Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

The value of navigation bronchoscopy in the diagnosis of peripheral pulmonary lesions: A meta-analysis

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Keywords
Diagnostic yield; electromagnetic navigation bronchoscopy (ENB); peripheral pulmonary lesions (PPLs); transbronchial lung biopsy (TBLB); virtual bronchoscopic navigation (VBN).

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Received: 25 December 2019;
Accepted: 12 February 2020.

doi: 10.1111/1759-7714.13373

Thoracic Cancer **11** (2020) 1191–1201

Abstract

Background: To compare the diagnostic yield of peripheral pulmonary lesions (PPLs) with and without navigation system.

Methods: Studies dating from January 1990 to October 2019 were collected from databases. Diagnostic yield of navigation bronchoscopy and non-navigation bronchoscopy was extracted from comparative studies. Subgroup analysis was adopted to test diagnostic yield variation by lesion size, lobe location of the lesion, distance from the hilum, bronchus sign and nature of the lesion.

Results: In total, 2131 patients from 10 studies were enrolled into the study. Diagnostic yield of navigation bronchoscopy was statistically higher than non-navigation bronchoscopy for PPLs (odds ratio [OR] 1.69, 95% confidence interval [CI] 1.32, 2.18, $P < 0.001$), particularly for PPLs in the peripheral third lung (OR 2.26, 95% CI 1.48, 3.44, $P < 0.001$) and for bronchus sign positive PPLs (OR 2.26, 95% CI 1.21, 4.26, $P = 0.011$). Navigation bronchoscopy had better performance than non-navigation bronchoscopy when PPLs were ≤ 20 mm (OR 2.09, 95% CI 1.44, 3.03, $P < 0.001$). It also elevated diagnostic yield of malignant PPLs (OR 1.67, 95% CI 1.26, 2.22, $P < 0.001$) and PPLs in the bilateral upper lobes (OR 1.50, 95% CI 1.09, 2.08, $P = 0.014$).

Conclusions: Navigation bronchoscopy enhanced diagnostic yield when compared to non-navigation bronchoscopy, particularly for PPLs in the peripheral third lung, PPLs being bronchus sign positive, PPLs ≤ 20 mm, malignant PPLs and PPLs in the bilateral upper lobes.

Key points

The current study provided systematic evaluation on the diagnostic value of navigation bronchoscopy by comparing it with non-navigation bronchoscopy, and exploring the factors affecting the diagnostic yield.

Introduction

Early diagnosis of pulmonary lesions is of great importance to reduce mortality due to lung cancer.[1] When endobronchial lesions can be directly visualized by flexible bronchoscopes, peripheral pulmonary lesions (PPLs), generally defined as lesions surrounded by normal pulmonary parenchyma without any computed tomography (CT) evidence of endobronchial abnormalities, are unlikely to be detected by ordinary bronchoscopes.[2,3] Transthoracic needle aspiration (TTNA) has been recommended for nonsurgical diagnosis of PPLs with a sensitivity of 90%, but the relatively high risk of pneumothorax and other complications has limited its application, in particular when PPLs are small or located far from the chest.[3–6] Flexible bronchoscopic biopsy has a lower risk of occurrence of complications; however, the overall sensitivity of PPLs has previously been reported to be only 69%.[5] Therefore,

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multi-instruments have been developed to improve the performance of bronchoscopy for PPL diagnosis. For example, ultrathin bronchoscopy (UTB) enables a bronchoscopist to access PPLs at the distal bronchus.[7] Endobronchial ultrasound (EBUS) confirms the arrival of biopsy instruments on site.[8,9] Navigation bronchoscopy, including virtual bronchoscopic navigation (VBN), electromagnetic navigation (ENB) and other navigation instruments, facilitates PPL diagnosis by directing a bronchoscope to its intended target via visualized three-dimensional lung models.[10,11] All have been reported to increase diagnostic yield.[12] Although there have been contradictory findings which report that navigation bronchoscopy only shortens the operation time of bronchoscopy instead of improving the diagnostic yield,[13] ENB has even been associated with a lower diagnostic yield.[14] In our analysis, in order to give a clear outline on the efficacy of navigation bronchoscopy, we pooled all the studies that directly compared diagnostic yield of bronchoscopy with or without navigation assistance.

Methods

Search strategy

Two reviewers independently searched records from PubMed, Ovid, Embase, Web of Science, Scopus, Science Direct, with a published date ranging from January 1990 to October 2019. The search strategy was as follows: "virtual bronchoscopic navigation" or "electromagnetic navigation bronchoscopy" and "peripheral pulmonary lesions:" their analogues were also included, and all the records were then summarized.

