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*Original Article*

# The effectiveness of rapid on-site cytological evaluation (ROSE) on the diagnostic yield of bronchoscopy in peripheral pulmonary lesions: a systematic review and meta-analysis

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**Abstract:** *Background*: Peripheral pulmonary lesions (PPLs) cannot be directly visualized during bronchoscopy sampling, and the quality of specimens affects the diagnostic yield. The rapid on-site cytological evaluation (ROSE) system provides immediate feedback regarding the adequacy of specimens and guides the operators to modify the bronchoscopy technique and the site and depth sampled. However whether ROSE can increase the diagnostic yield of bronchoscopy in PPLs sampling has not been systematically examined. *Methods*: We comprehensively searched PubMed, EMBASE and relevant reviews up through April 2018 and screened for studies investigating the effectiveness of ROSE on the diagnostic yield of bronchoscopy in PPLs. *Results*: 15 out of 125 studies (4035 patients from 7 countries) were eligible for qualitative analysis. The pooled diagnostic yield of all included studies was 0.84 (95% CI 0.77-0.90). ROSE significantly increased the diagnostic yield versus diagnosis without ROSE (RD 0.15, 95% CI, 0.12-0.18). The pooled yield was 0.80 (95% CI 0.62-0.91) when bronchoscopy was guided by fluoroscopy, 0.85 (95% CI 0.78-0.90) when EBUS was used and 0.85 (95% CI 0.78-0.90) when ENB was used. When the lesions > 2 cm, the pooled diagnostic yield was 0.90 (95% CI 0.87-0.93), while the yield was 0.79 (95% CI 0.72-0.84) when the lesions ≤ 2 cm. *Conclusion*: The use of ROSE increased the diagnostic yield of bronchoscopy in PPLs diagnosis, particularly in the context of lesions ≤ 2 cm, fluoroscopy-guided and EBUS-guided bronchoscopy, especially when the probe was adjacent to the lesions in EBUS-guided bronchoscopy.

**Keywords:** Peripheral pulmonary lesion (PPL), rapid on-site cytological evaluation (ROSE), bronchoscopic guidance technologies, bronchoscopy

## Introduction

Peripheral pulmonary lesions (PPLs) are generally considered to be lesions in the peripheral one-third of the lung that cannot be directly visualized by regular bronchoscopes. PPLs comprise 25% to 30% of all lung cancers [1], so it is imperative to quickly identify malignant nodules to guide treatment and to avoid unnecessary invasive interventions in case of benign lesions. The fast development of diagnostic bronchoscopy and guidance technology (such as fluoroscopic guidance, endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB)) have raised diagnostic yields and reduced complications, leading to minimally invasive bronchoscopy being widely considered as the preferential diagnostic approach for PPLs. Wang et al. [2] showed that the pooled diagnostic yield of these techniques for PPLs was 70%, and the complication rate was extremely low, with a pneumothorax rate of 1.6%, with only 0.7% requiring an intercostal tube and no reports of substantial bleeding or death. The yield of bronchoscopy is affected by the lesion size, the location, the computed tomography (CT) scan appearance, and whether the specimen collection is adequate [3-5].

The rapid on-site cytological evaluation (ROSE) system provides immediate feedback regarding the adequacy of the specimens obtained during

the examination and guides the operators to modify the bronchoscopy technique, the site and depth sampled, so that, theoretically, ROSE can decrease the number of passes needed for an adequate sample, improving the diagnostic yield and reducing the risk of complications [6, 7]. Although a recent review showed that ROSE neither improved the diagnostic yield nor reduced the procedure time during transbronchial needle aspiration (TBNA) [8], the Pulmonary Pathology Society still recommends its use in EBUS-TBNA for the diagnosis of lung cancer because ROSE can ensure that the targeted lesion is being sampled, enabling appropriate specimen triage and minimizing the need for repeat procedures for additional desired testing (i.e., molecular studies) [9]. However, a limited number of studies, most of which were small, single-institution case series, have assessed the diagnostic yield of bronchoscopy guided by various technologies combined with ROSE in diagnosing PPLs, and show a great heterogeneity [1, 7, 10-24]. Herein we summarize the available literature in order to provide a pooled estimated diagnostic yield of bronchoscopy combined with ROSE and to explore the main factors that affect the yield under different clinical conditions.

## Materials and methods

This systematic review was conducted according to the guidelines of the Items for Systematic Reviews and Meta-Analyses statement [25].

### *Search strategy*

We selected studies that evaluated the yield of bronchoscopy combined with rapid on-site cytological evaluation (ROSE) for the diagnosis of peripheral pulmonary lesions (PPLs). We searched PubMed and EMBASE up through April 2018. In consideration of various guidance technologies used in the studies, we adopted key words such as “virtual bronchoscopy”, “electromagnetic navigation bronchoscopy”, and “EBUS” to search. The following free text terms were: (“rose” OR (“rapid” AND “onsite” AND “evaluation”) OR (“rapid” AND “onsite” AND “cytological” AND “evaluation”)) AND ((“peripheral” AND “pulmonary” AND “lesion”) OR (“virtual” AND “bronchoscopy”) OR (“electromagnetic” AND “navigation” AND “bronchoscopy”) OR “EBUS”). We also reviewed the previous relevant review articles. Only publications in English were considered.

