Original Article

Efficacy of rapid on-site evaluation for diagnosing pulmonary lesions and mediastinal lymph nodes: a systematic review and meta-analysis

Xi Chen[1#], Bing Wan[2#], Yangyang Xu[3#], Yong Song[1,3,4], Ping Zhan[1,3,4], Litang Huang[4], Hongbing Liu[1,3,4], Dang Lin[5], Tangfeng Lv[1,3,4]

[1]Department of Respiratory and Critical Care Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China; [2]Department of Respiratory and Critical Care Medicine, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing 210002, China; [3]Department of Respiratory and Critical Care Medicine, Jinling Hospital, Nanjing Medical University, Nanjing 210002, China; [4]Department of Respiratory and Critical Care Medicine, Jinling Hospital, Medical School of Southeast University, Nanjing 210002, China; [5]Department of Respiratory and Critical Care Medicine, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou 215001, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: Y Song, T Lv, D Lin; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: X Chen, B Wan, L Huang; (V) Data analysis and interpretation: X Chen, P Zhan, H Liu, B Wan, Y Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]The authors have contributed equally to this work.

Correspondence to: Dang Lin. Department of Respiratory and Critical Care Medicine, The Affiliated Suzhou Hospital of Nanjing Medical University, 16 West BAITA Road, Suzhou 215001, China. Email: Danglin4067@163.com; Tangfeng Lv. Department of Respiratory and Critical Care Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China. Email: bairoushui@163.com.

Background: Although rapid on-site evaluation (ROSE) is gradually becoming an integral part of the modern Interventional Pulmonology, the clinical benefit of ROSE is still a matter of controversy. The objective of this meta-analysis was to clarify whether ROSE is effective in diagnosing pulmonary lesions and mediastinal lymph nodes, synchronously, to assess circumstances under which ROSE makes more sense.

Methods: MEDLINE and EMBASE were searched for studies comparing any outcome between ROSE and no-ROSE group in diagnosing pulmonary lesions and mediastinal lymph nodes. Statistical calculations were conducted using Review Manager, version 5.3, and Stata Release 12.0. Meta-analysis was completed using a random-effects model when $I^2 \geq 50\%$ or a fixed-effect otherwise. Heterogeneity was assessed by the I^2-statistic test. Publication bias was assessed by the Begg's test.

Results: This Literature search yielded 27 studies altogether. The pooled risk difference of adequate rate was 0.12 [95% confidence intervals (CI): 0.07–0.16, I^2=0%], the combined risk difference (RD) of diagnostic yield was 0.14 (95% CI: 0.09–0.18, I^2=57%) while the pooled RD of sensitivity for malignancy was 0.10 (95% CI: 0.06–0.14, I^2 =20%). Significant heterogeneity only existed in diagnostic yield (I^2=57%, P=0.001). Further subgroup analysis documented a higher increase in diagnostic yield when sampling solid pulmonary lesions than sampling hilar/mediastinal lymph nodes 0.16 (95% CI: 0.12–0.20, I^2=0%) versus 0.08 (95% CI: 0.04–0.13, I^2=10%) and when applied to patients with suspected/diagnosed lung cancer than unselected patients 0.12 (95% CI: 0.06 to 0.18) versus 0.11 (95% CI: –0.07 to 0.28).

Conclusions: ROSE is a useful technology in diagnosing pulmonary lesions and mediastinal lymph nodes, especially when sampling solid pulmonary lesions or applied to patients with suspected lung cancer.

Keywords: Mediastinal lymph nodes; meta-analysis; pulmonary lesions; rapid on-site evaluation (ROSE)

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Introduction

With a cytopathologist present on-site, rapid on-site evaluation (ROSE) can provide real-time feedback on the quality and quantity of needle biopsy samples. Specimens with the presence of excess blood or massive necrosis or numerous bronchial epithelial cells without adequate malignant cells and lymphocytes are identified by cytopathologists, guiding operators to change the site, depth or angle for the pinpoint. In like manner, once an adequate or diagnostic specimen is provided, operators are conducted to stop further trials and thus avoiding patients from additional procedures. Theoretically, ROSE offers advantages.

In early time, Davenport found that the inadequate rate of specimens by bronchoscopy decreases from 56% to 18% with the help of ROSE (1). Shortly afterward, several observational studies showed an increase with ROSE in diagnostic yield or adequate rate either by transthoracic fine needle aspiration (TTFNA) (2-5) or transbronchial needle aspiration (TBNA) with or without the guide of endobronchial ultrasound (EBUS) (6-9). Besides increasing the yield, ROSE also has the potential to decrease the complication rate by reducing the number of puncture sites or needle passes and avoiding additional diagnostic procedures (9-12). What's more, the utilization of ROSE is promising in saving the cost (10,13) and providing more cells for the ancillary test (14,15). With considerable merits showing above, ROSE is gradually becoming an integral technology in the modern Interventional Pulmonology.

However, the clinical benefit of ROSE is still a matter of controversy. A random controlled trial (RCT) conducted by Yarmus *et al.* failed to suggest a higher diagnostic yield with ROSE: ROSE, 55%; no-ROSE, 53% (P=1.000) (11). It is not unique but has its counterpart. Trisolini and his colleagues also found no significant difference in diagnostic yield between the ROSE and no-ROSE group in their RCT: ROSE, 78.3%; no-ROSE, 75.3% (P=0.64) (9). Opposition to the utilization of ROSE is provoked for the disappointing result on improving the diagnostic yield. The above two RCTs sampled lymph nodes in unselected patients with enlarged hilar/mediastinal nodes while there are additional RCTs (3,5) in which solid pulmonary lesions were sampled and all of these studies reported a considerable increase in diagnostic yield with ROSE. It is supposed that ROSE should be recommended in selected patients.

Consequently, this systemic review and meta-analysis aimed to conduct a comprehensive literature review not restricting study design, population, diagnostic method or sampling sites to clarify whether ROSE is useful for diagnosing pulmonary lesions and mediastinal lymph nodes, synchronously, to assess circumstances under which ROSE makes more sense.

Methods

This systematic review was conducted following guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (16) to assess the efficacy of rapid on-site evaluation for diagnosing pulmonary lesions and mediastinal lymph nodes.

Literature search

The MEDLINE (using PubMed as the search engine) and EMBASE databases were first searched on 13 October and last updated on December 11, 2018 with the following search strings: ((rapid on-site evaluation [Title/Abstract] OR ROSE [Title/Abstract] OR rapid on-site cytologic evaluation [Title/Abstract] OR immediate cytologic evaluation [Title/Abstract])) AND (lung OR pulmonary OR mediastinal). Only publications in English or Chinese language were screened, and there was no restriction on time or study design. SCOPUS, Web of Science and Google Scholar were also searched for the reference list of all the articles included.

Inclusion criteria

Original studies compared any outcome (e.g., adequate rate, diagnostic yield, sensitivity, accuracy, number of biopsy site, number of needle passes, complication rate, cost, ancillary test) between ROSE and no-ROSE group for diagnosing pulmonary lesions or mediastinal lymph nodes were eligible for inclusion. Two independent authors (Chen and Huang) reviewed all the titles/abstracts and selected studies meeting the following inclusion criteria. Disagreements were solved by discussion.

Exclusion criteria

(I) Review articles, letters, comments, editorials, case reports. (II) Abstract or conference abstract without full text available. (III) Studies not providing outcomes of ROSE group and no-ROSE group separately. (IV) Studies not providing the results of pulmonary lesions or mediastinal lymph nodes.

Quality assessment

Study quality was assessed utilizing the QUADAS-2(Quality Assessment of Diagnostic Accuracy Studies) tool. Risk of bias and concerns about applicability was evaluated synchronously in QUADAS-2. Risk of bias was assessed as low, high, or unclear in four main components: patient selection, index test, reference standard and, flow and timing. Concerns about lack of applicability were assessed in patient selection, index test, and reference standard.

