CHEST

Pleural Cryobiopsy
A Systematic Review and Meta-Analysis

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BACKGROUND: Pleural biopsy using either video-assisted thoracoscopic surgery or medical pleuroscopy is the current diagnostic criterion standard for pleural pathology with a high, yet imperfect, diagnostic yield. Cryobiopsy may provide greater tissue, increase depth of sampled tissue, and/or reduce crush artifact. However, its impact on diagnostic yield remains uncertain, and there are potential concerns regarding its safety too. We performed a systematic review and meta-analysis to investigate the same.

METHODS: We performed a systematic search of MEDLINE, Embase, and Google Scholar for studies evaluating the performance of pleural cryobiopsy, assessing the quality of each study using the Quality Assessment, Data Abstraction and Synthesis-2 tool. Using inverse variance weighting, we performed a meta-analysis of diagnostic yield estimations. We also reviewed specimen characteristics and complications related to the procedure.

RESULTS: Seven observational studies involving 586 pleural biopsies (311 cryobiopsies and 275 flexible forceps biopsies) were evaluated. All but one study used a semi-rigid thoracoscope. Meta-analysis generated a diagnostic yield of 96.5% for cryobiopsy and 93.1% for forceps biopsy with an inverse variance-weighted OR of 1.61 (95% CI, 0.71-3.66) and an I^2 of 16%. No instances of moderate to severe bleeding were reported with cryobiopsy. A funnel plot illustrated no major publication bias.

CONCLUSIONS: Based on analysis of relatively homogenous observational data, pleural cryobiopsy is safe but does not increase diagnostic yield over flexible forceps biopsy. Adequately powered multicenter randomized trials are needed for further investigation.

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KEY WORDS: cryobiopsy; meta-analysis; pleura; pleural biopsy; pleural effusion

ABBREVIATIONS: MP = medical pleuroscopy; VATS = video-assisted thoracoscopic surgery

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Pleural biopsy is well established as the diagnostic criterion standard in the evaluation of several neoplastic and nonneoplastic pleural diseases, ranging from pleural TB and pleural sarcoidosis to malignant mesothelioma and metastatic pleural disease.[1,2] Pleural tissue sampling can be performed either percutaneously or endoscopically. Percutaneously, it can be performed either via closed pleural biopsy (using an Abrams or Cope needle) or under real-time ultrasound guidance such as with an Achieve needle (Merit Medical Systems).[3,4] Alternatively, pleural tissue can be endoscopically visualized and sampled using either medical pleuroscopy (MP) or video-assisted thoracoscopic surgery (VATS).[5] MP and VATS are overlapping procedures that essentially involve the creation of one or more chest wall entry ports, thereby permitting ipsilateral lung collapse and pleural fluid evacuation to enable pleural cavity visualization through a camera lens and simultaneous tissue sampling. Endoscopic pleural tissue sampling is typically accomplished using rigid or flexible forceps; rigid forceps are used in conjunction with standard rigid thoracoscopic instruments used for VATS that may also be used for MP, whereas flexible forceps are passed through the working channel of a semi-rigid thoracoscope with a flexible distal tip resembling that of a flexible video bronchoscope that is frequently (but not exclusively) used for MP.[6] Endoscopic pleural biopsy (via MP or VATS) has the highest diagnostic yield among all available sampling modalities, with estimates approximating 90% when pooled from multiple studies.[7]

Why is there an imperfect rate of successful diagnosis despite pleural sampling under direct endoscopic vision, and how could this yield be improved on? It is theoretically conceivable that increasing the biopsy specimen size, particularly taking a more invasive biopsy that also involves deeper layers of tissue and/or avoiding the potential for crush artifact associated with forceps biopsies could potentially improve diagnostic yield. Pleural cryobiopsy promises all of these things.

Cryobiopsy during MP/VATS involves freezing a piece of pleural tissue and removing it en bloc instead of taking a bite of tissue using forceps.[8,9] This enables acquisition of larger—and possibly better preserved—pieces of pleural tissue.[9-11] However, its impact on diagnostic performance remains uncertain, with various studies showing inconsistent trends when compared with standard forceps biopsies.[8-15] Furthermore, there is at least a theoretical safety concern related to the use of cryobiopsy; borrowing from transbronchial cryobiopsy data, the potential association of pleural cryobiopsy with increased bleeding is a valid question that warrants careful investigation.[16-18] We performed a systematic review and meta-analysis of studies published to date to investigate the diagnostic and safety profile of pleural cryobiopsy compared with forceps-based pleural biopsy.