### *Study selection and data extraction*

Observational/interventional studies where the subjects underwent PPLs sampling using bronchoscopy with ROSE and studies providing outcomes of diagnostic yield were included. The following exclusion criteria were employed. 1) Studies describing PPLs sampling using bronchoscopy without ROSE. 2) Studies where the diagnostic yield for PPLs was not provided separately. 3) Studies describing the use of ROSE in transthoracic sampling. 4) Editorials, letters, review articles and case reports with fewer than five patients. 5) Manuscripts not published in English.

Two independent authors (Mingli Yuan and Yi Hu) firstly reviewed all titles/abstracts to identify potentially relevant articles. Then, study selection, based on a full-text review, was performed according to the predefined inclusion/exclusion criteria and disagreements were resolved by discussion. The following data were extracted: authors, title, year of publication, country, sample size, study design, diagnostic yield, study population, lesion size, and guidance technology used.

### *Quality assessment*

Two authors (Mingli Yuan and Yi Hu) independently evaluated the quality of each study included using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [26]. The QUADAS-2 tool assesses the risk of bias and applicability based on four key domains that discuss patient selection, index testing, the flow of patient selection, the timing of index tests, and reference standards.

### *Statistical analysis*

The statistical software R × 64 3.4.4 was used to perform the data analysis. Pooled estimates of the diagnostic yield and 95% confidence intervals (CI) were shown in forest plots. We also calculated the risk difference (RD) and CI for the diagnostic sensitivity of bronchoscopy with and without ROSE. Heterogeneity among studies was assessed by the $I^2$ test and the Cochran Q statistic, with $I^2 \geq 50\%$ or $P < 0.1$ indicating significant heterogeneity. All esti-