Data extraction

Two authors (Chen and Huang) independently extracted the following data onto standardized data extraction forms utilizing Excel: (I) publication details (authors, year of publication, country); (II) basic characteristics (study design, number of patients, diagnostic method, population, main sampling sites); (III) diagnostic indices: adequate rate, diagnostic yield, sensitivity for malignancy. (*Adequate* means that it contains sufficient cells for a diagnosis; *Diagnostic* means that not only sufficient material provided but also a specific diagnosis made (non-adequate cases were excluded); *Sensitivity for malignancy* is the ratio of malignant diagnosis in all malignant cases diagnosed by histopathology or clinical follow-up (non-diagnostic cases were excluded); (IV) procedural details: number of biopsy sites, number of needle passes, procedure time, complication rate; (V) other endpoints: concordance between ROSE and final diagnosis, cost, ancillary test.

Data analysis

All statistical analyses were performed by Revman (Review Manager, version 5.3: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata Release 12 (Stata Corp., College Station, TX, USA). The primary endpoints were diagnostic indices like adequate rate, diagnostic yield, and sensitivity for malignancy. Secondary endpoints were the amount of biopsy sites, amount of needle passes, procedure time, complication rate, cost, ancillary test, and concordance between ROSE and the final diagnosis. The risk difference (RD) with 95% confidence interval (CI) of each study was calculated for dichotomous variables. The mean difference (MD) with 95% CI of each study was calculated for continuous variables. A meta-analysis of concordance between ROSE and the final diagnosis was completed in the 'metan' routine defined in Stata. All the individual study estimates were pooled using a fixed effects model when the I^2 <50%, otherwise a random effects model was used. Forest plots were generated to display the combined estimates. The impact of heterogeneity in the individual outcomes was assessed using the I^2 test and Cochrane Q statistic. An I^2 value ≥30% indicates significant heterogeneity, equally, a P value <0.1 in the Cochrane Q test was considered to be significant. The presence of publication bias was evaluated utilizing the Begg's funnel plot and Begg's test. The plot resembles a symmetrical funnel and the P value <0.05 in the absence of publication bias. Subgroup analysis was carried out to compare different characteristics among included studies to analyze the heterogeneity and figure out under what circumstance ROSE makes more sense. Studies were evaluated and dichotomized according to study design (RCT or not-RCT), main sampling sites (solid pulmonary lesions or hilar/mediastinal lymph nodes), diagnostic methods (c-TBNA or EBUS-TBNA or TTFNA) and population (suspected/diagnosed lung cancer or unselected patients). Meta-regression was also performed to quantitatively determine whether the yield was related to previously defined subgroups.

Results

Summary of studies included

An initial search of MEDLINE and EMBASE databases yielded 7040 unique study titles and abstracts (3340 PUBMED, 5727 EMBASE). Screening of titles and abstracts provided a set of 138 studies eligible for inclusion. After reading the full text of these articles, only 21 studies (3,5,7,9-15,17-27) met our inclusion criteria. References list of the studies included provided additional 6 studies (1,2,4,6,8,28). Altogether, 27 studies were eligible to claim a qualitative and quantitative analysis. The flowchart of study selection process was shown in *Figure 1*.

The majority of the studies were prospective or retrospective cohort studies (19 out of 27) while 8 out of 27 were random controlled trials (RCTs). Diagnostic methods were multiple (5 c-TBNA, 11 EBUS-TBNA, 2 combined c-TBNA and EBUS-TBNA, 4 TTFNA, 1 FOB, 1 r-EBUS, 1 c-EBNA, 1 EBUS-FNA, 1 not restricted). Lymph nodes were mostly sampled in 17 studies. Pulmonary masses/nodules were sampled most in 8 studies, while the number of sampled lymph nodes and lung masses/nodules is equivalent in one study and the information of sampled lesions was not available in only one study. Some studies

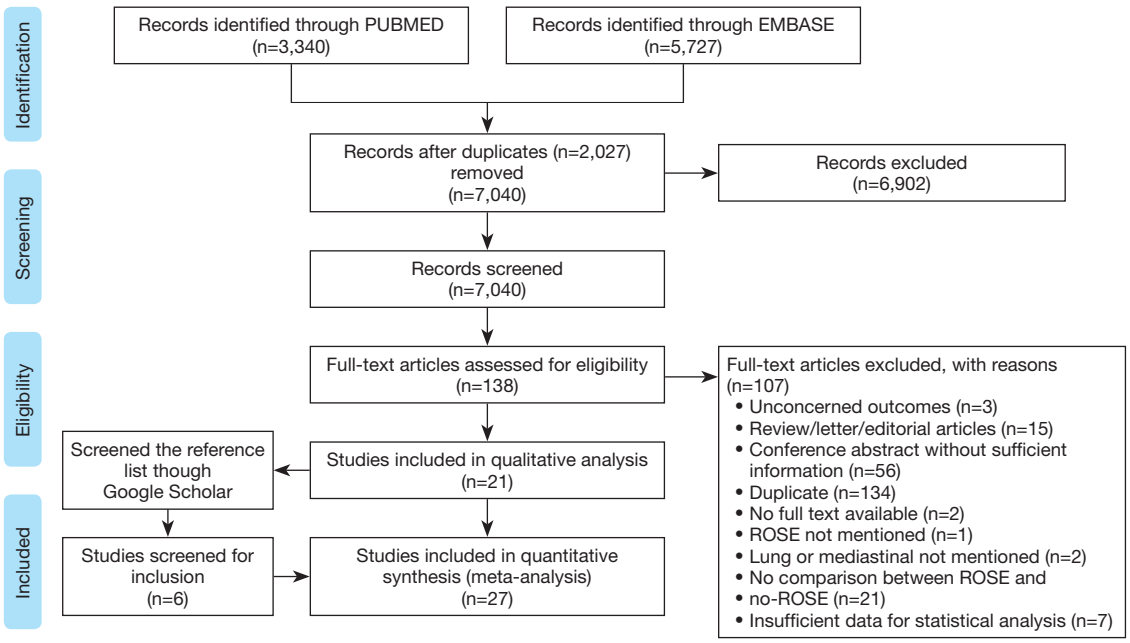

Figure 1 PRISMA study flow diagram.

enrolled patients with suspected or diagnosed lung cancer; some were conducted in unselected practice, only 1 study included patients with suspected sarcoidosis, the remaining 3 studies enrolled patients with SPN, PPL and central pulmonary lesions (*Table 1*). Adequate rate, diagnostic yield, and sensitivity for malignancy were reported on a per-case basis in 5, 18, and 12 studies, respectively. Nine studies were noticed to compare the number of biopsy sites and 13 compared the number of needle passes. The contrast of procedure time and complication rate between ROSE group and No-ROSE group were reported in 10 and 14 studies. Comparison of the cost was presented in 2 studies. The ancillary test was mentioned about in 4 studies. Concordance between ROSE and the final diagnosis can be extracted from 9 studies (*Table 2*).

Chin *et al.* 2002 (8) was excluded from the further meta-analysis. The primary endpoint of this study was to ascertain the average number of aspirates needed to make a definite cytological diagnosis successfully. The maximum number of aspirates with ROSE reached 7, which was applicable in daily clinical practice and greatly affected the diagnose efficacy.

Quality assessment

A quality assessment utilizing QUADAS-2 is displayed in *Table 3*. The overall risk of bias was low in 7 studies, the overall concerns about applicability were low in 9 studies, and seven of these studies met both conditions.

Primary endpoints

Adequate rate

Figure 2A showed the forest plot of pooled adequate rate. The meta-analysis of adequate rate assessed in 5 studies (3,5,11,17,27) was 0.12 (I^2=0%) using fixed-efforts, with the individual RD of adequacy varied from 0.07 to 0.16 (*Figure 2A*).

