailed in Appendix 1. Titles and abstracts were screened to identify potentially relevant studies, the full texts of which were then reviewed. The protocol for this review is published on the PROSPERO register (ID. CRD42016037172). The review was performed according to the PRISMA guidelines.[15]

Data extraction and assessment of bias

Publication details (authors, year of publication, country of origin), study design, number of subjects, diagnostic yield and complications associated with the procedure were recorded. Data were pooled and weighted according to published sample size for all outcomes of interest from those studies selected for inclusion in the review. Pooled diagnostic yield and complication rates were calculated by Freeman-Tukey transformation, using a DerSimonian random effects model in the presence of significant heterogeneity and are reported as percentage and 95% confidence interval (CI). Heterogeneity of results was assessed by I^2 statistic, where >50% indicates significant heterogeneity. Risk of bias was assessed using the Cochrane Collaboration risk of bias tool (RevMan v5.3, The Cochrane Collaboration, Copenhagen, Denmark). Data were analysed using Medcalc software (v16.2.1; Medcalc software, Ostend, Belgium).

Cost analysis

Actual UK National Health Service (NHS) costings were calculated from local institution NHS financial data, taking into account equipment costs, running and staff costs. The additional costs involved for transbronchial cryobiopsy includes the cryosurgical unit and cryoprobes, in addition to the maintenance contract and staffing costs. The cost of the unit and probes was spread over the first year of use, with savings calculated for the first year and then subsequent years on this basis. The expected costs from procedural complications were based on rates quoted in the literature for transbronchial cryobiopsy and VATS-biopsy. We based these calculations on procedures conducted under conscious sedation without anaesthetic support, performed in an endoscopy suite.

The minimum theoretical number of transbronchial cryobiopsy procedures per year was calculated by extrapolation from the number of referrals from the North Bristol ILD service for VATS-biopsy for diagnosis of ILD, making the assumption that all of these patients would first undergo transbronchial cryobiopsy rather than be exposed to the risk of surgery.

Payment by Results is the payment system in England enabling healthcare commissioners to reimburse healthcare providers for each patient seen or treated. National tariffs are set annually based on the average cost of services reported by NHS providers, taking into account the complexity of the

patient's needs. The PbR tariffs (2015/6) were used to calculate costs to the healthcare funding entity, in this case the Clinical Commissioning Group (CCG). Health Resource Group (HRG) codes are used within the NHS to assist calculation of reimbursement for procedures. The HRG codes used in this study were DZ54Z (complex bronchoscopy) and DZ04A (moderate thoracic procedure with co-morbidities).

Results

Systematic review

Searches were assessed as up to date on 10 February 2016. 166 studies were identified by searches relating to VATS-biopsy for the diagnosis of ILD, of which 24 were included. One study examining data from the USA Nationwide Inpatient Sample (NIS) process was based on survey data rather than direct analysis of patient records and was therefore not included in the data analysis.[16] 1010 studies were identified by searches relating to forceps transbronchial biopsy in the diagnosis of ILD, of which 11 were included. 13 studies were identified by searches relating to transbronchial cryobiopsy in the diagnosis of ILD, of which 11 were included. Figure 1 shows study attrition. Study characteristics are shown in Tables 1 and 2. A summary of findings is shown in Table 3. Results from individual studies are shown in the supplemental data.

The diagnostic yield from included studies suggests that transbronchial cryobiopsy is superior to forceps transbronchial biopsy in the diagnosis of ILD, however this is at the cost of a higher rate of both pneumothorax and bleeding. Reported bleeding risks and their classification are described in Table 4. Severe bleeding was only reported in two patients, for whom this was controlled by rigid bronchoscopy. The detail of reporting of bleeding was heterogeneous. Surgical mortality in

