EUROPEAN CLINICAL RESPIRATORY JOURNAL
2019, VOL. 6, 1565803
https://doi.org/10.1080/20018525.2019.1565803

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

# The value of computed tomography in discriminating malignant from non-malignant causes of unresolved unilateral pleural effusions: a systematic review

Simon Reuter [a,b], Therese Maria Henriette Naur [c], Paul Frost Clementsen[c,d,e] and Uffe Bodtger [a,b,d]

[a]Department of Respiratory Medicine, Naestved Hospital, Naestved, Denmark; [b]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark; [c]Copenhagen Academy for Medical Education and Simulation (CAMES), Rigshospitalet, University of Copenhagen and the Capital Region of Denmark, Copenhagen, Denmark; [d]Department of Respiratory Medicine, Zealand University Hospital, Roskilde, Denmark; [e]Department of Clinical Medicine, University of Copenhagen, Denmark

**ABSTRACT**

The scientific background in expert-opinion papers for recommending Computed Tomography (CT) in unilateral pleural exudates is based on studies including patients with other findings than unilateral pleural effusions or selected patients undergoing thoracoscopy. Therefore, we performed a systematic review investigating the sensitivity of CT for predicting malignancy in patients with unilateral, non-transudative, pleural effusions. A search strategy was developed with the assistance of a medical information specialist at our university library. We searched PubMed/MEDLINE, EMBASE and Cochrane Library, ClinicalTrials.gov and articles citing the included studies. No date restrictions were applied (the first included paper was published in 2001 (1)), and only literature in English was included. We used the Quality Assessment of Diagnostic Accuracy Studies 2 for bias assessment. We registered the protocol at PROSPERO (CRD42018094830). Five studies were included, two prospective and three retrospective, all performed in Western Europe. No study reported diagnostic values for patients with unilateral, non-transudative pleural effusions only; one study did for unilateral pleural effusions. In the remaining studies, most patients had unilateral effusions and non-transudative effusions. Patients were primarily males and >70 years. All but one study found a high incidence of malignancy, dominated by malignant pleural mesothelioma. All studies were limited by risk of bias and applicability, predominantly regarding study population, pretests and index test. The current evidence supporting the sensitivity of CT for predicting malignancy in unilateral pleural effusions (both non-transudative and all types of effusion) is very low and did not allow meta-analysis. Standardization of patient population and CT protocol may facilitate conclusions of futures studies.

**ARTICLE HISTORY**
Received 15 October 2018
Accepted 3 January 2019

**KEYWORDS**
Computed tomography; sensitivity; specificity; unilateral pleural effusion; cancer

## Introduction

With more than 50 causes, and a cancer incidence of 20–70% (depending on the study population), the investigation of a unilateral pleural effusion is a clinical challenge [1–5].

The British Thoracic Society (BTS) published in 2010 an internationally acknowledged guideline describing a systematic and stepwise approach to diagnosing unilateral pleural effusions [5]. This guideline recommends contrast-enhanced computed tomography (CT) of the chest in exudative effusions of unknown origin after initial work-up (medical history, physical examination, chest X-ray, and thoracentesis including pleural fluid cytology, culture and biochemical characterization as transudative or exudative effusions according to Lights criteria) [5,6].

However, the recommendation of CT [5] is based on five heterogeneous studies [7–11], of which only one investigated the value of CT in patients with pleural effusions [7]. A later expert review (2015) on the workup of pleural effusions [12] supported BTS' guidelines recommendation of CT in case of inconclusive initial workup, referring to two additional studies, which both included patients with bilateral effusions and transudates, without reporting of data concerning patients with unilateral, exudative effusion [13,14].

Consequently, three studies have investigated the value of CT in discriminating non-malignant effusion from malignant pleural effusions (MPE) [7,13,14]. Two studies were retrospective and included 40 *resp*. 70 patients [7,13]; the incidence of MPE was 80% and 57%, respectively, dominated by malignant pleural mesotheliomas (56% *resp*. 52%) [7,13]. The latter study found an MPE incidence of 34%, and 5% was found to have malignant pleural mesothelioma.

**CONTACT** Simon Reuter simonreuter@dadlnet.dk Department of Respiratory Medicine, Naestved Hospital, 61, Ringstedgade, NaestvedDK-4700, Denmark

Supplemental data can be accessed here.