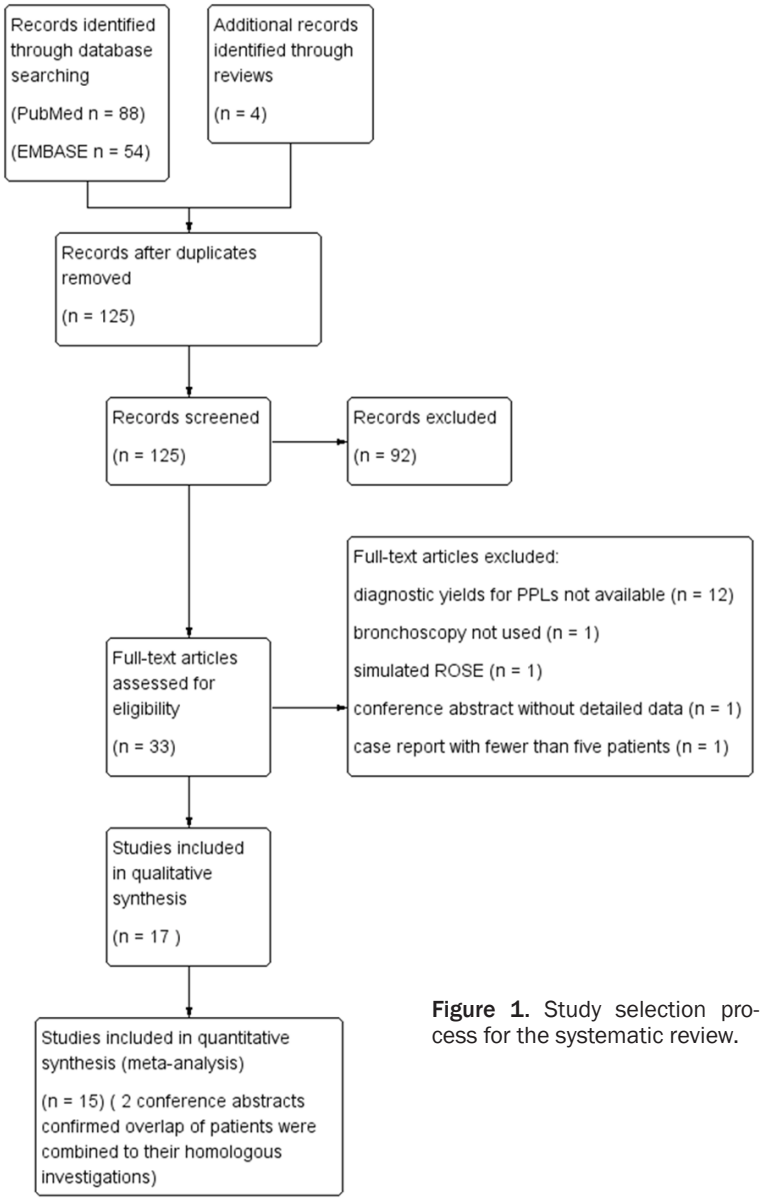



**Figure 1.** Study selection process for the systematic review.

criteria. Three articles were conference abstracts [20-22], and two of them [21, 22] confirmed an overlap of patients were combined to their homologous investigations [1, 7]. Thus, a total of 15 studies (4035 patients from 7 countries) were eligible for qualitative analysis (**Figure 1**). Seven studies [7, 10, 12, 16, 19, 21, 23, 24] were prospective investigations and the others were retrospective. Four studies [7, 12, 15, 20, 21] provided comparative yields with and without rapid on-site cytological evaluation (ROSE). Five studies [10-13, 16] performed bronchoscopy with fluoroscopic guidance, six studies [1, 14, 17-19, 22, 24] with electromagnetic navigation bronchoscopy (ENB) guidance, three studies [7, 15, 21, 23] with endobronchial ultrasound (EBUS) guidance, and one study [20] with all these guidance technologies combined together. The diagnostic yield for malignancy was separately provided by five studies [10, 12, 13, 17, 23]. Six studies [1, 12, 13, 17, 22-24] provided yield data according to the size of the lesions. The characteristics and data extracted from each study are summarized in **Table 1**.

mates were pooled with a random effects model. Studies were also stratified by several variances, such as different guidance technologies used (fluoroscopic guidance, endobronchial ultrasound (EBUS) guidance and electromagnetic navigation bronchoscopy (ENB) guidance), size of the lesions and malignancy of the lesions to further identify the causes of heterogeneity.

## Results

PubMed and EMBASE searches identified 88 and 54 articles respectively, and 4 articles [10, 11, 13, 16] were added after reading relevant reviews, of which 17 articles meet our inclusion

The pooled diagnostic yield of all included studies was 0.84 (95% CI 0.77-0.90), ($I^2$ 93.2%, 95% CI 90.4-95.2%) (**Figure 2**). When sampling peripheral pulmonary lesions (PPLs) via bronchoscopy, ROSE significantly increased the diagnostic yield versus without ROSE (RD 0.15, 95% CI, 0.12-0.18), ($I^2$ 0.0%, CI 0.0-66.7%) (**Figure 3**). According to various guidance technologies, the pooled yield was 0.80 (95% CI 0.62-0.91), ($I^2$ 97.7%, 95% CI 96.4-98.6%) when bronchoscopy was performed by fluoroscopic guidance (**Figure 4A**), 0.85 (95% CI 0.78-0.90), ($I^2$ 29.0%, 95% CI 0.0-92.6%) when EBUS was used (**Figure 4B**) and 0.85 (95% CI 0.78-0.90),

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

| Author year [ref.] | Country | Study design | Patients | Lesion size (size range) (cm) | Yield results | ROSE vs. Non-ROSE comparison | Stain | Bronchoscopic techniques used |
|---|---|---|---|---|---|---|---|---|
| Gasparini 1995 [9] | Italy | P | 511 unselected | 3.5 (0.8-8) | 69.1% for all<br>73.7% for malignancy | No | Modified Papanicolaou stain | Fluoroscopic guidance |
| Uchida 2006 [11] | Janpan | P | 657 unselected | N/A | 90.3% for all<br>74.4% for Non-ROSE<br>90.3% for malignancy<br>86.2% for lesions ≤ 2 cm<br>92.4% for lesions > 2 cm | Yes | Rapid Shorr stain | Fluoroscopic guidance |
| Iyoda 2006 [12] | Janpan | R | 1003 malignancy | N/A | 92.7% for all<br>86.4% for malignancy<br>75.9% for lesions ≤ 2 cm | No | Diff-Quik | Fluoroscopic guidance |
| Lamprecht 2009 [13] | Austria | R | 13 unselected | 3.0 (1.4-5.3) | 84.6% for all | No | N/A | ENB |
| Baba 2002 [10] | Janpan | R | 81 malignancy | N/A | 79.0% for all | No | Diff-Quik | Fluoroscopic guidance |
| Griffin 2011 [14] | America | R | 149 unselected | N/A | 91.7% for all<br>77.8% for Non-ROSE | Yes | N/A | EBUS |
| Leiro-Fernandez 2012 [15] | Spain | P | 36 unselected | N/A | 47.2% for all | No | Hematoxylin-eosin | Fluoroscopic guidance |
| Pearlstein 2012 [16] | America | R | 101 suspected malignancy | 2.8 (0.8-10) | 85.1% for all<br>81.7% for malignancy<br>72.7% for lesions ≤ 2 cm<br>85.0% for lesions > 2 cm | No | N/A | ENB |
| Lamprecht 2012 [23] | Austria | P | 112 unselected | 2.7 (0.6-4.6) | 73.9% for all<br>75.6% for lesions ≤ 2 cm<br>89.6% for lesions > 2 cm | No | N/A | ENB |
| Balbo 2013 [17] | Italy | R | 40 suspected malignancy | 2.35 | 76.7% for all | No | N/A | ENB |
| Karnak 2013 [18] | Turkey | P | 35 unselected | 2.31 (1-4.2) | 91.4% for all | No | Diff-Quick | ENB |
| Loo 2014 [1, 21] | America | R | 40 unselected | 2.6 (0.3-8) | 93.3% for all<br>87.5% for lesions ≤ 2 cm<br>100% for lesions > 2 cm | No | Diff-Quick | ENB |
| Chen 2015 [7, 20] | China | P | 815 unselected | N/A | 86.7% for all<br>71.8% for Non-ROSE | Yes | Rapid Liu stain | EBUS |
| Maekura 2017 [22] | Janpan | P | 45 unselected | 2.2 (1-2.9) | 77.8% for all<br>84.2% for malignancy<br>66.7% for lesions ≤ 2 cm<br>87.5% for lesions > 2 cm | No | Ultrafast Papanicolaou stain | EBUS |
| Patel 2013 [19] | America | R | 397 unselected | N/A | 93.9% for all<br>82.8% for Non-ROSE | Yes | N/A | Fluoroscopic guidance, ENB and EBUS |

