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Is the diagnostic yield of mediastinal lymph node cryobiopsy (cryoEBUS) better for diagnosing mediastinal node involvement compared to endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)? A systematic review

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ABSTRACT

Introduction: New tools such as cryobiopsy of mediastinal lymph nodes (cryoEBUS) have been described to improve the diagnostic usefulness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The literature suggests that this novel procedure could be associated with greater diagnostic usefulness than conventional EBUS-TBNA.

Methods: To develop a systematic analysis and meta-analysis on the diagnostic diagnostic yield and safety of cryobiopsy of hilar and mediastinal adenopathies compared to EBUS-TBNA.

Results: Seven studies that had included a total of 555 patients were considered in this review, with 365 (65.7%) of these patients having an etiology of malignant lymph node involvement. The overall diagnostic usefulness of cryoEBUS was higher compared to EBUS-TBNA (92% vs. 80%). However, when the results were analysed according to the specific aetiologies of the adenopathies, cryoEBUS was especially useful in cases of lymphomas or non-pulmonary carcinomas (83% vs. 42%) and in cases that were benign (87% vs. 60.1%), with no significant differences being found in specific cases of lung cancer. For lymphoma, cryoEBUS was diagnostic in 87% of cases compared to 12% for EBUS-TBNA and in addition, also allowed the characterisation of every lymphoma subtype. Genetic studies and immunohistochemical determination of PD-L1 was possible in almost all (97%) of the samples obtained by cryoEBUS, while this was only possible in 79% of those obtained by EBUS-TBNA. The most frequent complication was light bleeding, which was described in up to 85% of cases in some series.

Conclusion: CryoEBUS could represent a promising technique in the diagnostic algorithm used for mediastinal and hilar involvement. Although cryoEBUS did not significantly improve the diagnosis of lung cancer compared to EBUS-TBNA, the results were significantly better in patients with benign pathologies and other tumour types, including lymphomas. In addition, it seems that the samples obtained by cryoEBUS better defined the histological subtypes of lymphoma and allowed complete molecular characterisation in cases of lung cancer. The technique has proven to be safe and no serious complications were described after the procedure.

1. Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is currently the technique of choice for the study of hilar and mediastinal lymph nodes. The diagnostic yield, safety profile, and cost-effectiveness results compared to the gold standard technique, mediastinoscopy, make EBUS-TBNA the initial procedure of choice for intrathoracic lymphadenopathy [1–3]. The use of EBUS-TBNA has become paradigmatic for the diagnosis and staging of thoracic neoplasms. However, it also has other important indications such as in the characterisation of benign processes that affect the mediastinum, such as granulomatous diseases [1,4,5].

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In the specific case of non-small cell lung cancer (NSCLC), despite the fact that EBUS-TBNA shows a high level of diagnostic sensitivity, in approximately 5% of cases, the amount of tissue obtained is insufficient to establish a molecular diagnosis, which is essential in advanced cases [6]. Furthermore, published studies have shown a lower overall sensitivity in cases in which EBUS-TBNA was used to re-staging NSCLC after induction treatment [1]. However, the indication for EBUS-TBNA is more controversial in the case of mediastinal involvement in lymphoproliferative processes [1,2]. Although study by flow cytometry and immediate evaluation by a pathologist could improve the sensitivity of the technique, the samples are insufficient for the histopathological characterisation of lymphomas in up to 33% of cases. Indeed, difficulties in obtaining a diagnosis have been reported even in benign pathologies such as fibrotic phase sarcoidosis or tuberculous lymphadenitis.

In order to obtain a larger sample volume and improve the diagnostic usefulness of ultrasonography, the results obtained with different needle sizes and/or aspiration techniques have been studied, but with these variables having had little effect [2]. Other new tools such as mediastinal lymph node biopsy have shown good results, but with a high percentage of complications [5].

From among these alternatives, cryobiopsy is a technique based on the freezing, crystallization and subsequent recovery of tissue which has proven to be an excellent tool for the diagnosis of endobronchial and peripheral pulmonary lesions [7,8]. A study by Hetzel et al. describing their experience with endobronchial cryobiopsy showed that the diagnostic usefulness of these samples was greater than those obtained through conventional forceps biopsy (95% vs. 85%; $p = 0.001$) [8].