In summary, the current recommendations for CT in the workup of unilateral exudative effusions unresolved after initial workup are based on few and heterogeneous studies with – at best – sparse data on representative patients.

For these reasons, we performed a systematic review investigating the sensitivity of CT for predicting malignancy in patients presenting with a pleural effusion of unknown cause.

## Materials and methods

The protocol of this systematic review was registered at PROSPERO under the registration no. CRD42018094830.

### Outcomes

Primary: sensitivity of CT for predicting a malignant cause of unilateral, non-transudative pleural effusion of unknown etiology.

Secondary: sensitivity of CT for predicting a malignant cause of unilateral pleural effusions of unknown etiology.

### Eligibility criteria

Studies were included if they investigated yield and/or sensitivity of CT for predicting a malignant cause in patients with unilateral pleural effusions of unknown etiology.

Inclusion criteria were: diagnostic study design (retro- or prospective), CT (conventional/spiral) as index test, pleural cytology or other pathoanatomic verification as reference standard for malignancy, and reporting either sensitivity and specificity or sufficient data to create a $2 \times 2$ contingency table. We excluded abstracts presented at congresses, editorials, letters, and comments.

### Search and selection

The literature searches on PubMed/MEDLINE, EMBASE and Cochrane Library were developed with assistance of a medical information specialist at the library of the University of Southern Denmark. The complete search strategy is provided in online supplementary material A. No date restrictions were applied (the first included paper was published in 2001 [7]), and we only included literature published in English. The final searches were performed on 1 May 2018.

Titles and abstracts of the search results were examined by two independent investigators (S.R and T.N). If an article was considered eligible, both investigators independently assessed the corresponding full text article for inclusion with disagreements being solved by discussion. If necessary, a third investigator (P.F.C) made the final decision.

To identify additional relevant publications, one investigator (S.R) screened the reference lists of the included articles and all articles citing them (through Google Scholar). To identify unpublished studies, S.R also searched ClinicalTrials.gov without time limits. These additional searches were performed on 6 July 2018.

### Data extraction

One investigator (S.R) extracted data from all studies included, and data were subsequently verified by a second investigator (T.N). We extracted authors, year of publication, journal, study design, country, recruitment strategy, sample size, patient demographics (age, sex), prevalence of malignant pleural mesothelioma, prevalence of other malignancies, prevalence of non-MPE, reference standard, type of CT (e.g. dose and use of contrast), methods of CT image analysis, Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2), diagnostic values and data for construction of a $2 \times 2$ table.

### Quality assessment/assessment of risk of bias

Two reviewers (S.R and T.N) independently assessed the risk of bias in each study included, using the QUADAS 2 tool [15]. Disagreements were resolved by discussions and, if necessary, a third investigator (P.F.C) made the final decision.

### Data analysis

Continuous variables were expressed as means or medians and categorical variables as frequencies or percentages. The following diagnostic values were registered: sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios (LRs), diagnostic accuracy and area under receiver operating characterization curve. If possible, $2 \times 2$ contingency tables were constructed.

We did not investigate for publication bias, as Funnel plots and other tests have proven to be misleading in diagnostic accuracy studies [16].

## Results

### Literature search and study selection

Figure 1 depicts the search process and that 23,980 screened studies resulted in five included studies

[7,13,14,17,18]. Two investigators (S.R and T.N) independently screened the 23,980 articles and excluded 23,954 based on the title or abstract in accordance with the exclusion criteria.

Screening of reference lists and papers citing the included studies, resulted in full-text review of one additional study, which was excluded due to the type of CT (dual-energy spectral CT) [19]. Screening clinical trial registries identified two studies, both originating from our research group; one is currently including patients, and the other is completed (manuscript submitted).

### Study characteristics

No study reported data on unilateral non-transudative effusions, one study reported data on unilateral pleural effusions [18] and four studies reported data on uni- and bilateral effusions [7,13,14,17].

All studies were performed in either Spain or England between 2000 and 2016. Two studies were prospective [17,18], one paper did not state study design [14] and two were retrospective [7,13]; see Table 1.

In general, included patients were males and >70 years. The prevalence of malignancy and the prevalence of malignant pleural mesothelioma were highest in the earliest studies and in studies from England [7,13,17,18]; see Table 1. In three studies, the reference standard was tissue biopsies [13,17,18]; the latter two studies additionally used pleural fluid cytology in a few patients [7,14]. Inter-study follow-up duration of patients not diagnosed with a malignant cause of the pleural effusion was heterogeneous: until effusion resolved [14], 1 year [18], 1 year or until death [7], 2 years [13], or 3 years from index investigation [17].