Diagnostic yield

Eighteen studies (2,4-6,9-13,17-19,22-27) provided the data of diagnostic yield and Madan *et al.* (23) conducted the cohort study in both c-TBNA and EBUS-TBNA group. On average, the conjunction of ROSE led to a 14% improvement (95% CI: 0.09–0.18, I^2=57%) in diagnostic yield (*Figure 2B*).

Sensitivity for malignancy

With ROSE, the average increase of sensitivity for malignancy assessed in 12 studies (2,3,5,10-13,17,21,24,25,27) was 10% ranging from 6% to 14% (*Figure 2C*).

Table 1 Basic characteristic of included studies (Part A)

Author year	Country	Study design	No. of patients	Sampling method	Main sampling sites	Population	No. of biopsy sites		No. of needle passes	
							R	NR	R	NR
Madan *et al.*, 2016	India	RCT	80	c-TBNA/EBUS-TBNA	Lymph nodes	Patients suspected for sarcoidosis	NA	NA	NA	NA
Yarmus *et al.*, 2011	America	RCT	68	c-TBNA	Lymph nodes	Unselected patients with enlarged hilar/mediastinal lymph nodes	NA	NA	4.47	4.14
Oki *et al.*, 2013	Japan	RCT	108	EBUS-TBNA	Lymph nodes	Patients suspected for lung cancer	NA	NA	2.2±0.9	3.1±0.4
Trisolini *et al.*, 2015	Italy	RCT	197	EBUS-TBNA	Lymph nodes	Patients with known or Suspected lung cancer	1.3±0.5	1.4±0.5	4	4
Trisolini *et al.*, 2011	Italy	RCT	168	c-TBNA	Lymph nodes	Unselected patients with enlarged hilar/mediastinal lymph nodes	1	2	NA	NA
Murakami *et al.*, 2013	Japan	RCS	98	EBUS-TBNA	Lymph nodes	Patients with diagnosed small cell lung cancer	1.1	1.6	2.3	4.0
Li *et al.*, 2014	China	RCS	69	EBUS-TBNA	Lymph nodes	Patients with diagnosed lung cancer	NA	NA	2.4±0.2	4.6±0.4
Chin *et al.*, 2002	America	PCS	79	c-TBNA	Lymph nodes	Unselected patients underwent c-TBNA	NA	NA	6.2±2.5	4.5±1.7
Bruno *et al.*, 2013	Italy	RCS	120	c-TBNA	Lymph nodes	Patients suspected of lung cancer	NA	NA	NA	NA
Gianella *et al.*, 2018	Switzerland	PCS	348	EBUS-TBNA	Lymph nodes	Unselected patients underwent EBUS-TBNA	1.6±0.8	1.7±0.8	NA	NA
Cardoso *et al.*, 2015	Portugal	PCS	81	EBUS-TBNA	Lymph nodes	Unselected patients underwent EBUS-TBNA	NA	NA	3.4±1.7	4.5±1.7
Mondoni *et al.*, 2013	Italy	RCS	125	c-EBNA	Pulmonary nodules/masses	Patients with suspected central lung cancer	NA	NA	NA	NA
Baram *et al.*, 2005	America	PCS	42	c-TBNA/EBUS-TBNA	Lymph nodes	Unselected patients underwent TBNA	1.4	1.8	2.8±1.0	3.2±1.2
Chen *et al.*, 2015	China	RCS	815	r-EBUS+TBB/brushing	Pulmonary nodules/masses	Patients with peripheral pulmonary lesions	NA	NA	NA	NA
Diette *et al.*, 2000	America	PCS	204	FOB	NA	Unselected patients underwent FOB	NA	NA	5.2	4.4

Table 1 *(continued)*

Table 1 *(continued)*

Author year	Country	Study design	No. of patients	Sampling method	Main sampling sites	Population	No. of biopsy sites		No. of needle passes	
							R	NR	R	NR
Austin *et al.*, 1993	America	PCS	55	CT-guided FNA	Pulmonary nodules/masses	Patients with diagnosed lung cancer	NA	NA	1.7±0.9	1.3±0.5
Santambrogio *et al.*, 1997	Italy	RCT	220	CT-guided FNA	Pulmonary nodules/masses	Patients with indeterminate solid pulmonary lesions	1.2±0.5	1.1±0.3	NA	NA
Saleh *et al.*, 1996	America	RCS	159	CT-guided FNA	Pulmonary nodules/masses	NA	NA	NA	NA	NA
Küçük *et al.*, 2004	Turkey	RCT	96	CT-guided FNA	Pulmonary nodules/masses	Patients with diagnosed lung cancer	NA	NA	NA	NA
Davenport *et al.*, 1990	America	RCS	161	c-TBNA	Pulmonary nodules/masses	Unselected patients underwent TBNA	NA	NA	NA	NA
Collins *et al.*, 2012	America	RCS	680	EBUS-FNA	Lymph nodes	Unselected patients underwent EBUS-FNA	1.394	2.085	NA	NA
Griffin *et al.*, 2010	America	RCS	149	EBUS-TBNA	Lymph nodes	Unselected patients underwent EBUS-TBNA	NA	NA	NA	NA
Guo *et al.*, 2015	China	RCS	236	EBUS-TBNA	Lymph nodes	Patients with known or suspected lung cancer	2.1	2.3	2.7	2.9
Xiang *et al.*, 2018	China	RCS	141	EBUS-TBNA	Lymph nodes	Patients with suspected lung cancer	NA	NA	NA	NA
Chaiyakul *et al.*, 2018	Thailand	PCS	175	EBUS-TBNA	Pulmonary nodules/masses	Patients with central intrapulmonary lesions	NA	NA	3.4±0.66	6.07±1.34
Wong *et al.*, 2014	America	RCS	178	EBUS-TBNA	Lymph nodes	Unselected patients underwent EBUS-TBNA	1.5±0.7	1.9±0.8	2.5±0.9	2.5±1.0
Kern *et al.*, 2012	Slovenia	PCS	385	Not restricted	Equivalent	Unselected patients underwent TBNA/FNA	NA	NA	NA	NA

RCT, random controlled trial; RCS, retrospective cohort study; PCS, prospective cohort study; c-TBNA, conventional transbronchial needle aspiration; EBUS, endobronchial ultrasound; c-EBNA, conventional endobronchial needle aspiration; r-EBUS, radial probe endobronchial ultrasound; TBB, transbronchial biopsy; FOB, fiberoptic bronchoscopy; ROSE, rapid on-site evaluation; NR, without rapid on-site evaluation; NA, not available.