More recently, a prospective study that evaluated the accuracy of radial-EBUS-guided transbronchial cryobiopsies of peripheral pulmonary nodules also demonstrated greater diagnostic accuracy compared to conventional biopsy (87% vs. 82%) [9]. In addition, in recent years, new indications have been developed for this technique. In particular, cryobiopsy is safe and potentially useful in patients with suspected interstitial lung disease [10]. Medical thoracoscopy with pleural cryobiopsy has also proven to be highly useful for diagnostic of pleural effusion [11]. Thus, new applications such as cryobiopsy of mediastinal lymph nodes or cryoEBUS have been described to try to improve the diagnostic yield of EBUS-TBNA [12–14].

In fact, pioneers in the technique, Zhang A.M. and Herth F.J., recently demonstrated excellent results with this technique [12,13]. On the one hand, they found that the diagnostic usefulness of the combination of EBUS-TBNA and cryobiopsy for diagnostic of mediastinal lesions exceeded 90% and had an acceptable safety profile. On the other hand, cryobiopsy improved both the characterisation of other tumours such as lymphomas and the molecular diagnosis in cases of advanced NSCLC [12,13]. Since then, moregroups have published their results and have introduced some variants to the technique [14]. The literature suggests that the diagnostic value of cryobiopsy or cryoEBUS could be greater than that of conventional EBUS-TBNA for the diagnosis of mediastinal adenopathies.

Systematic reviews and meta-analyses are one of the important tools of evidence-based medicine and are used to support medical decisions on aspects related to diagnosis and/or treatment and are considered essential when preparing clinical practice guidelines. This type of publication constitutes the highest level of scientific evidence. Several publications aiming to analyse the value and safety of cryobiopsy in other pathologies such as interstitial lung disease, lung tumours, or pleural effusion have already been published [11,15].

Hence, the objectives of this present study were to review the published evidence on the diagnostic yield and safety of the cryobiopsy of hilar and mediastinal adenopathies by performing a grouped systematic analysis and meta-analysis of the literature and evaluating certain aspects of these studies, such as the implementation of this novel diagnostic technique in routine clinical practice.

2. Methods

We conducted a systematic review of the literature published up to March 2023 according to the items described in the PRISMA statement for systematic reviews and meta-analyses [16]]. A literature search for studies related to cryobiopsy of mediastinal lymph nodes was carried out in the PubMed (MEDLINE), Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov electronic databases. The terms used in the search were “lymph node cryobiopsy”, “transbronchial mediastinal cryobiopsy”, “cryo-nodal biopsy”, “cryo-biopsy EBUS”, and “mediastinal cryobiopsy”. To avoid the loss of studies or reviews not found in the electronic search we manually searched references of the included studies and main clinical practice guidelines. Meta-analyses, systematic and narrative reviews, cohort studies, case-control studies, and case series were included in the search. The search was not limited to any language. The inclusion criteria were studies that analysed the diagnostic yield and/or safety of cryobiopsies of mediastinal and/or hilar lymph nodes as their main objectives. Studies not conducted in humans or that had not been peer-reviewed were excluded.

Two authors (M.B.R. and I.L.R.) independently readed the abstracts for eligibility and excluded any studies that did not meet the inclusion criteria. Discrepancies were resolved by discussion with a third author (A.F·V.). The full texts of eligible studies were obtained and independently reviewed by the first two authors (M.B.R. and I.R.L.). The relevant information from each of the studies was collected using evidence tables.

The main variables described were the diagnostic yield of the lymph node samples obtained by the cryoprobe compared to those obtained by EBUS-TBNA and any complications. The technique was considered diagnostic when a specific histopathological diagnosis was obtained or when lymph node cellularity or non-specific inflammation was found, excluding other possible causes of lymphadenopathy.

Complications were classified as haemorrhage or bleeding that was minor (1 and 2; controlled with conservative management and cold saline and/or topical adrenaline) or moderate (3 and 4; if accompanied by haemodynamic instability and the need for vasoactive drugs) as well as infectious complications including mediastinitis, sepsis, or bacteraemia, pneumothorax, pneumomediastinum, respiratory failure, or death [17].