### Primary and secondary outcome (strict criteria)

No study provided sensitivity of CT for predicting a malignant cause of unilateral, non-transudative pleural effusions of unknown etiology.

Adhering strictly to the research question, only the study by Bintcliffe et al. [18] addressed the secondary outcome: Table 2 (first row) depicts a sensitivity of CT of 65% for predicting a malignant cause of unilateral effusion [18].

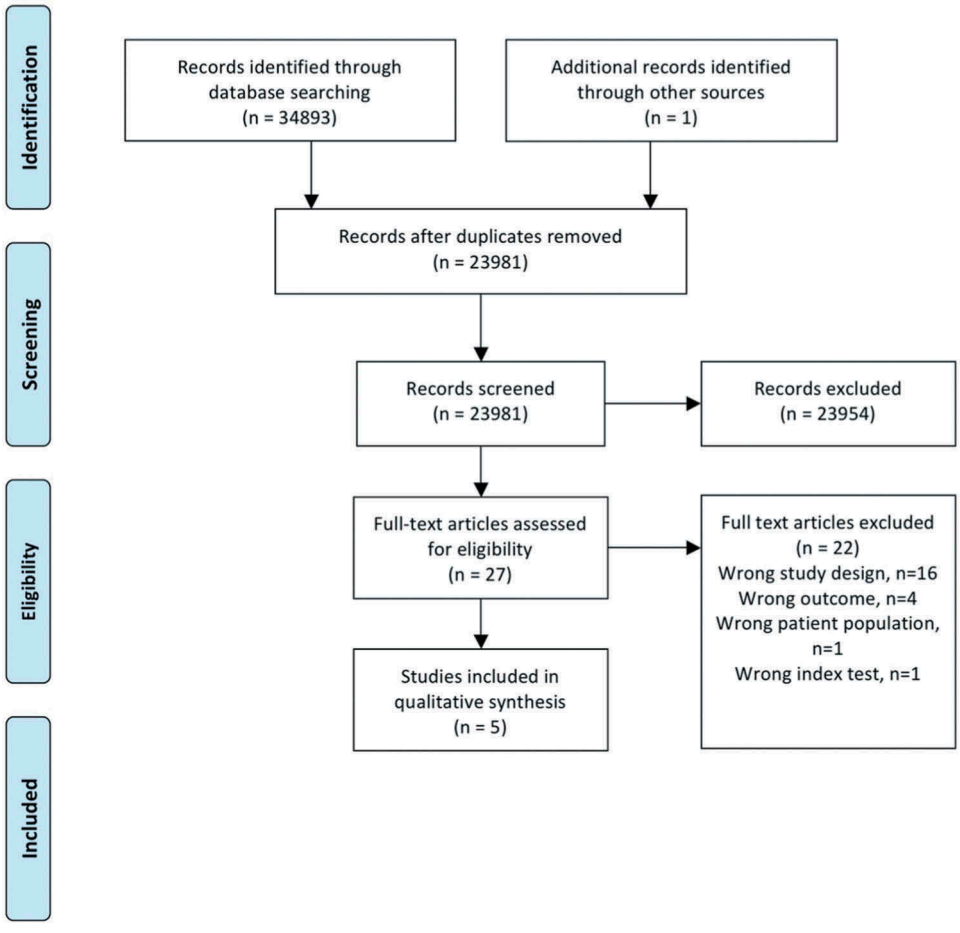


**Figure 1.** PRISMA flow chart.

**Table 1.** Characteristics of included studies.

| Study, year | Country | Design | Sample size | Age | Males, % (*n*) | Prevalence of malignancy % (*n*) | Malignant pleural mesothelioma % (*n*) | Other malignancies % (*n*) |
|---|---|---|---|---|---|---|---|---|
| Bintcliffe et al. [2016, 18] | UK | Prospective | 126 | 75 [67–79]§ | 66% (83) | 46% (58) | 31% (18) | 69% (40) |
| Porcel et al. [2015, 14] | Spain | NS | 343 | 69 [53–80][c] | 59% (201) | 34% (115) | 5% (5) | 95% (109) |
| Hallifax et al. [2014, 13] | UK | Retrospective | 370 | 72 (13)[b] | 71% (261) | 57% (211) | 55% (110) | 45% (101) |
| Ferrer et al. [2005, 17] | Spain | Prospective | 93 | NS | NS | 68% (63) | 35% (22) | 65% (41) |
| Traill et al. [2000, 7] | UK | Retrospective | 40 | 69 [45–88][a] | 70% (28) | 80% (32) | 56% (18) | 44% (14) |