Abbreviations: R, retrospective study; P, prospective study; N/A, data not available in the study; EBUS, endobronchial ultrasound guidance; ENB, electromagnetic navigation bronchoscopy guidance.

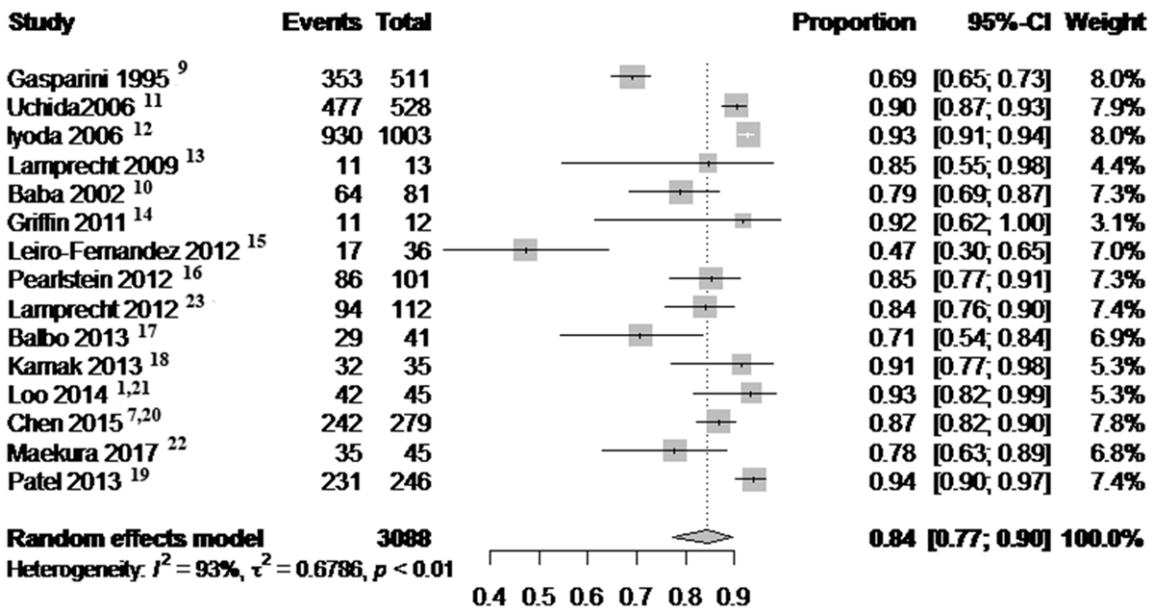



Figure 2. Forest plot of the diagnostic yields of all included studies. The diamond with horizontal lines represents the pooled yield with a 95% confidence interval. $I^2$=93.2% [95% CI 90.4-95.2%].

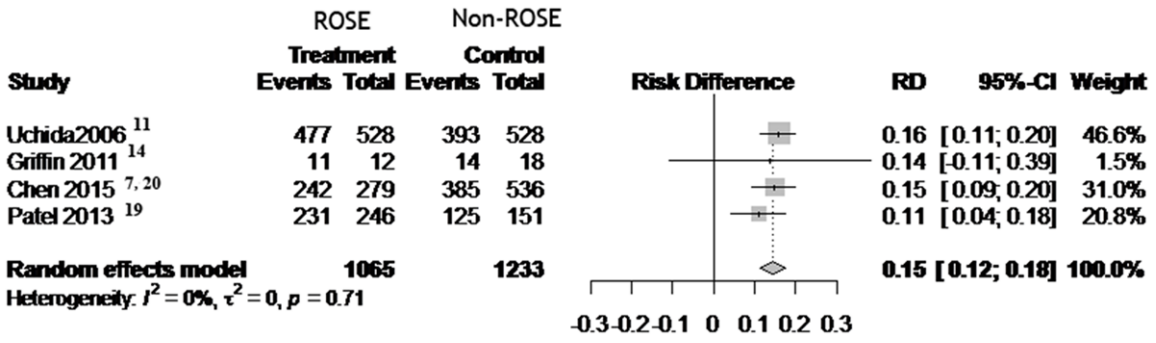



Figure 3. Forest plot of the risk differences comparing the diagnostic yields of bronchoscopy with and without ROSE. The risk differences of the individual studies are represented by a square through which runs a horizontal line (95% confidence interval). The diamond with horizontal lines represents the pooled risk difference with a 95% confidence interval. $I^2$=0.0% [95% CI 0.0-66.7%].