Table 2 The basic characteristics of the included studies (Part B)

Author year	Diagnostic outcome			Procedure time		Complication rate		Cost	Ancillary test	Concordance between ROSE and final diagnosis
	Adequacy	Diagnostic yield	Sensitivity for malignancy	R	NR	R	NR			
Madan *et al.*, 2016										
c-TBNA	NA	Reported	NA	21±2.8	20±3.8	0/20	1/20	NA	NA	NA
EBUS-TBNA	NA	Reported	NA	25±4.8	25±4.9	2/20	1/20	NA	NA	NA
Yarmus *et al.*, 2011	Reported	Reported	Reported	29.5	27.6	NA	NA	NA	NA	NA
Oki *et al.*2013	NA	Reported	Reported	22.3±15.9	22.1±7.7	0/55	0/53	NA	NA	NA
Trisolini *et al.*, 2015	Reported[a]	Reported	NA	17.8±8.34	17.9±5.61	3/98	4/99	NA	Reported	NA
Trisolini *et al.*, 2011	Reported[a]	Reported	NA	NA	NA	5/83	17/85	NA	NA	Reported
Murakami *et al.*, 2013	NA	Reported	Reported	NA	NA	0/77	0/23	NA	NA	NA
Li *et al.*, 2014	NA	Reported	Reported	NA	NA	4/37	10/32	Reported	NA	Reported
Chin *et al.*, 2002	NA	Reported	NA	NA	NA	NA	NA	NA	NA	NA
Bruno *et al.*, 2013	NA	Reported	Reported	NA	NA	NA	NA	Reported	NA	NA
Gianella *et al.*, 2018	NA	NA	Reported	NA	NA	NA	NA	NA	NA	NA
Cardoso *et al.*, 2015	Reported	Reported	Reported	NA	NA	0/41	0/40	NA	NA	NA
Mondoni *et al.*, 2013	NA	Reported	Reported	NA	NA	NA	NA	NA	NA	NA
Baram *et al.*, 2005	NA	Reported[a]	Reported[a]	39±20	39±14	0/32	0/12	NA	NA	Reported
Chen *et al.*, 2015	NA	Reported	NA	28.12±6.67	27.7±8.40	NA	NA	NA	NA	Reported
Diette *et al.*, 2000	NA	Reported	NA	39.1	32.6	NA	NA	NA	NA	Report
Austin *et al.*, 1993	NA	Reported	Reported	NA	NA	4/25	2/30	NA	NA	NA
Santambrogio *et al.*, 1997	Reported	NA	Reported	NA	NA	29/110	23/110	NA	NA	NA
Saleh *et al.*, 1996	NA	Reported	NA	NA	NA	NA	NA	NA	NA	NA
Küçük *et al.*, 2004	Reported	Reported	Reported	NA	NA	7/48	6/48	NA	NA	NA
Davenport *et al.*, 1990	Reported[a]	NA	Reported[a]	NA	NA	NA	NA	NA	NA	Reported
Collins *et al.*, 2012	Reported[a]	Reported[a]	NA	NA	NA	NA	NA	NA	NA	NA
Gariffin *et al.*, 2010										
Lymph nodes	NA	Repprted[a]	NA	NA	NA	NA	NA	NA	Reported	NA
Lung lesions	NA	Repprted[a]	NA	NA	NA	NA	NA	NA		NA
Guo *et al.*, 2015	Reported	Repprted[a]	NA	37.6	37.4	0/122	0/114	NA	NA	NA
Xiang *et al.*, 2018	Reported	Reported	Reported	NA	NA	1/81	7/60	NA	NA	Reported
Chaiyakul *et al.*, 2018	NA	Reported	NA	32.33±6.50	50.32±4.99	NA	NA	NA	NA	Reported
Wong *et al.*, 2014	NA	NA	NA	NA	NA	NA	NA	NA	Reported	Reported
Kern *et al.*, 2012	NA	Reported	NA	NA	NA	NA	NA	NA	NA	NA

[a], reported in per-lesion or per-speciman basis. c-TBNA, conventional transbronchial needle aspiration; EBUS, endobronchial ultrasound; ROSE, rapid on-site evaluation; NR, without rapid on-site evaluation; NA, not available.

Table 3 Quality assessment utilizing QUADAS-2

Author-year	Risk of bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Madan *et al.*, 2016	Low	Low	High	Low	Low	Low	High
Yarmus *et al.*, 2011	Low	Low	Low	Low	Low	Low	Low
Oki *et al.*, 2013	Low	Low	High	Low	Low	Low	High
Trisolini *et al.*, 2015	Low	Low	Unclear	Unclear	Low	Low	Unclear
Trisolini *et al.*, 2011	Low	Low	Low	Low	Low	Low	Low
Murakami *et al.*, 2013	High	Low	Low	Low	High	Low	Low
Li *et al.*, 2014	High	Low	Low	Low	High	Low	Low
Bruno *et al.*, 2013	Low	Low	Low	Low	Low	Low	Low
Gianella *et al.*, 2018	Low	Low	Low	Unclear	Low	Low	Low
Cardoso *et al.*, 2015	Low	Low	High	Low	Low	Low	High
Mondoni *et al.*, 2013	High	Low	Low	Low	High	Low	Low
Baram *et al.*, 2005	Unclear	Low	Low	Low	Unclear	Low	Low
Chen *et al.*, 2015	Low	Low	High	High	Low	Low	High
Diette *et al.*, 2000	Low	Low	High	Low	Low	Low	High
Austin *et al.*, 1993	High	Low	Low	Low	High	Low	Low
Santambrogio *et al.*, 1997	Low	Low	Low	Low	Low	Low	Low
Saleh *et al.*, 1996	Unclear	Low	High	Unclear	Unclear	Low	High
Küçük *et al.*, 2004	High	Low	Unclear	Low	Low	Low	Low
Davenport *et al.*1990	Low	Low	High	Low	Low	Low	High
Collins *et al.*, 2012	Low	Low	High	Low	Low	Low	High
Griffin *et al.*, 2010	Low	Low	Low	Low	Low	Low	Low
Guo *et al.*, 2015	Low	Low	Low	Low	Low	Low	Low
Xiang *et al.*, 2018	Low	Low	High	Low	Low	Low	High
Chaiyakul *et al.*, 2018	Low	Low	Low	Low	Low	Low	Low
Wong *et al.*, 2014	Low	Low	High	Low	Low	Low	High
Kern *et al.*, 2012	Low	Low	Unclear	Unclear	Low	Low	Unclear

Secondary endpoints

Amount of sampled sites and needle passes

Nine and 13 studies severally compared the amount of sampled lesions or needle passes between the ROSE and no-ROSE group, and only 4 (3,21,26,28) and 7 (2,7,10,12,17,18,28) of these studies severally provided enough data for meta-analysis. The pooled MD pointed out that ROSE did not affect the amount of sampled sites (–0.11, 95% CI: –0.29 to 0.08) (*Figure 3A*) but was inclined to decrease the amount of needles passes (–0.99, 95% CI: –1.89 to –0.09) (*Figure 3B*).

Procedure time and complication rate

Although the contrast of procedure time was mentioned in 9 studies, 3 of them lack ample data for meta-analysis. Pooled procedure time of the remaining 6 studies