NS = Not stated, [a]median and range, [b]mean and standard deviation, [c]median and quartiles.

| Study, year | Non-malignant Diseases % (n) | Type of CT | Image analysis | Reference standard |
|---|---|---|---|---|
| Bintcliffe et al. [2016, 18] | 54% (68) | NS | NS | Biopsy |
| Porcel et al. [2015, 14] | 66% (228) | CE-CT of the chest and upper abdomen | Quantitative | Cytology or biopsy |
| Hallifax et al. [2014, 13] | 43% (159) | NS | Scan report | Thoracoscopy |
| Ferrer et al. [2005, 17] | 32% (30) | NS | Qualitative | Thoracoscopy |
| Traill et al. [2000, 7] | 20% (8) | CE-CT of the chest and upper abdomen | Qualitative (2 observers) | Thoracoscopy, autopsy and pleural fluid cytology |

### *Primary and secondary outcome (broader criteria)*

Including the studies with uni- and bilateral effusions, the primary outcome was addressed in one study [14] with a sensitivity of CT of 74% for predicting a malignant cause of non-transudative effusions, equal to the sensitivity for the total group (Table 2).

Including the four studies introduces vast differences in sensitivity (64–92%) and specificity (75–100%); see Table 2.

A 2 × 2 contingency table could only be constructed from data in two papers [7,13]. All studies reported sensitivity and specificity, three studies reported PPV and NPV [7,13,18], and one study reported Likelihood Ratio positive (LR+) and Likelihood Ratio negative (LR−) [14]. Two studies reported subgroup results: pleural fluid cytology result [13] and Light's criteria [14]; see Table 2.

### *Initial workup and CT protocol*

Only one study described in detail the extent of initial work up [18], and two studies provided information about pleural fluid cytology [13,14]. However, only the latter two studies [13,14] acknowledged pleural fluid cytology when calculating the diagnostic value of CT; see Table 1.

No studies accounted for chest x-ray findings such as pleural thickening or mass lesions.

Two studies [7,14] provided a detailed CT protocol and CT interpretation. In one study [7], two observers read all images, and in another [14] an observer calculated an overall score to predict malignancy from predefined CT findings.

### *Study quality assessment*

Detailed information about the quality assessment are shown in Table 2. Risk of bias related to index test (CT) was impossible to assess in three studies without detailed CT protocol or description of interpretation [13,17,18].

Patient selection hampered applicability in all studies (Table 2). In four studies, it was unknown if participants had unilateral or bilateral pleural effusions [7,13,14,17]. In two studies, only patients who underwent thoracoscopy were included [13,17], and another included solely patients with suspicion of a MPE [7]. Initial workup was partly taken into account in two studies [13,14].

### *Clinical application*

If we apply the sensitivity and specificity found by Porcel et al. [14] on a hypothetical cohort of 1000 patients with unilateral pleural effusions, 220 patients