($I^2$ 46.1%, 95% CI 0.0-78.6%) when ENB was used (**Figure 4C**). When the lesions were > 2 cm, the pooled diagnostic yield was 0.90 (95% CI 0.87-0.93), ($I^2$ 18%, 95% CI 0.0-83.0%) (**Figure 5A**), while the yield was 0.79 (95% CI 0.72-0.84), ($I^2$ 52%, 95% CI 0.0-80.7%) when the lesions were ≤ 2 cm (**Figure 5B**). Chen et al. [7, 21] divided the lesions from 3 cm and showed that small PPLs (size < 3 cm) with negative bronchus signs had a significantly lower diagnostic yield than larger PPLs (≥ 3 cm) either with positive or negative bronchus signs and small PPLs (< 3 cm) with positive bronchus signs: 51.4% *vs.* 89.7%, 74.3%, and 74.7%, respectively. As to malignancy, the pooled yield was 0.84 (95% CI 0.76-0.90), ($I^2$ 92.2%, 95% CI 84.7-96.0%) (**Figure 6**).

The risk of bias and concerns about applicability judged with QUADAS-2 are shown in **Figure 7A** and **7B**, indicating an overall low methodological quality. One study was judged to have low concerns about applicability [16] and three [10, 14, 19] were at a low risk of bias.

## Discussion

To the best of our knowledge, this is the first review that extensively described and gathered