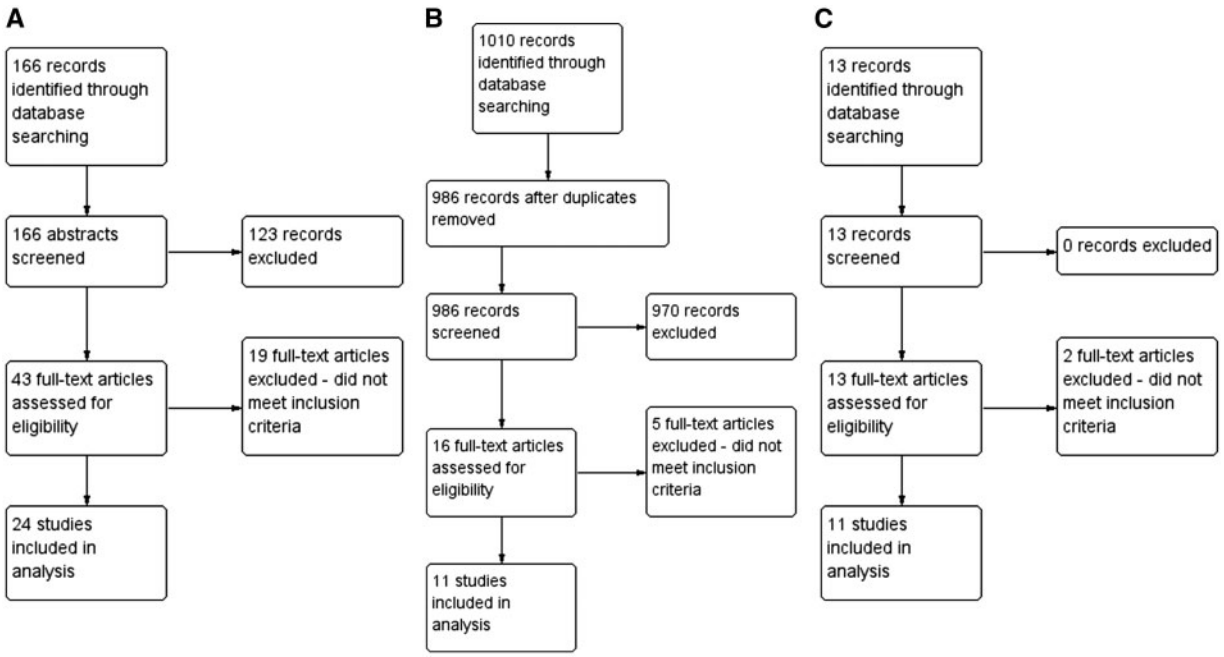

Figure 1. Study selection flow diagram—**A**: VATS-biopsy, **B**: Forceps transbronchial biopsy, C: Cryo-transbronchial biopsy.

Table 1. Characteristics for included studies

		Transbronchial cryobiopsy	VATS-biopsy	Forceps transbronchial biopsy
Study design, *n* (%)	Retrospective case series	8 (72.7)	23 (95.8)	8 (72.7)
	Prospective case series	2 (18.2)	1 (4.2)	2 (18.2)
	Randomised, controlled trial	1 (9.1)	0 (0)	1 (9.1)
Continent, *n* (%)	North America	2 (18.2)	3 (12.5)	2 (18.2)
	Europe	7 (63.6)	9 (37.5)	6 (54.5)
	South America	0 (0)	2 (8.3)	0 (0)
	Asia	2 (18.2)	9 (37.5)	3 (27.3)
Outcomes reported, *n* (%)	Diagnostic yield	10 (90.9)	22 (91.7)	10 (90.9)
	Survival morbidity	NA	18 (75)	NA
	Pneumothorax	9 (81.8)	NA	8 (72.7)
	Bleeding	6 (54.5)	NA	5 (45.5)
	Admission/Length of Stay	3 (27.3)	8 (33.3)	1 (9.1)
	Mortality	2 (18.2)	21 (87.5)	0 (0)