**Table 2.** Diagnostic values of CT in pleural effusions.

| | TP | FP | FN | TN | Sensitivity | Specificity | PPV | NPV | LR+ | LR- | Diagnostic accuracy | AUC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bintcliffe et al. [2016, 18] | NS | NS | NS | NS | 65% | 93% | 92% | 68% | NS | NS | NS | NS |
| Porcel et al. [2015, 14] All patients | NS | NS | NS | NS | 74% [65–81%] | 92% [88–95] | NS | NS | 9.4 [5.9–14.8] | 0.28 [0.21–0.39] | NS | 0.919 [0.849–0.990] |
| Exudates and no malignant cells at cytologic examination | NS | NS | NS | NS | 74% [55–87%] | 91% [85–95%] | NS | NS | 8.44 [4.5–16] | 0.28 [0.15–0.54] | NS | NS |
| Hallifax et al. [2014, 13] | 144 | 35 | 67 | 124 | 68% [62–75%] | 78% [72–84%] | 80% [75–86%] | 65% [58–72%] | 3.10 [2.28–4.21] | 0.41 [0.33–0.50] | 72% [68–77] | NS |
| No malignant cells at cytologic examination | NS | NS | NS | NS | 69% [62–76%] | 78% [72–85%] | 80% [74–87%] | 66% [59–74%] | NS | NS | NS | NS |
| Malignant cells detected at cytological examination | NS | NS | NS | NS | 64% [47–82%] | 75% [54–96%] | 82% [66–98%] | 55% [34–75%] | NS | NS | NS | NS |
| Ferrer et al. [2005, 17] | NS | NS | NS | NS | 92% | 81% | NS | NS | NS | NS | NS | 0.87 [0.79–0.95] |
| Trail et al. [2000, 7] | 28 | 0 | 4 | 8 | 86% [67–96%] | 100% [63–100%] | 100% | 67% [45–83%] | NA | 0.14 [0.06–0.35] | 89% [74–97%] | NS |

would be suspected of malignancy of whom 72 would have a non-malignant cause. The CT would not be suspicious for malignancy in 780 patients including 52 missed cases of malignancy; see Figure 2(a).

Using the diagnostic values found by Hallifax et al. [13] on the same hypothetical cohort as above would result in 328 patients being suspected of malignancy of whom 200 having a non-malignant cause. The CT would not be suspicious for malignancy in 672 patients including 72 missed cases of malignancy; see Figure 2(b).

## Discussion

We identified five studies evaluating the sensitivity of CT for predicting malignancy in pleural effusions [7,13,14,17,18], yet none reported data on unilateral, exudative effusions. One study reported data on unilateral effusions [18], and another on exudative effusions [14].

We included all five studies to provide a complete overview of the present evidence regarding CT in the work up of pleural effusions. Furthermore, because 30% of the patients with a unilateral pleural effusion have more than one cause (e.g. both heart failure and malignancy) and because the difference in cancer incidence between transudates and exudates is modest, the classification according to Light's criteria might not assist the clinician in the decision of performing CT [18,20–22].

Almost all studies had risks of bias due to multiple factors. First, the majority of studies were retrospective, which leads to a highly selected sample of patients; this produces estimates of diagnostic values that are difficult to reproduce.

The relatively high prevalence of malignancy and malignant pleural mesothelioma suggest selection bias. Two European studies investigating more than 3000 patients with pleural effusions found a prevalence of malignancy around 25% and malignant pleural mesothelioma 3% [1,2].

Lastly, it was not possible to evaluate biases related to CT, because protocol and/or interpretation was not described in the majority of studies [13,17,18].

There are several concerns regarding applicability of the included studies. First, only one study was performed in patients with unilateral effusions [18] and none with unilateral, non-transudative effusions. Second, all studies were performed at tertiary centers in two Western European countries. Third, three studies included highly selected patients undergoing thoracoscopy or with other suspicion of MPE [7,13,17]. Finally, no study evaluated the outcome of pretests i.e. pleural fluid cytology and chest x-ray.

Two studies stratified for pleural fluid cytology when calculating the value of CT [13,14], and

**Table 3.** Risk of bias and applicability judgments in QUADAS-2.

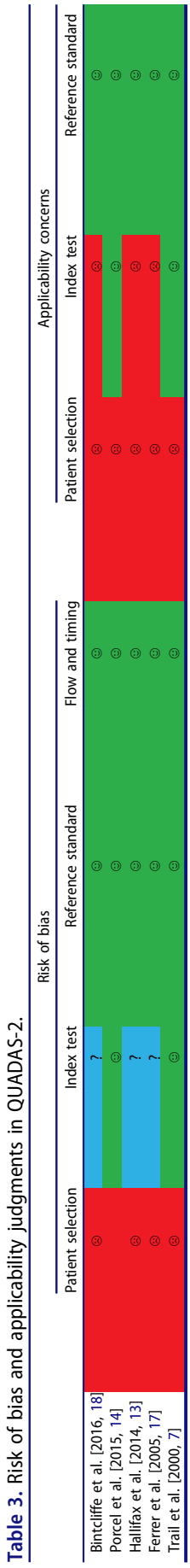


Figure 2 depicts the clinical application of CT in a hypothetical cohort.