Regarding the procedure, we analysed the size of the cryoprobe, and the needle used for puncture aspiration and the technique used, the freezing time of the cryoprobe (in seconds), number of passes, and the mean diameter of the punctured adenopathy. The type of sedation during echobronchoscopy was also noted.

In general, the clinical-epidemiological characteristics of the patients (age and sex) and the specific etiology of the lymph node pathologies were also described.

2.1. Assessment of the quality of the included studies and statistical analysis

The quality of the studies was assessed following the levels of evidence and degrees of recommendation described in the scientific guidelines [16,18]. Moreover, we summarised the QUADAS-2 assessment results of all the studies included in this systematic review. In addition to the systematic review, we aimed to conduct a meta-analysis, including analysis of the sensitivity, specificity, diagnostic usefulness, and percentage of complications. However, because of the limited number of studies and their heterogeneity, this was not possible and so only a qualitative synthesis of the results was performed.

3. Results

3.1. Overview of the reviewed studies

We identified 33 potentially eligible studies for screening. Of these,

24 were excluded after reading the title and abstract, one of them because it had been conducted in animals [19]. The full text of 9 articles were reviewed, after which 2 were excluded because their main objective differed to that of this present study [20,21]. Thus, only 7 articles were finally included in the pooled analysis [12–14,22–25].

The general characteristics of these studies are represented in Table 1. These articles had included a total of 555 patients and all 7 studies had prospective designs. In 5 of them, only the value of cryobiopsy was compared with EBUS-TBNA [14,22–25]. In one of the multicentre studies with the most cases, cryobiopsy combined with EBUS-TBNA was compared with blind TBNA [13], and the other large study also analysed whether the order of the technique used (cryobiopsy vs. needle) had influenced the diagnostic yield [12]. The cryoprobe puncture technique also differed between the studies; in 2 of them, a hight-frecuency needle-knife had been used first followed by introduction of the cryoprobe [12,13], while in the rest of the studies the procedure had been carried out by introducing the cryoprobe through the needle orifice, slowly pushing the cryoprobe with or without the help of the sheath [14,22–25]. The freezing time had been variable, and ranged from 3 to 7 s (Table 1).

3.2. Description of the study population

Most of the patients studied were men (65.7%; Table 2). The most frequent cause of lymph node involvement was neoplasms, found in 366 (65.9%) of the patients. Table 2 specifies, in detail, the specific aetiologies of the adenopathies. Node stations 7 and 4R were the most frequently punctured (Table 2).

3.3. Diagnostic efficacy

Compared to EBUS-TBNA alone, the overall diagnostic yield of cryoEBUS was significantly higher in the two large randomised trials [12,13]. However, when the results were analysed based on the specific aetiologies of the adenopathies, the greatest usefulness of the technique was in cases of lymphomas or non-pulmonary carcinomas and when these were benign, without finding significant differences in patients with lung cancer [10,11] (Table 3). Except, one study, the diagnostic yield for cryoEBUS was 92% and for EBUS-TBNA 78% [25].

In the specific case of lymphoma, the diagnostic yield of cryoEBUS compared to EBUS-TBNA was 80% and 50%, respectively in the study by Fan et al. [13] with 13 patients, and in the study by Zhang et al. [12], examining 8 lymphoma cases, it was 87% vs. 12% while also allowing the characterisation of every lymphoma subtype. In his first study, Ariza-Prota et al. [14] only included one case of lymphoma, and although EBUS-TBNA had also been diagnostic in this case, only cryoEBUS had been able to type the specific lymphoma subtype. More late, they conducted a posterior trial and all patients (4 cases) were diagnosed of lymphoma only with cryoEBUS [25].

Unlike the other studies included, in the work by Genova et al. [22], which had only examined 5 patients, EBUS-TBNA had had a higher diagnostic value. However, although both techniques were diagnostic, cryoEBUS and not EBUS-TBNA had allowed the characterisation of the lymphoma subtype [22].