Methods

We performed a comprehensive search of MEDLINE, Embase, and Google Scholar in March 2019 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[19] We used "cryobiopsy" OR "cryoprobe" OR "cryotechnology" AND "pleura" OR "thoracoscopy" OR "pleuroscopy" OR "pleural biopsy" OR "pleural effusion" as search terms to identify relevant studies. We applied these search terms to titles and abstracts. The bibliographies of shortlisted articles were also reviewed to identify any additional relevant studies. Conference abstract books were searched for additional studies that may have been presented but not yet published as manuscripts. We reviewed full texts of all shortlisted studies to identify all studies that met our Population, Intervention, Comparison, Outcome, Study Type criteria: patients included adult humans undergoing pleural biopsy via MP or VATS, intervention included cryobiopsy of the pleura, control included forceps biopsy of the pleura, outcome included overall diagnostic yield, and study type included observational or experimental.

Our exclusion criteria were the following: case reports or series with fewer than five subjects, nonstandardized procedures, studies with overlapping datasets, and review papers.

As previously indicated, the primary outcome of interest was overall diagnostic yield. This included malignant cases and nonmalignant cases, such as infection or nonspecific pleuritis. Of note, prolonged postprocedural follow-up would be required in the case of nonspecific pleuritis to account for the possibility of a false-negative biopsy result and the later discovery of a malignant process, as described in previous literature.[20]

Two authors (M. S. and J. S.) used the Quality Assessment, Data Abstraction and Synthesis-2 tool to assess the quality of included studies.[21] The two authors independently scored each study across the following four domains: patient selection, index test, reference standard, and flow and timing. Within each domain, the risk of bias for each included study was rated as low, high, or unclear. The first three domains were also scored for applicability (or lack thereof). Interrater agreement was calculated using Cohen kappa statistic.

Meta-analysis of the diagnostic yield estimations was performed using RevMan software version 5.3 (The Cochrane Collaboration). We used inverse variance weighting to aggregate diagnostic yield proportions across studies and to enable calculation of a pooled OR. Study heterogeneity was measured using the I^2 index, with a plan to use the fixed effects model if the I^2 index was $< 40\%$ and the random effects model otherwise. We also generated a funnel plot to assess for publication bias.

Because the study involved secondary analysis of aggregated data from previously published sources, institutional review board approval was not required.

Results

Figure 1 illustrates the study selection process. After removing duplicates across various search databases, a total of 127 unique titles and abstracts were screened. Out of these, 24 studies (12 published studies and 12 abstracts) were selected for detailed review. Where needed, we reached out to corresponding authors of the publications to try and obtain additional data. Seventeen out of these (five published studies and 12 abstracts) were ultimately excluded. Among these, six studies had overlapping study populations with one or more of the included studies and were therefore excluded to prevent duplication of patients. Eight studies were excluded because of lack of pertinent or adequate data.

A total of seven observational studies representing 586 biopsies (311 cryobiopsies and 275 flexible forceps biopsies) were analyzed.[9-15] Our assessment of study quality is available in e-Appendix 1. In most instances, the risk of bias was assessed to be low or unclear. The Cohen kappa statistic for interrater agreement in assessing study quality was 88%.

Table 1 illustrates salient features and summary data from the included studies, whereas Table 2 lists the materials and procedural techniques used in each study. Pleural biopsy was performed for diagnostic evaluation of an unexplained pleural effusion in all studies, except that 10% of the patients reported by Chen et al[15] underwent pleural biopsy for purposes of ancillary testing in the setting of known metastatic non-small cell lung cancer and one patient in the Thomas et al cohort[11] had pleural thickening without pleural effusion. All studies used both cryobiopsies and flexible forceps biopsies, whereas all but one study used a semi-rigid thoracoscope. Wurps et al[12] used a rigid thoracoscope instead, and sequentially used rigid forceps (four samples), flexible forceps (one to two samples), and the cryoprobe (one to two samples); only the latter two techniques were included in our analysis for purposes of consistency. In all studies except one, both cryobiopsy and flexible biopsy were performed on the same patient; in Tousheed et al,[14] the first 52 consecutive patients underwent only flexible forceps biopsy because of unavailability of cryobiopsy equipment and the final 87 consecutive patients underwent only cryobiopsy with no change in the procedural indication.