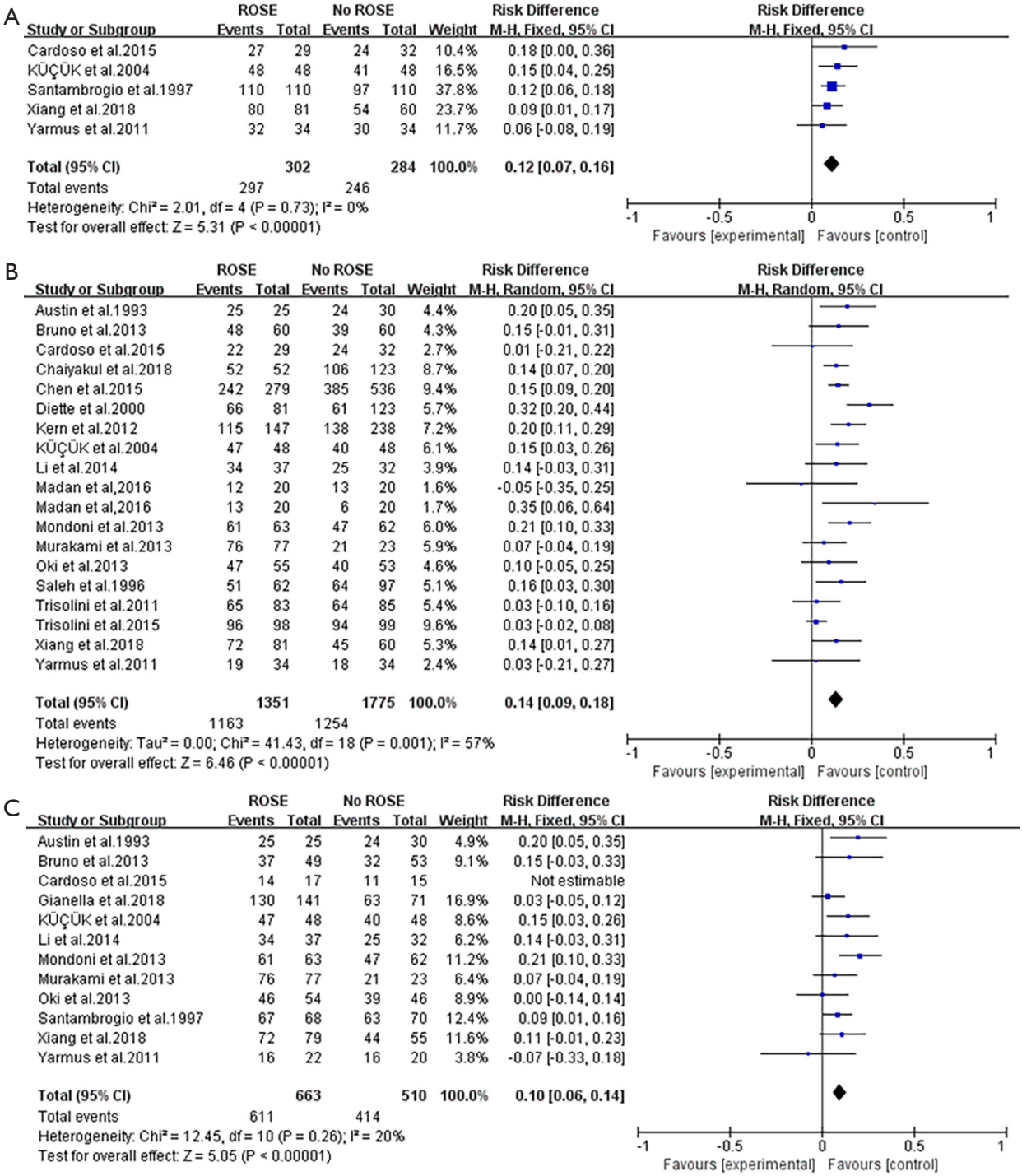

Figure 2 Forest plots of primary endpoints. (A) Forest plot of the RD comparing the adequate rate of ROSE or without ROSE in the included studies; (B) forest plot of the RD comparing the diagnostic yield of ROSE or without ROSE in the included studies; (C) forest plot of the RD comparing the sensitivity in diagnosing malignancy of ROSE or without ROSE in the included studies. RD, risk difference; ROSE, rapid on-site evaluation.

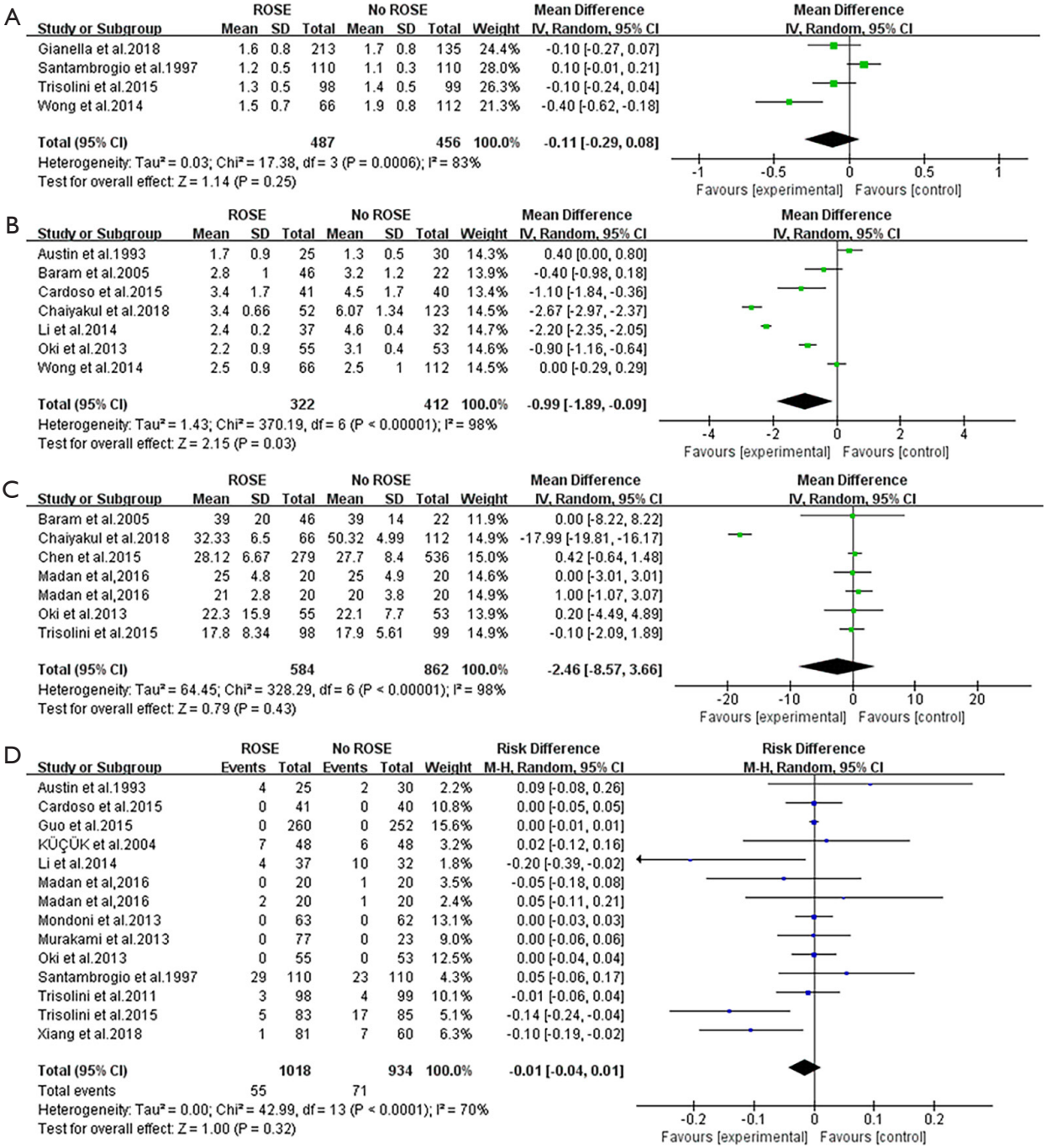

Figure 3 Forest plots of secondary endpoints. (A) Forest plot of the MD comparing the number of sampled sites of ROSE or without ROSE in the included studies; (B) forest plot of the MD comparing the number of needles passes of ROSE or without ROSE in the included studies; (C) forest plot of the MD comparing the procedure time of ROSE or without ROSE in the included studies; (D) forest plot of the RD comparing the complication rate of ROSE or without ROSE in the included studies. MD, mean difference; RD, risk difference; ROSE, rapid on-site evaluation.