The usefulness of these techniques for the molecular study of NSCLC was specifically addressed in 3 studies. In the work of Zhang et al., 93% of the cryobiopsies had been adequate for the study of mutations, compared to 73% of the samples obtained by EBUS-TBNA [12]. In the study by Fan et al. genetic studies and immunohistochemical determination of PD-L1 had been possible in almost all of the samples obtained by cryoEBUS, 97%, while this was only possible in 79% of those obtained by EBUS-TBNA ($p = 0.03$) [13]. In the Genova and Ariza-Prota series, cryoEBUS had allowed the molecular study of all the patients with NSCLC that had been included [14,22]. In last study, cryoEBUS diagnosed 6 cases of lung adenocarcinoma and 4 cases of squamous cell lung carcinoma that had been previously classified by EBUS-TBNA as insufficient sample. In all cases in wich a definite diagnosis of lung cancer was obtained by cryobiopsy, it allowed to perform an optimal molecular testing [25].

The order of the biopsy device used (needle or cryoprobe first) had not influenced the diagnostic yield of these techniques [12].

Table 1
Study characteristics.

	Desing	N	Equipament used	Small incision in the wall	Procedure	Number passes	Time rapid cooling
Zhang J (2021)[13]	Open-lavel, randomised multicentre	197[a]	22G or 21 G needle cryo-probe 1,1 mm NO ROSE	High-frequency needle-knife	Moderate sedation	4 passes of TBNAs more 3 passes with cryo-probe	7 s
Fan E (2022)[14]	Randomised trial, multicentre	271[c]	Needle ¿? cryo-probe 1,1 mm NO ROSE	High-frequency needle-knife	Conscious sedation	4 passes of TBNAs more 1 passe with cryo-probe vs 4 passes of TBNAs	7 s
Genova C (2022)[23]	Prospective, 1 centre	5	19G needle cryo-probe 1,1 mm NO ROSE	Advancing the cryo-probe by previous puncture site	Moderate sedarion	3 passes of TBNAs vs 2 with cryo-probe	4 s
Gershman E (2022)[24]	Prospective, 1 centre	27″	22G needle cryo-probe 1,1 mm or 1,7 mm[b] NO ROSE	Fluoroscopy. Laser YAG or Advancing the cryo-probe by previous puncture site	Moderate sedarion and laryngeal mask	2-4 passes of TBNAs vs 2–4 with cryo-probe	3–4 s
Gonuguntla HK (2021)[25]	Prospective, 1 centre	4	21G, 19G y 22G needle cryo-probe 1,1 mm ROSE	Advancing the cryo-probe by previous puncture site	–	TBNA vs 1–2 with cryo-probe	3 s
Ariza-Prota MA (2022)[15]	Prospective, 1 centre	4	22G needle, cryo-probe 1,1 mm ROSE	Advancing the cryo-probe by previous puncture site	Conscious sedation	4 passes of TBNAs vs 3 with cryo-probe	3 s
Ariza-Prota MA (2022)[26]	Prospective, 2 centres	50	22G needle, cryo-probe 1,1 mm NO ROSE	Advancing the cryo-probe by previous puncture site	Conscious sedation	TBNAs vs 3 with cryo-probe	4 s

ROSE = *rapid on site-evaluation*; TBNA = *transbronchial needle aspiration*.
[a] 2 patients lost to follow-up, and 1 patient not tolere the procedure.
[b] Cryo-probe 1,1 mm (N = 16) and cryo-probe 1,7 mm (N = 8)**.
[c] 4 patients lost to follow-up; ” 3 patients lost to follow-up.

Table 2
Demographic, clinical and pathological characteristics of the cohort.