Studies used a variable length of postprocedural follow-up for nonmalignant biopsy results; where reported, this ranged from 6 to 12 months (Table 1).

Meta-analysis yielded a pooled diagnostic yield of 96.5% for cryobiopsies and 93.1% for flexible forceps biopsies with an inverse variance-weighted OR of 1.61 (95% CI, 0.71-3.66) and an I^2 (heterogeneity index) of

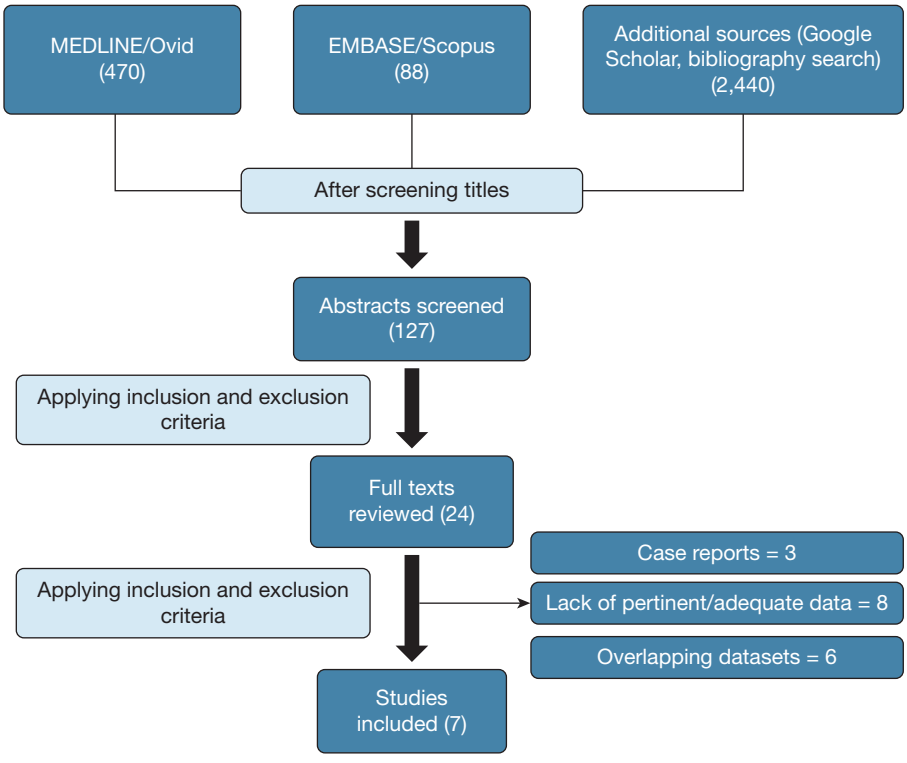

Figure 1 – *Flowchart illustrating the study selection process.*

TABLE 1] Summary of Included Studies

Study/Year	Study Design	Selection Criteria	Age (y)[a]	% of Total Females	Minimum Length of Follow-Up for Patients With Nonspecific Pleuritis on Biopsy (mo)	Cryobiopsy Yield (Diagnostic Cases/ Total Cases)	Flexible Forceps Biopsy Yield (Diagnostic Cases/ Total Cases)
Rozman et al[9]/2016	Prospective observational	Unexplained unilateral pleural effusion	61 (33-83)	20	12	14/14	15/15
Maturu et al[10]/2015	Case series	Unexplained exudative pleural effusion	50	33	Unknown	6/6	3/4
Thomas et al[11]/2015	Retrospective	Unexplained pleural effusion	72 (47-89)	5	6	20/22	20/22
Wurps et al[12]/2016	Prospective observational	Unexplained exudative pleural effusion	67.5 ± 13.5	Unknown	Unknown	73/80	74/80
Pathak et al[13]/2017	Prospective observational	Unexplained exudative pleural effusion	69 ± 11	50	8	10/10	10/10
Tousheed et al[14]/2018	Retrospective	Unexplained exudative pleural effusion	54.51 ± 14.99	46, 44[b]	Unknown	86/87	50/52
Chen et al[15]/2018	Prospective observational	Unexplained pleural effusion (90%); NSCLC genotyping (10%)	64 (22-92)	35	Unknown	91/92	84/92

NSCLC = non-small cell lung cancer.
[a]Values are mean ± SD, mean, or median (range).
[b]46% of patients undergoing cryobiopsy; 42% of patients undergoing flexible forceps biopsy.