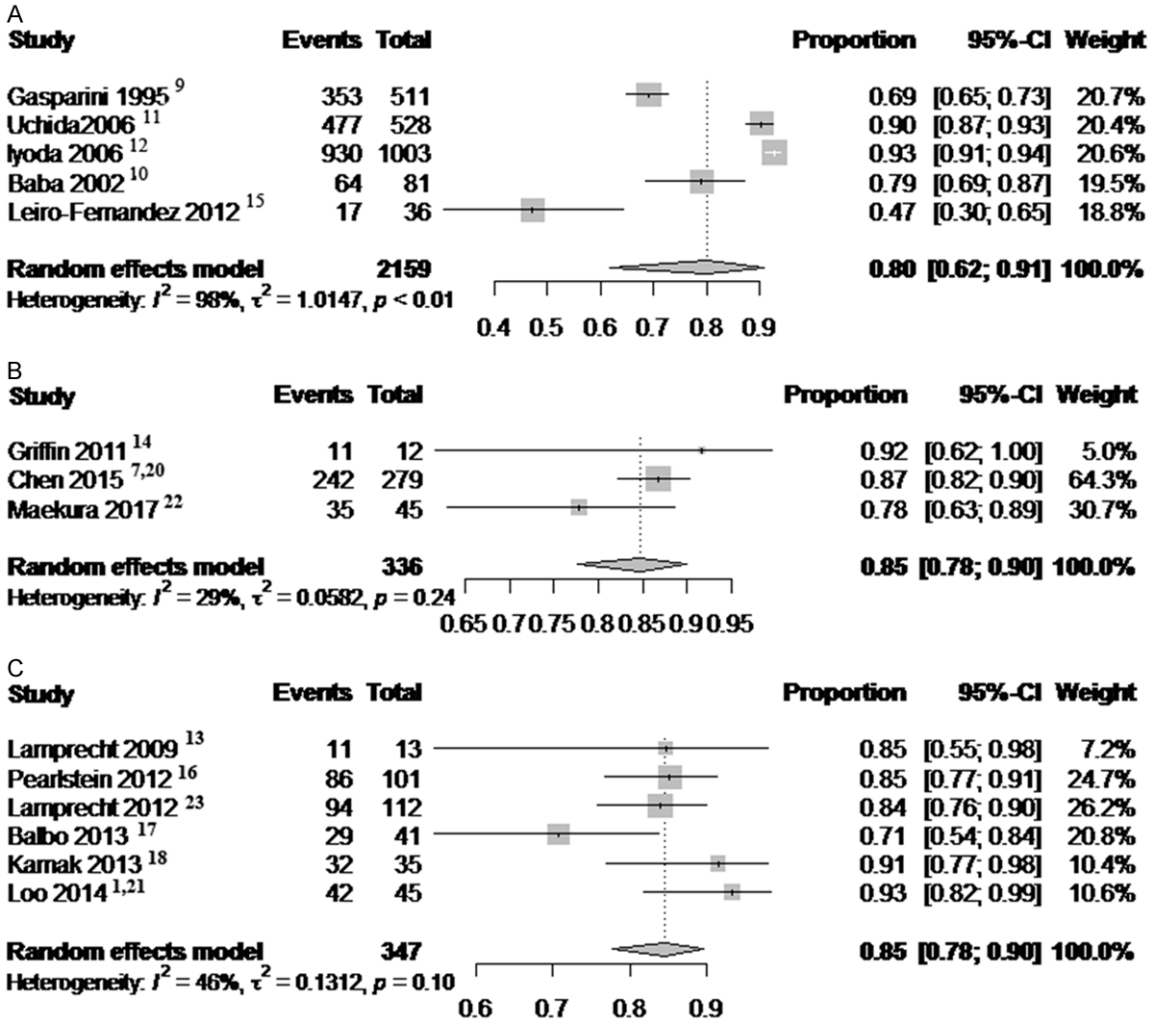



**Figure 4.** Diagnostic yield of bronchoscopy according to various guidance technologies. A: Fluoroscopic guidance. $I^2$=97.7%, [95% CI 96.4-98.6%]. B: EUBS was used. $I^2$=29%, [95% CI 0.0-92.6%]. C: ENB was used. $I^2$=46.1%, [95% CI 0.0-78.6%]. The diamond with horizontal lines represents the pooled yield with a 95% confidence interval.

results from published studies evaluating the effectiveness of rapid on-site cytological evaluation (ROSE) on the diagnostic yield of bronchoscopy in peripheral pulmonary lesions (PPLs). It is quite important to get feedback on the quality of specimens when sampling PPLs, because bronchoscopists can't directly visualize the lesions by regular bronchoscopy. ROSE can provide immediate feedback, leading bronchoscopists to stop the operation once sufficient material is harvested or to modify the bronchoscopy technique, and to enable appropriate specimen triage, thus bringing about an improved adequacy rate of specimens and a reduced risk of procedure complication for additional sampling [6, 7]. A recent systematic review [3] found that the whole pooled diagnostic sensitivity of fluoroscopy-guided transbronchial needle aspiration (TBNA) for PPLs was (0.53, 95% CI 0.4-0.6), and a subgroup analysis revealed an increased yield in the ROSE group. Wang et al. [2] showed an overall pooled diagnostic yield of various guided bronchoscopic techniques for PPLs was 70%. The whole pooled diagnostic yield in our study (0.84 (95% CI 0.77-0.90)) was much higher than the data aforementioned, and a subgroup analysis also showed ROSE increased the diagnostic yield. Thus, we drew the conclusion that the use of the ROSE technique and bronchoscopic guidance technology increased the diagnostic yield in PPLs. On the contrary, it was reported that the use of ROSE did not improve the diagnostic yield during TBNA in mediastinal lymph node

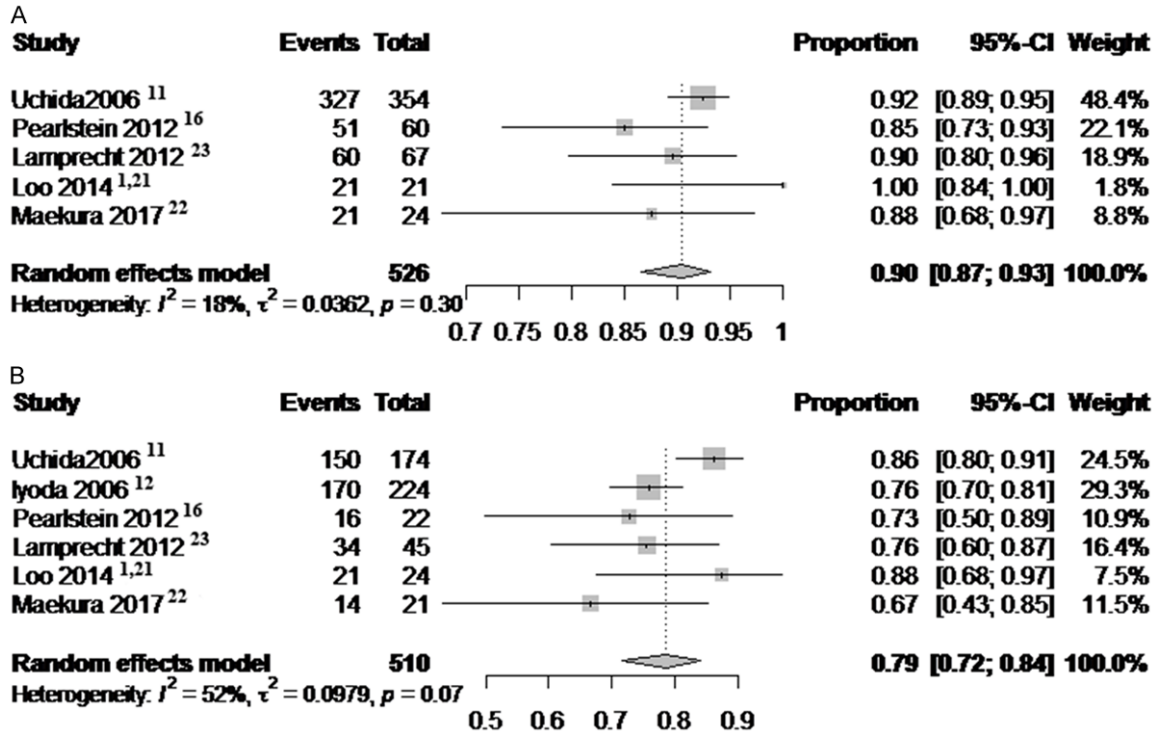



Figure 5. Diagnostic yield of bronchoscopy according to the size of the lesions. A: Lesions > 2 cm. $I^2$=18%, [95% CI 0.0-83.0%]. B: Lesions ≤ 2 cm. $I^2$=52%, [95% CI 0.0-80.7%]. The diamond with horizontal lines represents the pooled yield with a 95% confidence interval.