Chest x-ray, compared to low-dose CT, was found to have half the diagnostic yield of predicting malignancy in patients who were screened for lung cancer [23]. Inclusion of patients with a chest x-ray highly suggestive of intrathoracic malignancy would affect the diagnostic value of CT in the workup of unilateral pleural effusions. To our knowledge, no study incorporating chest x-ray being suggestive of malignancy or not has been published.

A strength of this review was the thorough search strategy (see online supplementary material A) developed in collaboration with a medical information specialist at our University library. The heterogeneity in patient population, study design, pretests (chest x-ray and pleural fluid cytology), choice of and interpretation of the index test (CT) and the low number of relevant paper hindered the performance of meta-analyses.

Because of costs, invasiveness and availability of thoracoscopy [5], a better performance of CT in ruling out malignancy is desirable. A meta-analysis of positron emission tomography (PET)/CT for differentiating benign from MPE found a higher negative than positive likelihood ratio [24]. Thus, PET/CT might reduce the number of futile invasive procedures in patients with non-MPE but that remains to be investigated in prospective trials. However, since current evidence does not support the superiority of PET-CT, chest x-ray or thoracic ultrasound, the guidelines recommendations of CT are still valid in clinical setting.

Consequently, larger and prospective studies are needed focusing on everyday clinical life patients with unilateral pleural effusions, well-defined CT protocol, systematic pleural fluid analysis, and bioptic techniques as reference standard, e.g. similar to the pragmatic design used in the TARGET trial [25].

## Conclusion

The use of CT in the workup of unilateral, non-transudative pleural effusions is firmly established [5,12], but this review shows that the evidence for CT is sparse, and that the most relevant studies are hetereogeneous in design, data reporting and patient populations. Improving the evidence of rational use of imaging techniques in unilateral pleural effusions of unknown cause needs investigation in prospective studies with well-defined criteria for baseline work-up, patient population and CT protocol.

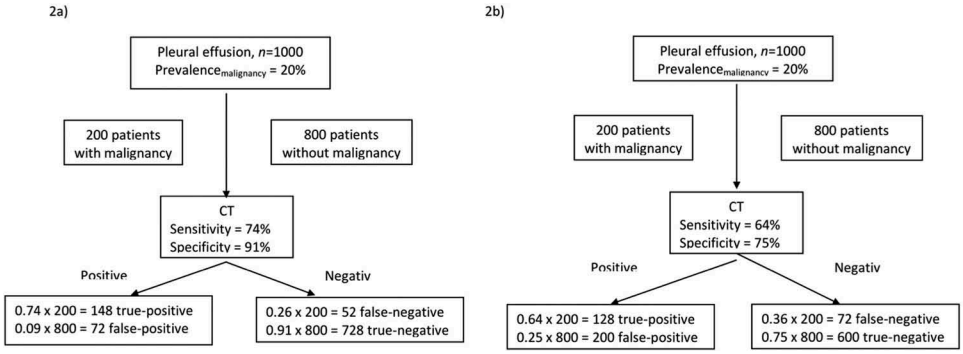


**Figure 2.** Consequence of CT in a hypothetical cohort of 1000 patients with a unilateral pleural effusion. (a) Dianostic values from Porcel et al. (14); (b) diagnostic values from Hallifax et al. (13). We choose a prevalence of malignancy of 25% which equals findings in Europe (1,2).

## Author Contributions

S.R developed the search strategy. S.R and T.N screened the studies and retrieved the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.R and T.N did the evaluation of bias. The study concept and design was made by all authors. S.R and T.N undertook the analysis and interpretation of data as well as drafting of the manuscript. All authors participated in study design and manuscript writing.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## Funding

No funding has been received.

## Notes on contributors

*Simon Reuter* is a PhD. student and medical doctor, his primary interest is diagnostics and malignant thoracic diseases.

*Therese M H Naur* has authored papers on fine needle aspiration of mediastinal lymph nodes from the trachea and oesophagus. Furthermore, she has written review articles on simulation-based training in the same field. She has been involved in research since she was a medical student and now as a doctor, she is still involved in national and international research groups.

*Paul Frost Clementsen* is particularly interested in real-time guided fine needle biopsy from lung tumors, mediastinal lymph nodes and other structures via the esophagus (EUS-FNA and EUS-B-FNA) and via the trachea (EBUS-TBNA) and conventional bronchoscopy. He has been teaching many Danish and international courses and is a supervisor for medical doctors writing PhD thesis and medical students. He is a coauthor of original articles, review papers and international guidelines about lung diseases and interventional pulmonology. Paul Frost Clementsen is working half time in the clinical setting and half time with simulation-based training and assessment in the procedures.