TABLE 2] Materials and Methods Used Across Individual Studies

Study/Year	Cryoprobe Size (mm)	Freezing Time (s)	No. of Cryobiopsies	No. of Flexible Biopsies
Rozman et al[9]/2016	2.4	3-6	3	Unknown
Maturu et al[10]/2015	1.9	3	≥ 3	6-8
Thomas et al[11]/2015	2.4	3	Unknown	15-20
Wurps et al[12]/2016	2.4	Unknown	1-2[a]	1-2
Pathak et al[13]/2017	2.4	3	≥ 3	≥ 3
Tousheed et al[14]/2018	2.4	6-10	≥ 2-3	Unknown
Chen et al[15]/2018	1.9	3	4	Unknown

[a]In this study, four rigid forceps biopsies were also obtained per patient.

16%. Figure 2 shows the forest plot for this meta-analysis.

Table 3 summarizes the results of secondary outcomes of interest. Studies consistently showed larger specimen sizes with cryobiopsy; the specific metric used to denote size differed across studies. Three studies also reported fewer instances of crush artifact.[10,11,15] None of the studies reported any instances of major bleeding with cryobiopsy; the definition of major bleeding was not uniformly stated, however.

A funnel plot illustrated no obvious publication bias (Fig 3).

Discussion

Our systematic review and meta-analysis of published observational data to date showed that pleural cryobiopsy is safe and consistently yielded larger tissue specimens than flexible forceps biopsy. However, cryobiopsy is not associated with a statistically significant improvement in diagnostic yield. These findings are based on a review of seven observational studies with relatively low heterogeneity and a low to indeterminate overall risk of bias.

To our knowledge, this is the first systematic review and meta-analysis evaluating pleural cryobiopsy as a diagnostic tool. Given the growing interest in use of cryotechnology across areas relevant to interventional pulmonology and thoracic surgery, and given the current absence of multicenter randomized trial data on this subject, this study is both timely and crucial in advancing our understanding of the role of cryobiopsy in pleural tissue sampling.[6,7,22]

The ability of cryobiopsy to yield comparatively larger tissue specimens is intuitively obvious. The flexible forceps have fairly limited jaw opening (available sizes include 2.0 and 2.8 mm) and can therefore only be expected to provide modest biopsy sizes. The adherent and activated cryoprobe, on the other hand, can tear off large pieces of tissue when it is pulled off of the surface of the pleura. Furthermore, this mechanism also results

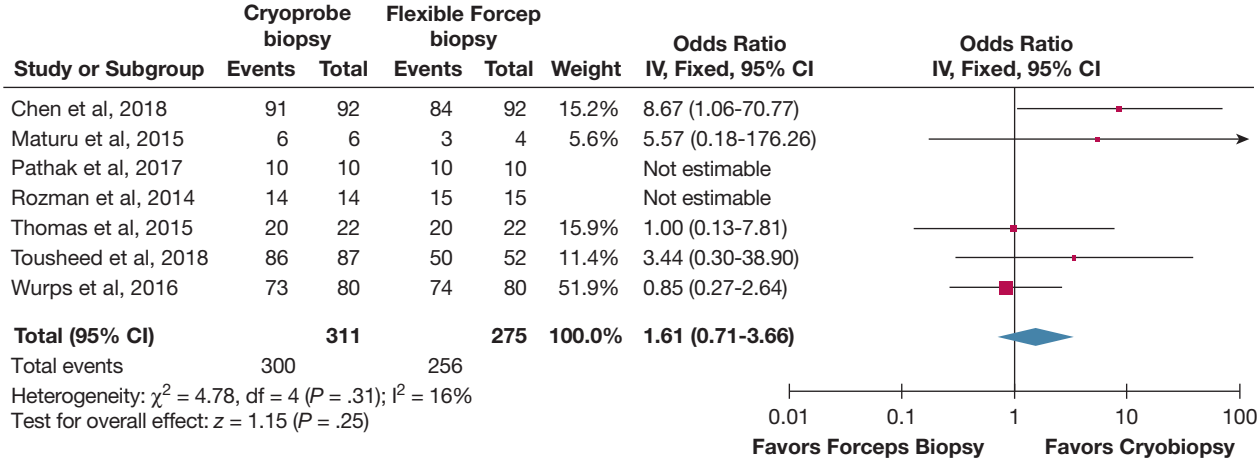

Figure 2 – *Meta-analysis of diagnostic yield based on biopsy technique. IV = inverse variance.*