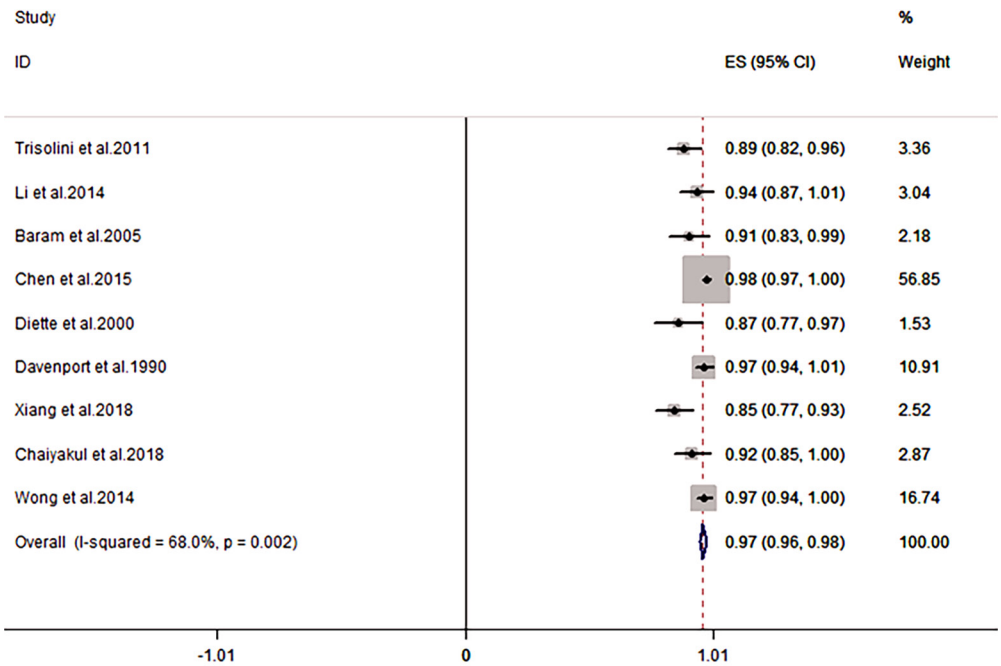

Figure 4 Forest plot of the pooled concordance between ROSE and final diagnosis in the included studies. ROSE, rapid on-site evaluation.

(7,12,18,19,23,26) was not statistically different between the ROSE and No-ROSE group with pooled MD −0.46 (95% CI: −0.87 to 3.66) (*Figure 3C*). Pooled complication rate between the two groups in 14 studies (2,3,5,7,9,10,12,15,17,23-27) did not reach statistical difference [pooled RD =−0.01 (95% CI: −0.04 to 0.01)] either (*Figure 3D*).

Cost and ancillary test

Li *et al.* (10) found that the cytology diagnostic cost decreased to 130.8±2.5 RMB with ROSE from 140.3±4.6 RMB. Bruno *et al.* (13) found that a considerable amount of euros (19413) was saved when using TBNA with ROSE as first diagnostic approach compared to using TBNA without ROSE when calculating the costs of combined procedures performed while diagnosing patients with mediastinal lymphadenopathy suspected for lung cancer.

Wong and his colleagues reported a larger proportion of satisfactory cell block after the utilization of ROSE (74%pre-ROSE *vs.* 90% post-ROSE) (28). Griffin *et al.* (14) reported that 92% of cell blocks were obtained with ROSE compared to 88% without ROSE, and more samples detected by immunochemistry (29% *vs.* 15%). Xiang *et al.* once reported similar results in immunochemistry. What's more, a randomized controlled trial carried out by Trisolini *et al.* (26) demonstrated that ROSE is associated with a 10% improvement of the complete genotyping achieved, though not reaching statistical significance, implies the prevention of redo procedures to gain genetic information for targeted therapy (*Table S1*).

Concordance between ROSE and final diagnosis

The combined concordance between ROSE and final diagnosis was 97% (95% CI: 0.96–0.98, I^2=68%) (1,6,7,9,10,18,19,27,28) (*Figure 4*).

Subgroup analysis and univariate analysis

Subgroup analysis was conducted to assess the heterogeneity across studies in diagnostic yield and to amplify circumstances in which ROSE has more significance (*Table 4*). The pooled RD of diagnostic yield in RCTs was 0.10 (95% CI: 0.03–0.17), and the pooled RD in not-RCTs was 0.16 (95% CI: 0.12–0.20). The subgroup difference was not significant at a P value of 0.14. The pooled RD (95% CI) of the diagnostic yield in studies mostly sampling lung masses/nodules was 0.07 (0.03–0.12), while the pooled RD (95% CI) of studies mostly sampling lymph nodes was 0.16 (0.12–0.20) and the subgroup difference was significant (P=0.005).According to the diagnostic method, the pooled

Table 4 Subgroup analysis of diagnostic yield

Subgroup	No. of studies	Pooled RD of diagnostic yield	Heterogeneity (I^2)	Subgroup difference (P value)
Study design				0.14
RCT	7*	0.10 (95% CI: 0.03 to 0.17)	55%	
No-RCT	11	0.16 (95% CI: 0.12 to 0.20)	21%	
Main sampling sites				0.005
Solid pulmonary lesions	6	0.16 (95% CI: 0.12 to 0.20)	10%	
Hilar/mediastinal lymph nodes	10*	0.07 (95% CI: 0.03 to 0.12)	0%	
Diagnostic method				0.2
c-TBNA	5	0.11 (95% CI: 0.03 to 0.18)	29%	
EBUS-TBNA	7	0.08 (95% CI: 0.04 to 0.12)	29%	
CT-guided TTFNA	3	0.16 (95% CI: 0.08 to 0.25)	0%	
Population				0.98
Unselected patients	4	0.11 (95% CI: −0.07 to 0.28)	77%	
Suspected sarcoidosis	1*	0.15 (95% CI: −0.24 to 0.54)	72%	
Suspected/diagnosed lung cancer	9	0.12 (95% CI: 0.06 to 0.18)	52%	

*, one study provided a diagnostic yield of c-TBNA and EBUS-TBNA separately. RD, risk difference; RCT, random controlled trial; c-TBNA, conventional transbronchial needle aspiration; EBUS, endobronchial ultrasound; TTFNA, transthoracic fine needle aspiration.

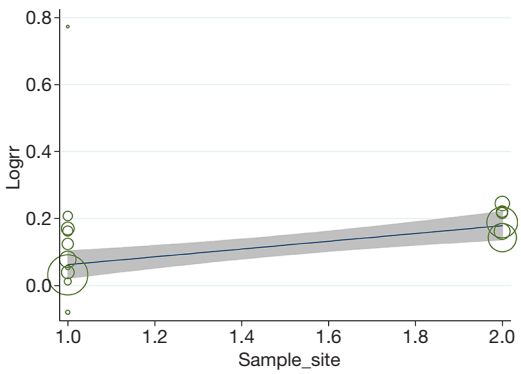

Figure 5 Meta-regression analysis of the primary sampling sites.

RD (95% CI) of diagnostic yield was 0.11 (0.03–0.18) with c-TBNA, 0.08 (0.04–0.12) with EBUS-TBNA, 0.16 (0.08–0.25) with TTFNA. The subgroup difference was not significant (P=0.20). A pooled RD of 0.12 (95% CI: 0.06–0.18) was found in the diagnostic yield of patients with suspected or diagnosed pulmonary malignancy, 0.15 (95% CI: −0.24 to 0.54) in suspected sarcoidosis and 0.11 (95% CI: −0.07 to 0.28) in an unselected population.

Univariate analysis was performed on variables that considered as possible sources of heterogeneity; Meta-regression model showed that the main sampling sites (lung masses or lymph nodes) explained 94.24% between-study variability in the change in diagnostic yield due to ROSE (*Figure 5*).

Publication bias

The publication bias did not impact the adequacy rate, diagnostic yield and sensitivity for malignancy in this meta-analysis, as shown by the Begg's funnel plots (*Figures S1-S3*) and the P value of Begg's test for adequacy rate, diagnostic yield and sensitivity rate were 0.806, 0.944 and 0.436 respectively.

Discussion

This systemic review and meta-analysis firstly provided such a comprehensive description of the main results in all published studies comparing any aspect between ROSE and no-ROSE cohort in diagnosing pulmonary lesions and mediastinal lymph nodes at a single site. We figured out that, on average, ROSE contributed to a 12%, 14%, and 10% rise in per-case adequate rate, diagnostic yield, and sensitivity for malignancy respectively. Although utilization

of ROSE was inclined to decrease the number of needle passes (–0.99, 95% CI: –1.89 to –0.09), ROSE neither impacted the procedure time nor complication rate. Sub-analysis demonstrated a higher improvement of diagnostic yield with ROSE when diagnosed by CT-guided TTFNA, sampling pulmonary masses/nodules or applied to patients with suspected/diagnosed lung cancer and in no-RCT studies.