NA, Not Available

Table 2. Included study characteristics

Procedure	First author	Year	Country	Patients, *n*	Study design	Patient selection bias
Transbronchial cryobiopsy	Babiak[22]	2009	Germany	41	Retrospective	High
	Kropski[23]	2013	USA	25	Retrospective	High
	Casoni[24]	2014	Italy	69	Prospective	High
	Fruchter[25]	2014	Israel	75	Retrospective	High
	Griff[26]	2014	Germany	52	Retrospective	High
	Pajares[27]	2014	Spain	39	RCT	Low
	Mikolasch[28]	2015	UK	14	Retrospective	High
	Hagmeyer[29]	2015	Germany	32	Retrospective	High
	Hernandez-Gonzalez[21]	2015	Spain	33	Retrospective	High
	Gershman[20]	2015	Israel	300	Retrospective	High
	Ramaswamy[19]	2016	USA	56	Retrospective	High
VATS-biopsy	Shah[30]	1992	UK	432	Retrospective	High
	Molin[31]	1994	USA	37	Retrospective	High
	Mouroux[32]	1997	France	41	Retrospective	High
	Rena[33]	1999	Italy	58	Retrospective	High
	Ayed[34]	2000	Kuwait	32	RCT	
	Qureshi[35]	2003	UK	70	Retrospective	High
	Ayed[36]	2003	Kuwait	79	Prospective	High
	Yamaguchi[37]	2004	Japan	30	Retrospective	High
	Ooi[38]	2005	UK	78	Retrospective	High
	Sakamoto[39]	2006	Japan	110	Retrospective	High
	Kreider[40]	2007	USA	68	Retrospective	High
	Quadrelli[41]	2007	Argentina	52	Retrospective	High
	Morell[42]	2008	Spain	141	Retrospective	High
	Ishie[43]	2009	Brazil	48	Retrospective	High
	Sigurdsson[44]	2009	Iceland	73	Retrospective	High
	Zhang[45]	2010	China	418	Retrospective	High
	Fibla[46]	2012	Spain	224	Prospective	High
	Kayatta[47]	2013	USA	194	Retrospective	High
	Luo[48]	2013	China	32	Retrospective	High
	Blackhall[49]	2013	UK	103	Retrospective	High
	Sonobe[50]	2014	Japan	64	Retrospective	High
	Morris[51]	2014	UK	66	Retrospective	High
	Bagheri[52]	2015	Iran	38	Retrospective	High
	Samejima[53]	2015	Japan	285	Retrospective	High
Forceps transbronchial biopsy	Hanson[54]	1976	USA	58	Retrospective	High
	Kalra[55]	1989	India	28	Retrospective	High
	Pirozynski[56]	1991	Poland	69	Retrospective	High
	Milman[57]	1994	Denmark	126	Retrospective	High
	Descombes[58]	1997	Switzerland	530	Retrospective	High
	Morell[42]	2008	Spain	252	Retrospective	High
	Romagnoli[59]	2008	Italy	33	Retrospective	High
	Pajares[27]	2014	Spain	38	RCT	Low
	Sindhwani[60]	2015	India	49	Retrospective	High
	Gershman[20]	2015	Israel	300	Retrospective	High
	Ramaswamy[19]	2016	USA	56	Retrospective	High

Table 3. Pooled analysis of studies. VATS, CI

Procedure	Studies	Total patients	Diagnostic yield, % (95% CI)	Mortality	Morbidity, % (95% CI)
Transbronchial cryobiopsy	11	704	84.4 (75.9–91.4)	0.5% (3 deaths)	Pneumothorax—10.0 (5.3–16.1) Moderate/Severe Bleeding—20.99 (5.6–42.8)
Forceps transbronchial biopsy	11	1214	64.3 (52.6–75.1)	No deaths reported	Pneumothorax—6.0 (3.2–9.6) Bleeding—10.1 (4.4–17.8)
VATS-biopsy	24	2665	91.1 (86.9–93.2)	2.3% (1.3–3.6%)	Surgical morbidity—12.9 (9.3–16.9)

VATS-biopsy is 2.3% in this literature review, which is consistent with other published work,[17] and also consistent with data from the NIS in the USA[16].

Length of stay was only reported in a limited number of studies for VATS-biopsy, giving a weighted average of 3.8 days (from 467 patients, range 2.8–5.5 days). Patient admission and length of stay

Table 4. Bleeding in transbronchial cryobiopsy literature

Study	Year	Bleeding reported
Babiak[22]	2009	No bleeding requiring intervention
Kropski[23]	2013	No bleeding requiring intervention
Casoni[24]	2014	One case of prolonged bleeding with no intervention[a]
Fruchter[25]	2014	Moderate bleeding in 3 patients (4%)
Griff[26]	2014	No bleeding requiring intervention
Pajares[27]	2014	Twenty two patients (56.4%) had moderate bleeding
Mikolasch[28]	2015	Two patients (14.3%) had moderate bleeding
Hagmeyer[29]	2015	Fifteen patients (53%) had moderate and 2 (6%) severe bleeding
Hernandez-Gonzalez[21]	2015	Seven patients (21%) had moderate bleeding
Gershman[20]	2015	Sixteen patients (5.25%) had moderate bleeding
Ramaswamy[19]	2016	One case of massive haemoptysis

[a]All cases used a Fogarty catheter to minimise bleeding.

were not reported in studies of forceps transbronchial biopsy and transbronchial cryobiopsy.