TABLE 3] Specimen Characteristics and Bleeding Rates

Study/Year	Cryobiopsy: Average Specimen Size (Metric)	Flexible Forceps Biopsy: Average Specimen Size (Metric)	Cryobiopsy: Rate of Major Bleeding (Total Occurrences/Total Cases)	Flexible Forceps Biopsy: Rate of Major Bleeding (Total Occurrences/Total Cases)
Rozman et al[9]/2016	NR	NR	0/14	0/15
Maturu et al[10]/2015	9.17 ± 1.84 mm[a] (depth; mean ± SD)	3.75 ± 0.96 mm (depth; mean ± SD)	0/6	NR
Thomas et al[11]/2015	10 (7-15.8) $mm^{2,a}$ (cross-sectional area; median, range)	4 (3-8) mm^2 (cross-sectional area; median, range)	0/22	0/22
Wurps et al[12]/2016	14.4 ± 12.8 $mm^{2,a}$ (surface area; mean ± SD)	7.1 ± 9.3 mm^2 (surface area; mean ± SD)	0/80	0/80
Pathak et al[13]/2017	320 $mm^{3,a}$ (mean cumulative tissue volume)	80 mm^3 (mean cumulative tissue volume)	NR[b]	NR[b]
Tousheed et al[14]/2018	13.2 ± 6.7 mm[a] (size; mean ± SD)	6.8 ± 3.3 mm (size; mean ± SD)	0/87	0/52
Chen et al[15]/2018	9.1 ± 4.5 mm[a] (size; mean ± SD)	4.0 ± 2.1 mm (size; mean ± SD)	0/92	0/92

NR = not reported.
[a]*P* value for comparison with flexible forceps biopsy < .05.
[b]Authors reported that there was no morbidity or mortality among these groups of patients.

in fewer instances of crush artifact than forceps biopsy.[10,11,15] Nonetheless, available data does not demonstrate a statistically significant improvement in diagnostic yield with the use of cryobiopsy.

A few caveats need to be borne in mind before generalizing these findings. First and foremost, our findings are limited by the observational nature of included studies. Second, the number and size of available studies on this subject is relatively limited, thereby limiting the statistical power of our analyses (number of subjects undergoing cryobiopsy: 311; number of subjects undergoing flexible forceps biopsy: 275). One of the problems with pleural cryobiopsy is that there is no standardized methodology to perform it. Table 2 illustrates some of the variations in materials and methods used across individual studies, including cryoprobe size and freezing time. Similarly, there are considerable variations in the practice of flexible forceps biopsy, such as using 2.0- vs 2.8-mm forceps, using serrated vs cupped vs spiked forceps, using a peeling vs nonpeeling biopsy technique, and going back to the same biopsy site for additional biopsies or not. Whether or not these factors impact diagnostic yield remains to be studied.

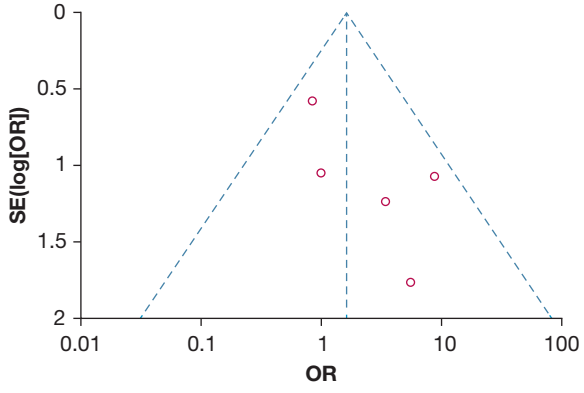

Figure 3 – *Funnel plot illustrating diagnostic yield estimates of included studies (expressed as ORs).*