	Age (years)	Sex (Male)	Etiology	Etiology	Lesion station Lesion short axis diameter (cm)	Lesion station only cryobiopsy
Zhang J (2021)[13]	57.6 (15–88)	117 (59%)	Malignant: 147 (75.7%) Benign: 47 (24.2%)	NSCLC 109 (56%) SCLC 26 (13.2%) Lymphoma 8 (4.1%) Others tumours 4 (2%) Sarcoidosis 15 (7.7%) Tuberculosis 16 (8.2%) Pneumoconiosis 7 (3.6%)	7 and 4R 2.2(1–8.6)	7 (n = 49) 4R (n = 67) 2R (n = 4) 4L (n = 19) 2L (n = 3) 12R (n = 4) 11R (n = 14) 10R (n = 18) 12L (n = 2) 11L (n = 7) 10L (n = 10)
Fan E (2022)[14]	56.7	165 (60.8%)	Malignant: 159 (59.3%) Benign: 77 (28.7%) No diagnosis: 32 (11.9%)	NSCLC 82 (30.5%) SCLC 44 (16,4%) Others tumours 20 (7,4%) Lymphoma 13 (4.8%) Sarcoidosis 28 (10,4%) Tuberculosis 30 (11.9%) Pneumoconiosis 19 (7%)	7 and 4R 2.1 ± 0.8	7 (n = 47) 13R (n = 1) 12R (n = 2) 11R (n = 15) 10R (n = 2) 4R(n = 30) 2R(n = 4) 13L (n = 1) 11L (n = 6) 10L (n = 6) 4L (n = 16) 2L (n = 6)
Genova C (2022)[23]	64	5 (100%)	Malignant: 3 (60%) Benign: 1 (20%) No diagnosis: 1 (20%)	NSCLC 1 (20%) SCLC 1 (20%) Lymphoma 1 (20%) Benign 1 (20%) No diagnosis 1 (20%)	7	7 (n = 4) 10R (n = 1)
Gershman E (2022)[24]	60.12 ± 10.16	17 (70.8%)	Malignant 13 (48.1%) Benign: 11 (40.7%) No diagnosis 3 (11%)	NSCLC 8 (29,6%) SCLC 2 (7,4%) Others tumours 3 (11,1%) Sarcoidosis 11 (40,7%) No diagnosis 3 (11%)	7 >1	7 (en todos los casos)
Gonuguntla HK (2021)[25]	–	–	Malignant: 2 (50%) Benign: 2 (50%)	NSCLC 1 (25%) Others tumours 1 (25%) Tuberculosis 1 (25%) Sarcoidosis 1 (25%)	7 and 11L >1	7 (n = 3) 11L (n = 3) 4L (n = 1)
Ariza-Prota MA (2022)[15]	60.25	2 (50%)	Malignant 3 (75%) Benign 1 (25%)	NSCLC 1 (25%) SCLC 1 (25%) Lynphoma 1 (25%) Benign 1 (25%)	7 0.53	7 (n = 3) 11R (n = 1)
Ariza-Prota MA (2022)[26]	63 ± 11.8	32 (64%)	Malignant 38 (76%) Benign 12 (24%)	–	7 and 4R 25.66 ± 8.78 and 17,33 ± 8.35	7 (n = 24) 4R (n = 7) 4L (n = 3) 2R (n = 1)

NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer.

Tabla 3
Diagnostic yields of EBUS-TBNA and cryobiopsy.

	Diagnostic yield cryobiopsy	Diagnostic yields of EBUS-TBNA ± cell block	p	Diagnostic yield cryobiopsy vs TBNA benign pathology (p)	Diagnostic yield cryobiopsy vs TBNA malignant pathology (p)
Zhang J (2021)[13]	91.8%	79.9%	0.001	80.9% vs 53.2% (0.004)	LC: 94,1% vs 95,6% (0,58) Others tumours: 91.7% vs 25% (0.001)
Fan E (2022)**[14]	93%	81%	0.03	94% vs 67 (0.0004)	LC: 94% vs 91% (0.4) Others tumours: 76% vs 59% (0.47)
Genova C (2022)[23]	60% (3/5)	80% (4/5)	not calculated	–	–
Gershman E (2022)[24]	20/24 (83,3%)	21/24 (87.5%)	not calculated	–	–
Gonuguntla HK (2021)[25]	4/4 (100%)	3/4 (75%)	not calculated	–	–
Ariza-Prota MA (2022)[15]	4/4 (100%)	3/4 (75%)	not calculated	–	–
Ariza-Prota MA (2022)[26]	96%	82%	not calculated	100% vs 60%	LC: 92.9 vs 78%

LC = lung cancer; TBNA = *transbronchial needle aspiration.*
** Cryobiopsy + TBNA vs TBNA.

3.4. Complications

The most frequently described complication was bleeding, although the vast majority of cases were minor (Table 4). No cases of infections or serious complications such as respiratory failure or mortality were described.