Significant heterogeneity in reporting and study methodology was noted, with statistical heterogeneity observed for diagnostic yield in studies of all diagnostic modalities (transbronchial cryobiopsy $I^2 = 80.4\%$, forceps transbronchial biopsy $I^2 = 92.9\%$, VATS-biopsy $I^2 = 96.2\%$). Risk of bias was assessed as high in the majority of studies due to their retrospective nature and the risk of reporting and selection bias.

Theoretical cost analysis

Thirty five patients are referred from the North Bristol ILD service for VATS-biopsy on average. Assuming a diagnostic yield of 84% for transbronchial cryobiopsy, six of these would also require VATS-biopsy.

Cost of transbronchial cryobiopsy was calculated at £2702 in the first year, having accounted for equipment costs and £2265 in subsequent years. Cost of VATS-biopsy was calculated at £3515. The cost saving from transbronchial cryobiopsy in the first year would be £7350, based on 35 transbronchial cryobiopsy with six patients referred for VATS-biopsy after a non-diagnostic transbronchial cryobiopsy. In subsequent years, the cost saving, assuming a constant rate of referral, would be £22652. This represents a saving of £210 per patient in the first year and £647 per patient in subsequent years.

On the assumption of reimbursement based on the HRG code DZ54Z, for complex bronchoscopy for transbronchial cryobiopsy and DZ04A, for a moderate thoracic surgical procedure for VATS-biopsy, annual savings to the CCG would be £1391, or £40 per patient.

Discussion

Summary of findings

This systematic literature review and cost analysis suggests that transbronchial cryobiopsy is associated with a diagnostic yield of 84%, which is substantially greater than the 64% seen for conventional forceps transbronchial biopsy. This is accompanied with increased rates of complications, particularly a significant risk of moderate bleeding (20.99%) requiring endobronchial intervention. The increased diagnostic yield does not match that of VATS-biopsy (91%); however, morbidity and mortality appear to be significantly lower. The overall quality of evidence is low and there is significant heterogeneity both statistically and in reporting, especially in the reporting of complications and the interventions required for these.

The new procedure, even after accounting for the costs of implementation, provides significant cost savings at both an institutional and commissioning level, while reducing the procedural risk to patients. On the basis of a purchase cost of £15000 for a cryobiopsy unit and probes (ERBE, personal communication, February 2016), the initial investment would be recouped in savings after less than 18 months.

Strengths and limitations

We acknowledge the limitations of this study. The quality of published evidence in the area of both diagnostic yield and complications from all three procedures is low. There is also significant heterogeneity in the reporting of these procedures and also in the technical details of how transbronchial cryobiopsy was performed, with a diverse range of approaches including both general anaesthetic and conscious sedation. This may limit the generalisability of findings regarding diagnostic yield and complications.

The latter point is important to highlight as there is a great diversity in the approach to transbronchial cryobiopsy.[8] The most significant issue is the risk of bleeding, which is not robustly reported in many published studies. There are approaches to minimise the risk of major bleeding, including bronchial blockers and endobronchial adrenaline, however these have not been studied systematically. One potential solution is the use of a smaller 1.1 mm cryoprobe, as reported in the only study of this by Franke et al.[18] While this appears to give an improved yield as compared to forceps transbronchial biopsy, it is at the cost of the vaunted advantage of specimen size given by other, larger cryoprobes.

There are also potential issues with the cost analysis. We have used locally estimated incurred costs for each procedure, based on financial information acquired from our institution, using the assumption of conscious procedural sedation, without anaesthetic support, in an endoscopy suite. We have also referred to the 2015-6 NHS tariffs in our calculations, which will in due course be superseded. We have made assumptions around the VATS-biopsy procedures, which can be performed as day-case operations, to deliberately under-estimate cast savings with transbronchial cryobiopsy. This cost analysis is only directly applicable to the UK NHS, however the principles underlying the calculations could be applied to other healthcare funding systems.

How this fits with previous knowledge

This work is an attempt to draw comparisons between the three main approaches to histopathological diagnosis for ILD. Previous comparisons have been made between forceps transbronchial biopsy and transbronchial cryobiopsy,[19,20] both of which concluded an increased diagnostic yield for the latter. A recent comparison has been made between VATS-biopsy and transbronchial cryobiopsy, examining diagnostic confidence in an MDT setting,[11] which concluded similar increases in confidence for the two procedures.