Importantly, our analysis only compares cryobiopsy with flexible forceps biopsy and not with rigid forceps biopsy. Previously published studies comparing rigid vs flexible forceps point to similar diagnostic yields from the two techniques, with the possible exception of rigid thoracoscopic biopsy being superior in cases requiring simultaneous lysis of adhesions.[23-25] Using a rigid thoracoscope can also be considered advantageous from the point of view of being potentially more freely available in resource-limited settings, being a cheaper alternative to the semi-rigid thoracoscope, and being less prone to damage. Cryobiopsy, which can also be performed using the rigid thoracoscope, can potentially retain these advantages independently of its promise as a diagnostic tool. The only study that compared rigid forceps biopsy with cryobiopsy showed that rigid forceps biopsy was superior to cryobiopsy, whereas there was no significant difference between flexible forceps biopsy and

cryobiopsy.[12] Why would this be the case? It is conceivable that the 3-mm rigid forceps bite off larger pieces of tissue and cause less tissue shearing than the smaller-sized flexible forceps. It is also conceivable that rigid forceps preserve the tissue architecture better than cryobiopsy's freeze-thaw treatment—even though freeze artifacts were not reported in the study. However, we recommend against drawing definitive conclusions from this single-center observational study that compared four rigid biopsies per patient with one to two cryobiopsies per patient (Table 2). A multicenter, randomized study is needed for further investigation.

Could it be that cryobiopsy has a role to play in only certain subsets of patients? For example, none of the studies included in our analysis differentially analyzed cryobiopsy of an endoscopically visualized pleural nodule as opposed to the parietal pleura itself. It is not inconceivable that the yield of cryobiopsy might be different based on the specific findings visualized during thoracoscopy. It is generally understood that there is a distinct need for sampling deeper layers of tissue (including adjoining adipose tissue) to optimize diagnostic yield for malignant mesothelioma; therefore, cryobiopsy could well be a potentially superior strategy in settings with higher prevalence of asbestos-related pleural disease.[10,26,27] Another question relevant to the current era of ancillary testing for malignancies would be whether cryobiopsy improves the rate of acquiring sufficient tissue to permit all ancillary testing (eg, immunohistochemical staining for programmed death-ligand 1 expression, genetic testing for driver oncogenes). Whether cryobiopsy has a role in that setting also remains to be systematically investigated.

In addition to a lack of obvious diagnostic superiority, widespread enthusiasm for pleural cryobiopsy is likely also hindered by the theoretical risk of increased complications, particularly major bleeding.

Comparatively higher bleeding rates have been demonstrated in multiple studies involving transbronchial cryobiopsy of the lung, making this a valid concern.[16-18] Theoretically, it makes sense that an abrupt detachment of the cryoprobe and adjoining frozen pleura could shear pleural tissue and adjacent blood vessels in unpredictable ways and increase the prospects of a major bleeding secondary to vessel rupture. On the other hand, forceps biopsy may theoretically offer a more precise application of injury to the pleural tissue that the operator could direct away from intercostal vessels using their anatomic knowledge and visual-spatial awareness. In this review of 311 cryobiopsy procedures, major bleeding was not reported in even one instance; however, studies did not uniformly identify what would and would not have constituted as such. What also limits the interpretability of these data is the lack of a uniform freezing time across studies, which would correlate with the depth of biopsy and therefore the extent of cryobiopsy's impact on tissue structures (Table 2). Furthermore, several of the analyzed studies were retrospective in nature, making it less likely that all bleeding episodes were reliably captured. Until more rigorous data on this subject become available, this question cannot be deemed to have been definitively addressed.

In summary, based on analysis of all available published data, pleural cryobiopsy appears safe but does not appear to increase diagnostic yield over flexible forceps biopsy under thoracoscopic visualization. Nonetheless, it does appear to be a promising tool with a potential to increase diagnostic yield, tissue sufficiency, or both—at least in a subset of patients depending on risk factors and/or endoscopic findings. Rigid forceps biopsy as a third alternative may potentially hold promise too, based on results from a single-center study. Adequately powered, multicenter, randomized trials are needed for further investigation.

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Additional information: The e-Appendix be found in the Supplemental Materials section of the online article.