## Competing interests

The authors all declare that they have no competing interests.

## ORCID

Simon Reuter http://orcid.org/0000-0002-2256-2034
Therese Maria Henriette Naur http://orcid.org/0000-0002-7197-297X
Uffe Bodtger http://orcid.org/0000-0002-1231-9209

## References

[1] Porcel JM, Esquerda A, Vives M, et al. Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses. Arch Bronconeumol. 2014;50(5):161–165.
[2] Marel M, Zrustova M, Stasny B, et al. The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia. Chest. 1993;104(5):1486–1489.
[3] Prakash UB, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. Mayo Clin Proc. 1985;60(3):158–164.
[4] Hirsch A, Ruffie P, Nebut M, et al. Pleural effusion: laboratory tests in 300 cases. Thorax. 1979;34(1):106–112.
[5] 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):ii4–17.
[6] Light RW, Macgregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972;77(4):507–513.
[7] Traill ZC, Davies RJ, Gleeson FV. Thoracic computed tomography in patients with suspected malignant pleural effusions. Clin Radiol. 2001;56(3):193–196.
[8] McLoud TC, Flower CD. Imaging the pleura: sonography, CT, and MR imaging. AJR. 1991;156(6):1145–1153.

[9] Waite RJ, Carbonneau RJ, Balikian JP, et al. Parietal pleural changes in empyema: appearances at CT. Radiology. 1990;175(1):145–150.
[10] Leung AN, Muller NL, Miller RR. CT in differential diagnosis of diffuse pleural disease. AJR. 1990;154 (3):487–492.
[11] Scott EM, Marshall TJ, Flower CD, et al. Diffuse pleural thickening: percutaneous CT-guided cutting needle biopsy. Radiology. 1995;194(3):867–870.
[12] Porcel JM, Azzopardi M, Koegelenberg CF, et al. The diagnosis of pleural effusions. Expert Rev Respir Med. 2015;9(6):801–815.
[13] Hallifax RJ, Haris M, Corcoran JP, et al. Role of CT in assessing pleural malignancy prior to thoracoscopy. Thorax. 2015;70(2):192–193.
[14] Porcel JM, Pardina M, Bielsa S, et al. Derivation and validation of a CT scan scoring system for discriminating malignant from benign pleural effusions. Chest. 2015;147(2):513–519.
[15] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–536.
[16] Leeflang MM, Deeks JJ, Gatsonis C, et al. Systematic reviews of diagnostic test accuracy. Ann Intern Med. 2008;149(12):889–897.
[17] Ferrer J, Roldan J, Teixidor J, et al. Predictors of pleural malignancy in patients with pleural effusion undergoing thoracoscopy. Chest. 2005;127(3):1017–1022.
[18] Bintcliffe OJ, Hooper CE, Rider IJ, et al. Unilateral pleural effusions with more than one apparent etiology. A prospective observational study. Ann Am Thorac Soc. 2016;13(7):1050–1056.
[19] Zhang X, Duan H, Yu Y, et al. Differential diagnosis between benign and malignant pleural effusion with dual-energy spectral CT. PloS one. 2018;13(4): e0193714.
[20] Moltyaner Y, Miletin MS, Grossman RF. Transudative pleural effusions: false reassurance against malignancy. Chest. 2000;118(3):885.
[21] Walker S, Maskell N. Identification and management of pleural effusions of multiple aetiologies. Curr Opin Pulm Med. 2017;23(4):339–345.
[22] Gonlugur TE, Gonlugur U. Transudates in malignancy: still a role for pleural fluid. Ann Acad Med Singapore. 2008;37(9):760–763.
[23] Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the lung screening study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer. 2005;47(1):9–15.
[24] Porcel JM, Hernandez P, Martinez-Alonso M, et al. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. Chest. 2015;147(2):502–512.
[25] de Fonseka D, Underwood W, Stadon L, et al. Randomised controlled trial to compare the diagnostic yield of positron emission tomography CT (PET-CT) TARGETed pleural biopsy versus CT-guided pleural biopsy in suspected pleural malignancy (TARGET trial). BMJ Open Respir Res. 2018;5(1): e000270.