This meta-analysis illustrated that ROSE was associated with a statistical increase not only in adequate rate, but also in diagnostic yield and sensitivity for malignancy. Adequate means sufficient material provided, which was reported by per-specimen basis or per-case basis. Davenport offered a criterion for adequacy: the presence of malignant cells or numerous benign lymphoid cells that indicates the sample was obtained from a lymph node or a specific no neoplastic lesion (1). Even though the criteria in each study differed, the foundation of adequacy was cellularity. Improved adequacy rate means the improved quantity of cells gained from specimens. However, adequate is not sufficient for diagnostic. Once a specimen was described as adequate, it just means that it contains sufficient cells for a diagnosis. Whether a specific diagnosis can be made ultimately depended on the quality of the limited cells. Improved diagnostic yield means improved quality of specimens. Higher sensitivity for malignancy is another evidence for a better quality of specimens. Improved diagnostic yield means more diagnosis made but higher sensitivity for malignancy means more accurate the diagnosis was. Accordingly, the main finding of this meta-analysis is that ROSE is of great benefit to improve the quality and quantity of specimens.

Besides improvement in yield, ROSE was reported to have an impact on procedure details such as reducing the amount of sampling lesions or needle passes (1), shorting the procedure time (18) and eventually decreasing the complication rate (9,10,27). The present analysis revealed that the use of ROSE contributed to a reduction in the number of needle passes (*Figure 3B*). In theory, a decrease in needle passes should lead to shorter procedure time and then less complication rate. For example, Chaiyakul *et al.* reported a reduction of needle passes and shorter procedure time accordingly and Li *et al.* reported reduced needle passes and correspondingly fewer complications. Nevertheless, there was a statistical difference between groups neither in procedure time nor in complication rate (*Figure 3D*). The probable reason for the indistinctive impact on procedure time might be that ROSE itself needed time such as staining and analyzing quick smears. Additional time of ROSE might weaken the impact of the reduction of needle passes on the whole procedure time. As for complication rate, though it is bound up with the amount of sampling lesions and needle passes, pooled complication rate between the two groups failed reach statistical difference. Further subgroup analysis suggested that complication rate was reduced in c-TBNA and EBUS-TBNA but not in TTFNA (*Figure S4*). Possible explanation might be that the needle passes of these two studies contacted TTFNA didn't reduce. Apart from decreasing the needle passes (7), the lower requirement of additional procedures was recorded as well by several studies. In spite of indistinctive impact on procedure time and complication rate, the reduction of needle passes and additional procedures logically translated into cost saving. Li *et al.* (10) reported a slight decrease in cytologic diagnostic cost when utilizing ROSE, whereas Bruno *et al.* (13) reported a considerable reduction in the cost of combined procedures needed in the diagnostic process of suspected lung cancer. Despite the lack of sufficient literature for a meta-analysis, the incline of saving the cost is observable by reducing the needle passes and preventing from additional procedures.

What's more, in the current era of personalized medicine, lung cancer treatment such as chemotherapy and targeted therapy are assigned by histology and molecular testing. Xiang *et al.* and Griffin *et al.* (14) reported a higher rate of samples sufficient for immunochemistry, and then a higher rate of successful histological classification could be differentiated. Furthermore, Trisolini *et al.* (26) demonstrated that completing genotyping was obtained in more patients in the ROSE arm. ROSE could increase the number of samples with a high proportion of neoplastic cells, thus improved the rate of successful immunochemistry and molecular genotyping. There has been limited literature reporting on this aspect of ROSE by far. However, the advantage of the ancillary test would be promising in the coming era of individual pharmacotherapy.

All in all, ROSE is a useful technology for diagnosing pulmonary lesions with the advantage of improving the quality and quantity of specimens for histology and even molecular diagnosis, reducing the number of needle passes and saving the cost.

We found significant heterogeneity across studies in diagnostic yield, and we performed subgroup analyses to analyze the heterogeneity and try to figure out circumstances under which ROSE weighs more (*Table 4*). The leading cause of heterogeneity was mainly sampling

sites. (We divided the sampling sites as mainly sampling pulmonary masses/nodules or hilar/mediastinal lymph nodes because most studies sampled both locations but always with a dominant one.) The rise of diagnostic yield was higher when primarily sampling solid pulmonary lesions than primarily sampling lymph nodes. Meta-regression further showed that this sub-analysis explained 94.24% between-study variability in the change in diagnostic yield due to ROSE. Recently, a meta-analysis comparing the diagnostic yield of TBNA demonstrated that the addition of ROSE does not enhance the diagnostic yield or reduce the procedure time of c-TBNA and EBUS-TBNA in mediastinal lymph node sampling (29). But this meta-analysis only included 5 RCTs sampling mediastinal lymph nodes by c-TBNA and EBUS-TBNA, there are additional RCTs sampling lung masses/nodules with other diagnostic procedures and reported a significant increase in diagnostic yield with ROSE (3,5,24). Distinct cytological characteristics between solid lesions and adenopathy might explain this observation. As we know, ROSE guides the diagnostic process by assessing the specimen in the form of adequate or diagnostic. For lymph nodes, once diagnostic cells or numerous benign lymphoid cells were acquired, a specimen was considered to be adequate, and the diagnostic process terminated. For solid lesions, the process was inclined to end when a diagnostic specimen was gained. Acquisition of numerous benign lymphoid cells which regarded as adequate might be a non-diagnostic or false negative. In other words, ROSE affected the solid pulmonary lesions in the form of diagnostic yield while affected lymph nodes in the form of both adequacy and diagnostic yield. Thus it might limit the influence of ROSE on diagnostic yield when sampling lymph nodes. For different diagnostic methods, ROSE increased the diagnostic yield of all the three diagnostic methods as c-TBNA, EBUS-TBNA, and TTFNA. Meanwhile, the subgroup difference didn't reach statistical difference (P=0.20). What's more, the advantage of ROSE was not certified when applied to unselected patients or patients with suspected sarcoidosis, while a combined 12% increase was discovered when applying ROSE to patients with suspected or diagnosed lung cancer. Three of the 4 studies applied to unselected patients sampled lymph nodes for diagnosis (9,11,17). As we hypothesized above, the acquisition of numerous benign lymphoid cells might be non-diagnostic or false-negative and limits the impact of ROSE when sampling lymph nodes. Similarly, when sampling lymph nodes, the influence of ROSE is even less in unselected patients with a higher rate of benign lesions compared to patients suspected with lung cancer. Therefore, we recommend ROSE to patients with suspected lung cancer rather than unselected patients, especially when sampling lymph nodes.

We also first evaluated the combined concordance between ROSE and final diagnosis. The pooled concordance was 97%. High concordance between ROSE and definitive diagnosis signifies the remarkable accuracy of ROSE. The highly accurate ROSE in the diagnostic process can prevent inappropriate termination or unnecessary repetition of the sampling process.

Though detailed and comprehensive, our meta-analysis still has few limitations. First, to examine the role of ROSE in different patient groups, only one study (23) selected patients with suspected sarcoidosis. The impact of ROSE in diagnosing sarcoidosis still needs to be explored with more researches in the future. Besides, alternative evaluators (AEs) such as respiratory physicians and thoracic surgeons are advocated to perform ROSE for the limited availability of cytopathologists, and several studies reported comparative yield by AEs (30,31). This review did not offer a comparison between cytopathologists and AEs. Finally, Davenport (1) once figured out that ROSE may have a more significant impact in peripheral pulmonary lesions while this meta-analysis failed to compare the effects of ROSE between central and peripheral pulmonary lesions with limited literature.