4. Discussion

The main objective of this systematic review was to determine if cryobiopsy improved the diagnostic yield of EBUS-TBNA without increasing the number of complications. Despite the fact that our search found very few studies, the results demonstrated that cryoEBUS could represent a promising technique in the diagnostic algorithm of intrathoracic lymphadenopathy. Although cryoEBUS did not significantly improve the diagnosis of lung cancer compared to EBUS-TBNA, the results were significantly better in patients with benign pathologies and other tumour types, including lymphomas. In addition, it seems that the samples obtained by cryoprobe better defined the histological subtypes of lymphoma and allowed a complete molecular characterisation in cases of lung cancer. The technique has proven to be safe, and no serious complications were described after the procedure.

Although there are some narrative reviews on this novel procedure in the scientific literatura [26,27], to the best of our knowledge, this is the first systematic review on the diagnostic yield and safety of cryoEBUS.

Other authors have published systematic reviews and meta-analyses that refer to the role of cryobiopsy in other pathologies. For instance, Ganganah et al. published a systematic review and meta-analysis on the efficacy and safety of cryobiopsy in interstitial disease and in the diagnosis of lung tumours [15]. Of the 8 studies considered in this current work, 4 referred to lung tumours [16]. The diagnostic usefulness of cryobiopsy of endobronchial lesions and peripheral tumour lesions was higher than when compared with conventional forceps (92% vs. 76% and 61% vs. 48%, respectively) [15]. In the specific case of interstitial disease, the value of cryobiopsies in some of the included studies was 100% without significantly increasing the risk of bleeding [15]. Sryma et al. evaluated the efficacy of radial-EBUS-guided cryobiopsy for the diagnosis of peripheral lung lesions [28]. After the systematic review, the authors concluded that the efficacy of transbronchial cryobiopsy was 77% versus 72% for conventional forceps guided radial EBUS [27].

Tabla 4
Follow up and adverse events of cryobiopsy.

	Follow up	Adverse events
Zhang J (2021)[13]	Post-procedural chest radiography Follow up for 4 weeks after biopsy	2 (1%) Pneumothorax 1 (0.5%) Pneumomediastinum 169 (87.1%) Bleeding grade 1-2
Fan E (2022)[14]	Post-procedural chest radiography Follow up for 4 weeks after biopsy	3 (2%) Bleeding grade 3–4 of cryobiopsy 2 (1%) Bleeding grade 3–4 of TBNA (p = 1)
Genova C (2022)[23]	–	0
Gershman E (2022)[24]	Post-procedural chest radiography 7-day course of prophylactic antibiotics	0
Gonuguntla HK (2021)[25]	–	1 (25%) Bleeding grade 1-2
Ariza-Prota MA (2022)[15]	–	1 (25%) Bleeding grade 1-2
Ariza-Prota MA (2022)[26]	Post-procedural chest radiography or ultrasound pleural Follow up for 2 weeks after biopsy	2 (4%) Bleeding grade 1-2

TBNA = transbronchial needle aspiration.

Although they found no significant differences, radial-EBUS-guided cryobiopsy proved to be effective and safe, without increasing the number of complications [28]. In 2020, our group published a systematic review and meta-analysis on the diagnostic usefulness and safety of pleural cryobiopsy during rigid and semi-rigid medical thoracoscopy that considered 7 studies [11]. Our analysis found that the efficacy of cryobiopsy vs the conventional flexible forceps was 95% vs. 91%, respectively, although when the results of the cryobiopsy were compared with those of the rigid forceps, the diagnostic yield was similar. As in the previously described studies, cryobiopsy proved to have a high diagnostic usefulness and safety profile for the diagnosis of pleural effusion [11].

Similar results were described in studies that had analysed the value of cryoEBUS. Cryobiopsy of adenopathies is a recent and promising technique that is useful in the diagnosis of mediastinal and/or hilar lymph node involvement. The data suggest that the addition of cryobiopsy increases the diagnostic yield [13,14] although it must be considered that in some studies a pass was performed with the cryoprobe [13]. The potential to increase this number of punctures is unknown. Nor can we know the value of the rapid on site-evaluation (because it was not used) or if it could increase the efficacy of EBUS-TBNA [14]. In turn, the false negatives of cryoEBUS could be justified because the cryoprobe is always advanced in the same location [15]. As reflected in the recommendations on technical aspects for performing EBUS-TBNA, it appears that optimal diagnostic values can be obtained after a minimum of 3 separate needle passes be performed per sampling site but this recommendation refers to the diagnosis and staging of the lung cancer [2]. There are no data on the number of needle passes required to obtain sufficient throughput for lymphoma or other non-malignant diseases. Thus, future studies on the need to evaluate the usefulness of the number of passes with the cryoprobe in different regions of the same adenopathy will be necessary.