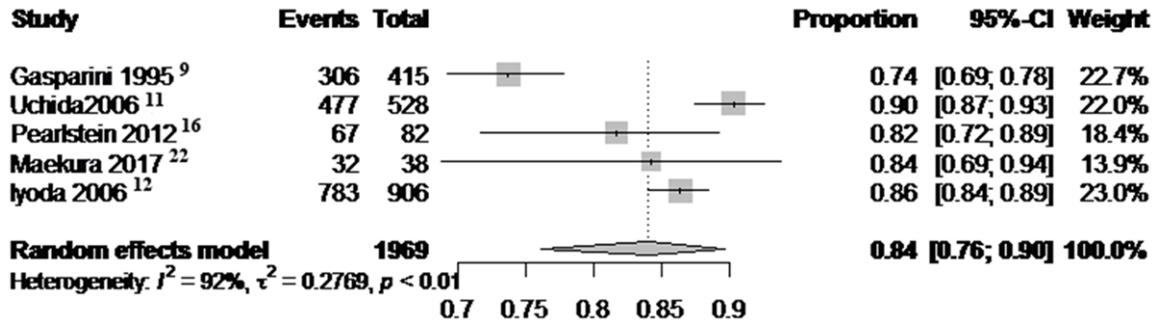
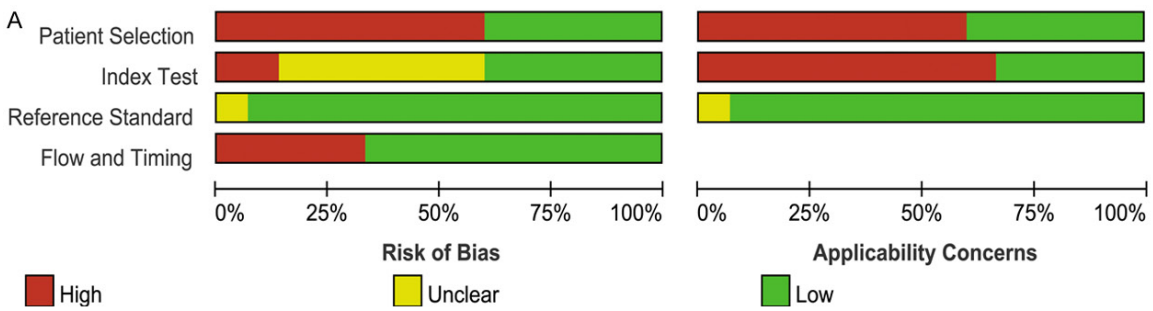



Figure 6. Diagnostic yield of bronchoscopy for malignancy. $I^2$=92.2%, [95% CI 84.7-96.0%]. The diamond with horizontal lines represents the pooled yield with a 95% confidence interval.

sampling [8]. We speculated that ROSE played a more important role in PPLs sampling due to the special anatomical position of the lesions. One study [7] included indicated a similar procedure time in the ROSE and non-ROSE groups. Consistently, Sehgal et al. [8] reported the use of ROSE could not reduce the procedure time during TBNA in their review. This is probably due to the extra time required to process and review the slides which might negate the time saving benefits of ROSE [27].