A systematic review of VATS-biopsy for ILD reported a diagnostic yield of 95% and post-operative mortality of 3.6%.[17] Of the 23 studies included in this review, 17 were retrospective 4 were prospective and only two were randomised. Perioperative morbidity was not reported in this study; however, significant heterogeneity of studies was highlighted. These findings are generally consistent with our own.

Only one previous cost analysis has been published, based on the Spanish healthcare system.[21] This demonstrated significant cost savings for transbronchial cryobiopsy over VATS-biopsy amounting to £47486 over 33 patients (£1439 per patient).

Guidelines advocate MDT diagnosis based on the addition of histology to the clinico-radiological appearances in cases of ILD for whom the radiology does not indicate definite a usual interstitial pneumonia (UIP) pattern.[4] The reality is that only a minority of patients with ILD are able to undergo VATS-biopsy due to the co-morbidities frequently encountered. Transbronchial cryobiopsy would allow a histological diagnosis for a greater number of patients. It has been reported that this increases diagnostic confidence in making a diagnosis of idiopathic pulmonary fibrosis in a multidisciplinary setting, with very good inter-observer correlation for the histological appearance of UIP and overall levels of confidence analogous to those seen for comparative VATS-biopsy.[11]

Conclusion

Transbronchial cryobiopsy appears to be an effective approach to histological diagnosis of ILD, however it is accompanied by a significant risk of moderate bleeding. This procedure has the potential to significantly improve confidence in making management and prognostic judgements in ILD by increasing the number of patients in whom a histological diagnosis can be made, however risks and benefits must be balanced.

Transbronchial cryobiopsy also has the potential to deliver significant cost savings as compared to VATS-biopsy since it can be undertaken by respiratory physicians with interventional bronchoscopy skills in an endoscopy suite under conscious sedation without requiring thoracic surgeon, general anaesthesia and a theatre team. Direct comparison of VATS-biopsy and transbronchial cryobiopsy through a randomised, controlled trial would be valuable to inform a transition to this new technique.

Supplementary material

Supplementary material is available at *QJMED* online.

Acknowledgments

CS, HA and AM conceived the study and reviewed studies. CS extracted and collated data and performed the cost analysis. CS and MM performed the meta-analysis. CS composed the manuscript and all authors were involved in review and approval of this.

Conflict of interest: None declared.

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Appendix 1—search strategies

Surgical Lung Biopsy

((‘lung diseases, interstitial’[MeSH Terms] OR (‘lung’[All Fields] AND ‘diseases’[All Fields] AND ‘interstitial’[All Fields]) OR ‘interstitial lung diseases’[All Fields] OR (‘interstitial’[All Fields] AND ‘lung’[All Fields] AND ‘disease’[All Fields]) OR ‘interstitial lung disease’[All Fields]) AND (‘pathology’[Subheading] OR ‘pathology’[All Fields] OR ‘biopsy’[All Fields] OR ‘biopsy’[MeSH Terms]) AND (‘thoracic surgery, video-assisted’[MeSH Terms] OR (‘thoracic’[All Fields] AND ‘surgery’[All Fields] AND ‘video-assisted’[All Fields]) OR ‘video-assisted thoracic surgery’[All Fields] OR ‘vats’[All Fields]))

Transbronchial Lung Biopsy

((‘lung diseases, interstitial’[MeSH Terms] OR (‘lung’[All Fields] AND ‘diseases’[All Fields] AND ‘interstitial’[All Fields]) OR ‘interstitial lung diseases’[All Fields] OR (‘interstitial’[All Fields] AND ‘lung’[All Fields] AND ‘disease’[All Fields]) OR ‘interstitial lung disease’[All Fields]) AND (‘pathology’[Subheading] OR ‘pathology’[All Fields] OR ‘biopsy’[All Fields] OR ‘biopsy’[MeSH Terms]) AND transbronchial[All Fields]))

Transbronchial Cryobiopsy

((‘lung diseases, interstitial’[MeSH Terms] OR (‘lung’[All Fields] AND ‘diseases’[All Fields] AND ‘interstitial’[All Fields]) OR ‘interstitial lung diseases’[All Fields] OR (‘interstitial’[All Fields] AND ‘lung’[All Fields] AND ‘disease’[All Fields]) OR ‘interstitial lung disease’[All Fields]) AND (‘pathology’[Subheading] OR ‘pathology’[All Fields] OR ‘biopsy’[All Fields] OR ‘biopsy’[MeSH Terms]) AND cryobiopsy[All Fields]))