Conclusions

In conclusion, ROSE offers the opportunity to raise quality and quantity of specimens for histology and even molecular diagnosis, reduce the number of needle passes and save the cost in the diagnosing procedure without increasing the procedure time or complication rate. ROSE plays a more significant role when sampling pulmonary masses/nodules and in the patient group with suspected lung cancer. Moreover, ROSE is highly consistent with the final diagnosis, which means that real-time feedback of ROSE is entirely accurate.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Detailed information about cost and ancillary test

Author year	Cost or Ancillary test	R	NR
Li *et al.*, 2014	Cytology diagnostic cost	130.8±2.5 RMB	140.3±4.6 RMB
Bruno *et al.*, 2013	Total expenses incurred for the diagnostic procedure	61,224 euro	80,637 euro
Wong *et al.*, 2014	Satisfactory cell block	90%	74%
Griffin *et al.*, 2010	Cell block	92%	88%
Griffin *et al.*, 2010	Immunochemistry stains	29%	15%
Xiang *et al.*, 2018	Immunochemistry stains	40.74%	15%
Trisolini *et al.*, 2015	Complete genotyping	85.7%	80.5%

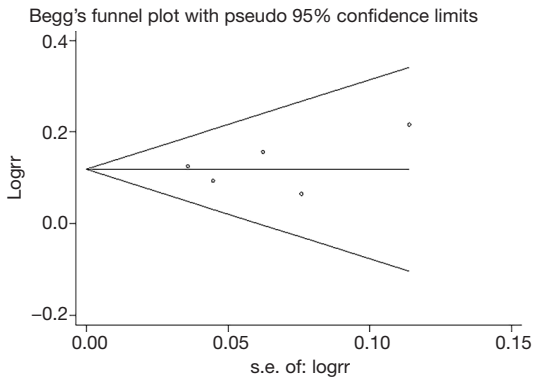

Figure S1 Funnel plot evaluating the adequacy of ROSE or without ROSE in the included studies. ROSE, rapid on-site evaluation.

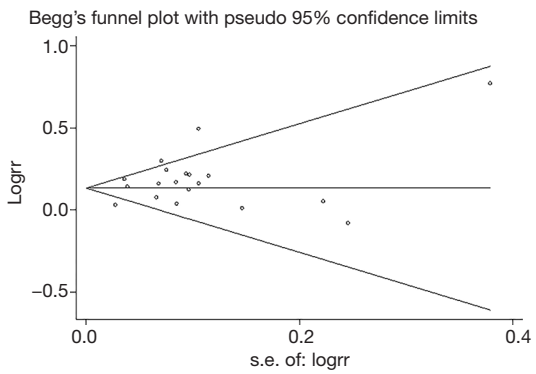

Figure S2 Funnel plot evaluating the diagnostic yield of ROSE or without ROSE in the included studies. ROSE, rapid on-site evaluation.

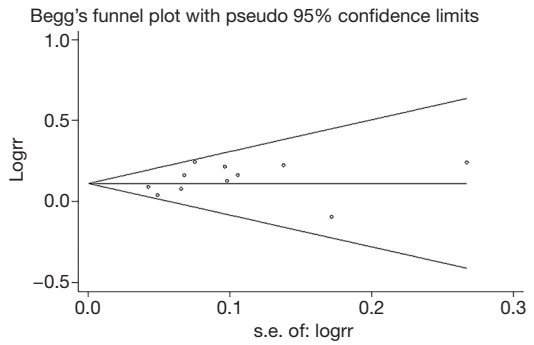

Figure S3 Funnel plot evaluating sensitivity for malignancy of ROSE or without ROSE in the included studies. ROSE, rapid on-site evaluation.

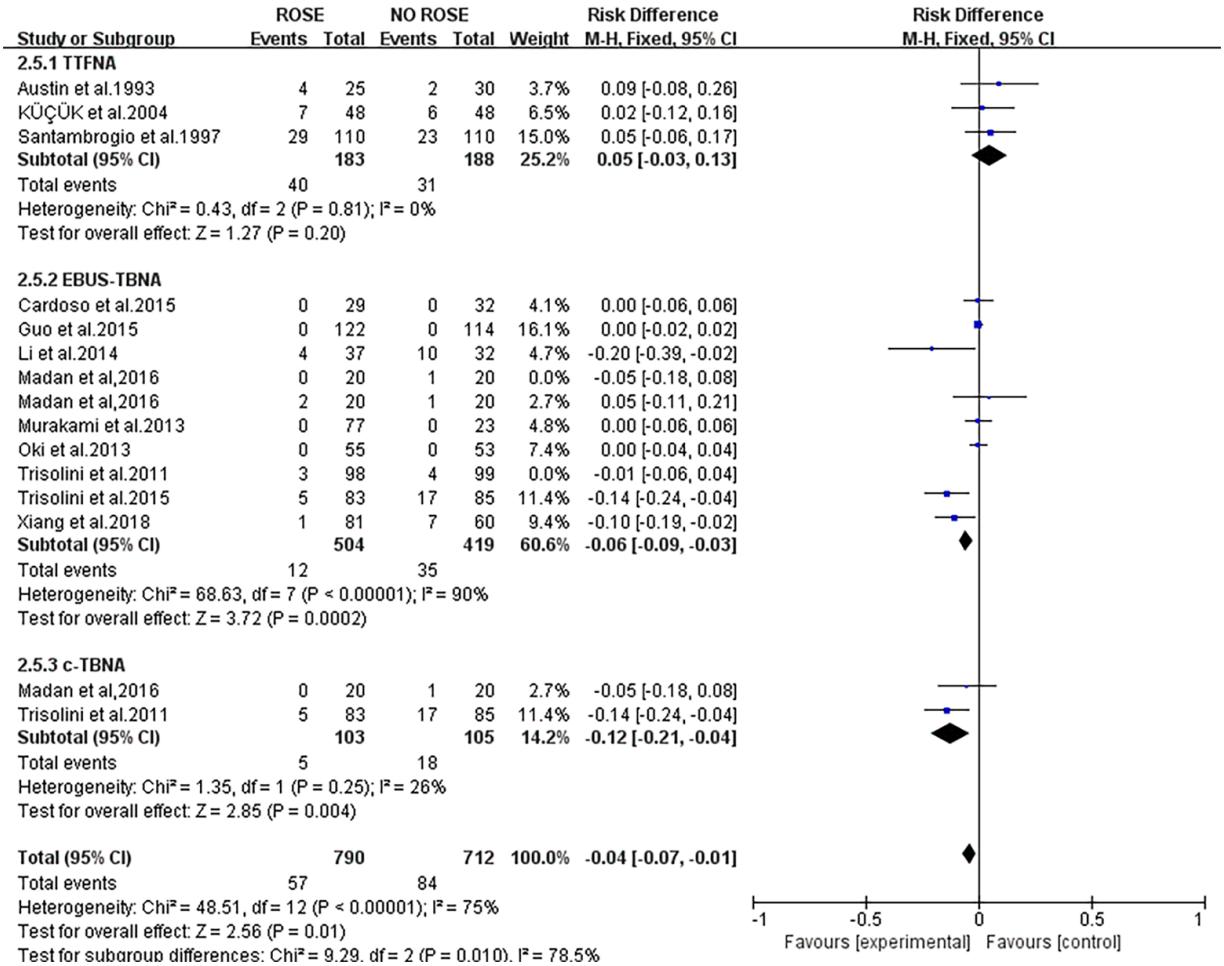

Figure S4 Forest plot of the RD comparing the complication rate of ROSE or without ROSE in subgroup analysis of different diagnostic methods. RD, risk difference; ROSE, rapid on-site evaluation.