Compared with fluoroscopic guidance in diagnosing PPLs, a much higher yield of bronchoscopy guided by electromagnetic navigation bronchoscopy (ENB) or endobronchial ultrasound (EBUS) were observed, regardless of whether ROSE was used [4]. Based on previous reviews, the overall sensitivity of fluoroscopy-guided bronchoscopy for the diagnosis of PPLs is 53% [3], 70% of EUBS [28] (42% when the probe was adjacent to the lesion [29]), and 82% of ENB [30]. Our analysis showed higher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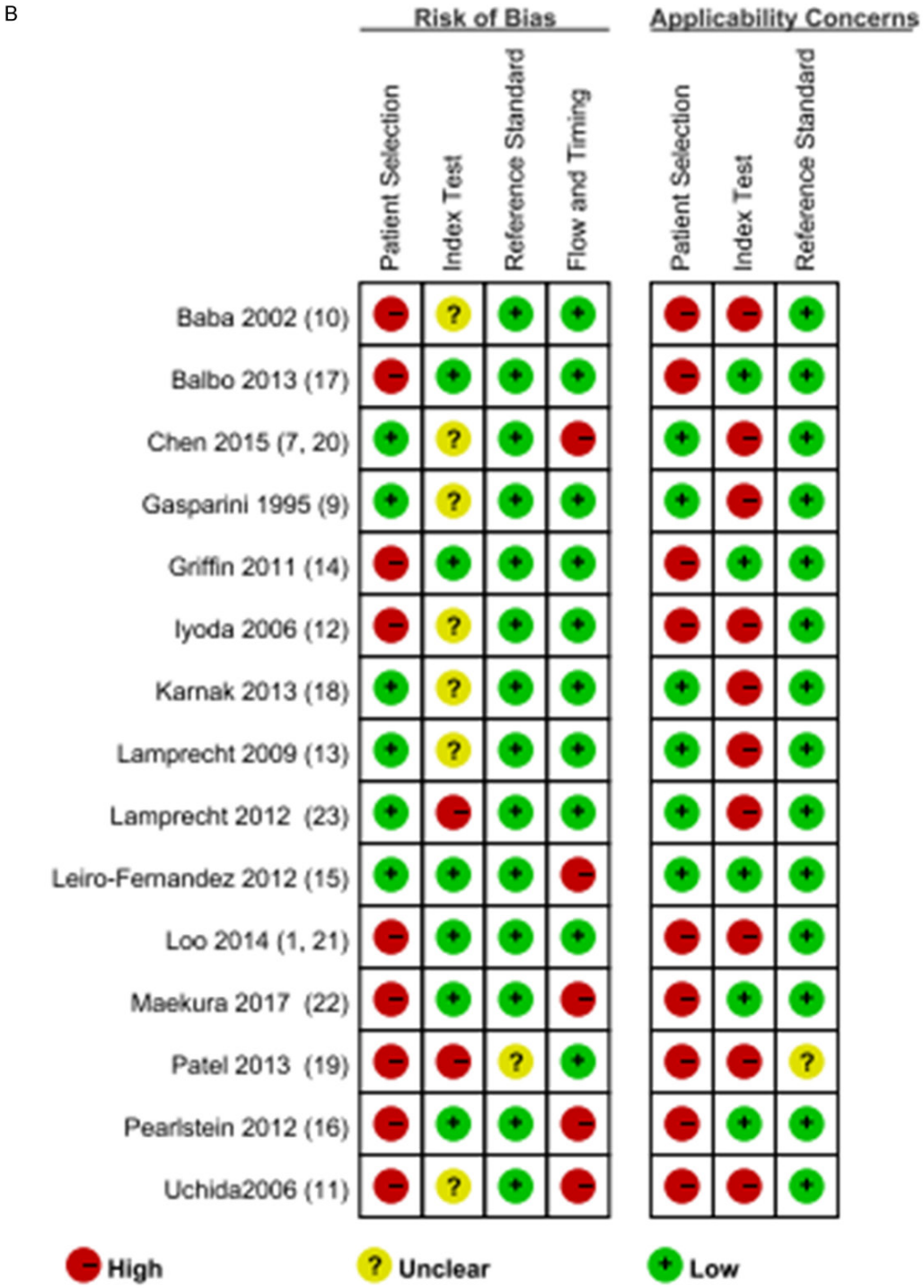
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Leiro-Fernandez 2012 (15)
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Patel 2013 (19)
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**Figure 7.** The risk of bias and concerns about the applicability of the included studies judged with QUADAS-2. (A) Overall and (B) by study.

yields in all these subgroups (80%, 85% and 85%, respectively), indicating ROSE significantly increased the diagnostic yields of fluoroscopy-guided and EBUS-guided bronchoscopy, especially when the probe was adjacent to the PPLs [7].

The reporting yields of guided bronchoscopy were 60.9% in PPLs ≤ 2 cm, and 82.5% in PPLs > 2 cm [2], and our subgroup analysis exhibited that ROSE significantly increased yields in both groups, especially in those ≤ 2 cm. Interestingly, previous studies have reported that yields increased with an increasing size of the nodules [2, 31], while Chen et al. [7] drew a different conclusion showing that the diagnostic yields decreased with an increasing size of nodules above 7 cm because once the tumor size became bigger, the tumor had a central necrotic part which caused higher false negative results, so the ROSE technique can increase the diagnostic rate not only for a PPL size less than 3 cm but also for lesions more than 7 cm.

Malignant lesions were associated with a higher diagnostic yield than benign lesions [3, 4]. However, it is worth noting that larger nodules which had a higher prevalence of malignancy were easier to sample [28], and that several of the cohorts included in our analysis have selected suspected or known malignancy as their study populations.

Our analysis has a few limitations. Firstly, there was high heterogeneity in the pooled data. We speculated the following factors might account for the heterogeneity: most studies included were small and retrospective, study populations were selected based on the physician's direction, the location and characteristics of PPLs were different, the criteria for an adequate specimen to be detected by ROSE were not clarified, and the techniques used as well as the operator's ability varied. Then, several issues such as whether the use of ROSE can reduce the procedure time, complication rate, or cost were not addressed in the analysis. Multicenter, prospective, randomized control trials are expected to further clarify the effectiveness of ROSE on bronchoscopy in sampling PPLs.

In conclusion, the use of ROSE increased the diagnostic yield of bronchoscopy in PPLs diagnosis, particularly in the context of lesions ≤ 2 cm, and fluoroscopy-guided and EBUS-guided bronchoscopy, especially when the probe was adjacent to the PPLs.

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## Disclosure of conflict of interest

None.

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