In the specific case of NSCLC, with targeted treatment and immunotherapy, this strategic treatment alternative requires a greater amount of tissue to establish the molecular and immunological profiles of the tumour because this is key in therapeutic options. In this sense, the main objective of the study by Arimura et al. [21] was to assess the quality of the samples and PD-L1 expression compared to cryoEBUS and EBUS-TBNA; detection of PD-L1 > 1% was more frequent in cryoEBUS samples than in EBUS-TBNA samples (56% vs. 37%, respectively) [21]. In our systematic review, when we jointly analysed the results of all the studies that had performed molecular determinations with samples obtained from patients with lung cancer [12,14–22], the efficacy of cryoEBUS compared to EBUS-TBNA always exceeded 90%. As occurs in other situations such as malignant pleural effusion or malignant peripheral pulmonary nodules, it seems that samples obtained using a cryoprobe are adequate for the molecular characterisation of NSCLC [7].

The value of EBUS-TBNA in the diagnosis of lymphomas is controversial [29]]. While EBUS-TBNA may be the first diagnostic test used in cases of suspected lymphoma recurrence, in new diagnoses, especially Hodgkin lymphoma, its diagnostic usefulness is low and negative results do not exclude the diagnosis [1,29]. Although the sensitivity of cryoEBUS was greater than that of EBUS-TBNA for the diagnosis of lymphoma and also allowed specific disease typing [12,13], in our review the total number of patients with lymphoproliferative diseases was very low (27 cases) and so this technique should be specifically evaluated in this population.

However, the indication for ultrasonography in the diagnostic algorithms of mediastinal and/or hilar adenopathies of other benign pathologies is not so clear. In the specific case of sarcoidosis, EBUS-TBNA has shown a diagnostic usefulness of approximately 80% and in the case of mycobacterial diseases such as tuberculosis, this varies from 75% to 85% [5]. In both situations, cryoEBUS has been shown to significantly increase the efficacy to above 90%.

Regarding complications, EBUS-TBNA has proven to be a safe technique with a reported rate of complications of around 1.4% [2,17].

Mediastinitis, pneumonia, or sepsis have not been described with cryoEBUS, with bleeding being the most frequent complication. As described in our results, the use of this type of puncture does not increase the risk of serious complications from ultrasonography endobronchial.

Regarding the procedure, there were differences between the use of a cutting probe to introduce the cryoprobe or its introduction through the puncture hole left by the needle. The cryoprobe can be advanced slowly towards the puncture site and then pushed through the hole created by the previous needle, regardless of the type of needle, while trying to maintain the same degree of probe angulation to avoid resistance or complications [14,24]. It should also be considered that most of the punctured lymph nodes were at station 7 or 4R, which could have influenced the results from the use of this technique.

Nonetheless, despite excellent results, wider adoption of this technique may be limited by multiple factors. Cryobiopsy is currently available in only a few selected centres. Moreover, the learning curve for the technique when used in the mediastinum or with the optimal sampling strategy (number of passes or optimal freezing time) are still unclear or unknown. However, we believe that the diagnostic accuracy of cryoEBUS in patients with lymphoproliferative processes and benign disorders should be evaluated in larger cohorts. In addition, specific studies that aim to determine the diagnostic value of molecular profiling of NSCLC and the prognosis of NSCLC adenopathy cryobiopsies should be designed.

Although we initially planned to perform a meta-analysis in this current work, because of the small number of studies included and their heterogeneity, it was impossible to apply the appropriate statistical techniques for quantitative analysis of the results. Therefore, we conducted a qualitative systematic review, with a description of the evidence and without statistical analysis.

As conclusions, recent scientific literature suggests that cryoEBUS is associated with a high diagnostic yield and good safety profile, however, further well-designed prospective randomised studies in larger patient cohorts will be needed to standardise the technique and to include it as a tool in diagnostic algorithms for mediastinal and hilar lymph node involvement.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107389.

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