References

1. Hooper C, Lee YC, Maskell N. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease guideline 2010. *Thorax*. 2010;65(suppl 2):ii4-ii17.
2. Feller-Kopman D, Light R. Pleural disease. *N Engl J Med*. 2018;378(18):1754.
3. Kirsch CM, Kroe DM, Jensen WA, Kagawa FT, Wehner JH, Campagna AC. A modified Abrams needle biopsy technique. *Chest*. 1995;108(4):982-986.
4. Koegelenberg CF, Bolliger CT, Theron J, et al. Direct comparison of the diagnostic yield of ultrasound-assisted Abrams and Tru-Cut needle biopsies for pleural tuberculosis. *Thorax*. 2010;65(10):857-862.
5. Loddenkemper R, Lee P, Noppen M, Mathur P. Medical thoracoscopy/pleuroscopy: step by step. *Breathe*. 2011;8(2):156-167.
6. Lee P, Folch E. Thoracoscopy: advances and increasing role for interventional pulmonologists. *Semin Respir Crit Care Med*. 2018;39(6):693-703.
7. Murthy V, Bessich JL. Medical thoracoscopy and its evolving role in the diagnosis and treatment of pleural disease. *J Thorac Dis*. 2017;9(suppl 10):S1011-S1021.
8. Bonniot JP, Homasson JP, Roden SL, Angebault ML, Renault PC. Pleural and lung cryobiopsies during thoracoscopy. *Chest*. 1989;95(3):492-493.
9. Rozman A, Camlek L, Marc Malovrh M, Kern I, Schonfeld N. Feasibility and safety of parietal pleural cryobiopsy during semi-rigid thoracoscopy. *Clin Respir J*. 2016;10(5):574-578.
10. Maturu VN, Sehgal IS, Dhooria S, et al. Pleuroscopic cryobiopsy: case series and systematic review. *J Bronchology Interv Pulmonol*. 2015;22(3):e11-e13.
11. Thomas R, Karunarathne S, Jennings B, et al. Pleuroscopic cryoprobe biopsies of the pleura: a feasibility and safety study. *Respirology*. 2015;20(2):327-332.
12. Wurps H, Schonfeld N, Bauer TT, et al. Intra-patient comparison of parietal pleural biopsies by rigid forceps, flexible forceps and cryoprobe obtained during medical thoracoscopy: a prospective series of 80 cases with pleural effusion. *BMC Pulm Med*. 2016;16(1):98.
13. Pathak V, Shepherd RW, Hussein E, Malhotra R. Safety and feasibility of pleural cryobiopsy compared to forceps biopsy during semi-rigid pleuroscopy. *Lung*. 2017;195(3):371-375.
14. Tousheed SZ, Manjunath PH, Chandrasekar S, et al. Cryobiopsy of the pleura: an improved diagnostic tool. *J Bronchology Interv Pulmonol*. 2018;25(1):37-41.
15. Chen CH, Cheng WC, Wu BR, et al. Feasibility and safety of pleuroscopic cryobiopsy of the pleura: a prospective study. *Can Respir J*. 2018;2018:6746470.
16. Sethi J, Ali MS, Mohananey D, Nanchal R, Maldonado F, Musani A. Are transbronchial cryobiopsies ready for prime time?: a systematic review and meta-analysis. *J Bronchology Interv Pulmonol*. 2019;26(1):22-32.
17. Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease. a systematic review and metaanalysis. *Ann Am Thorac Soc*. 2016;13(10):1828-1838.
18. Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. *QJM*. 2017;110(4):207-214.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341.
20. Janssen J, Maldonado F, Metintas M. What is the significance of non-specific pleuritis? A trick question. *Clin Respir J*. 2018;12(9):2407-2410.
21. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Int Med*. 2011;155(8):529-536.
22. Shafiq M, Lee H, Yarmus L, Feller-Kopman D. Recent advances in interventional pulmonology. *Ann Am Thorac Soc*. 2019;16(7):786-796.
23. Khan MA, Ambalavanan S, Thomson D, Miles J, Munavvar M. A comparison of the diagnostic yield of rigid and semirigid thoracoscopes. *J Bronchology Interv Pulmonol*. 2012;19(2):98-101.
24. Dhooria S, Singh N, Aggarwal AN, Gupta D, Agarwal R. A randomized trial comparing the diagnostic yield of rigid and semirigid thoracoscopy in undiagnosed pleural effusions. *Respir Care*. 2014;59(5):756-764.
25. Rozman A, Camlek L, Marc-Malovrh M, Triller N, Kern I. Rigid versus semi-rigid thoracoscopy for the diagnosis of pleural disease: a randomized pilot study. *Respirology*. 2013;18(4):704-710.
26. Rokicki W, Rokicki M, Wojtacha J, Rydel MK. Malignant mesothelioma as a difficult interdisciplinary problem. *Kardiochir Torakochirurgia Pol*. 2017;14(4):263-267.
27. Arif Q, Husain AN. Malignant mesothelioma diagnosis. *Arch Pathol Lab Med*. 2015;139(8):978-980.