Study selection and quality assessment

Inclusion criteria: (i) Clinical studies which reported the diagnostic yield of navigation bronchoscopy for PPL diagnosis, including VBN, ENB and other navigational instruments for bronchoscopy, as well as the diagnostic yield of comparative non-navigation bronchoscopy. (ii) The search was limited to reports published in English and humans. (iii) When data were presented in more than one article, the latest update details were extracted. Exclusion criteria: (i) Conference, reviews, case reports, and pilot studies. (ii) Studies with less than 30 subjects in each group.

Data extracted from records

Information extracted from the records included first author's family name, publication date, study design, nationality, bronchoscopy, navigation system, biopsy instruments and other auxiliaries. Overall diagnostic yield and diagnostic yield by lesion size, lobe location of the lesion, distance from hilum, bronchus sign, and nature of the lesion (malignant or benign) were also distilled. All the information was recorded independently by two reviewers. A divergence of views was discussed until an agreement was reached. The quality of included studies was assessed with the quality assessment of diagnostic accuracy studies tool-2 (QUADAS-2).

Statistical analysis

Since both randomized control trials (RCT) and case-control studies were included in this analysis, we applied odds ratio (OR) to evaluate diagnostic yield variance between bronchoscopy with and without navigation. The OR of diagnostic yield was analyzed by Stata (version 14.0). A statistical test with $P < 0.05$ was considered statistically significant. Publication bias was explored by Begg's test. Duval's trim and fill analysis was adopted to adjust the result when prominent publication bias was displayed.[15] A random effect model was applied when heterogeneity was prominent (I-square > 25%); if not, a fixed effect model was adopted. Sensitivity analysis and meta-regression were conducted to analyze the heterogeneity. Subgroup analysis was carried out to review the diagnostic yield changes according to lesion size, lobe location of the lesion, distance from the hilum, bronchus sign and nature of the lesion.

Results

Study selection

A total of 1117 records were collected from PubMed, Ovid, Embase, Web of science, Scopus, Science Direct from January 1990 to October 2019. After checking for duplicates, 588 records were removed. By screening titles and abstracts, 28 records were found. By analyzing the full text, 14 comparative studies which provided information for analysis were determined. Among these studies, four, including two with patients with less than 30 in each group,[16,17] one with prominent selection bias beyond adjustment,[14] and one with a latest update,[18,19] were excluded from the analysis (Fig 1).

Characteristics of included studies

In total, 10 clinical trials met the inclusive criteria,[13,19–27] of which, nine trials compared diagnostic yield of bronchoscopes with and without VBN, and only one study elevated the diagnostic value of ENB. In this study, when the control group was assisted by EBUS-GS, the navigation group incorporated ENB with EBUS. These two groups were comparable because an extending working channel (EWC) of ENB performed almost equal to a thick guide sheath, as they had the same outer diameter and compatible biopsy channel. More details on bronchoscopies, navigation systems, biopsy methods and other auxiliaries are listed in Table 1.

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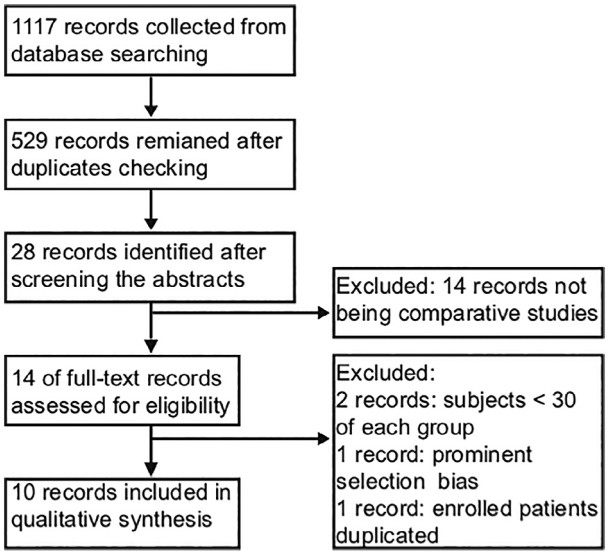

Figure 1 Study search and selection flow.

The quality of included studies assessed with QUADAS-2 is shown in Figures S1 and S2. Risk of bias came primarily from patients who dropped out of the study and not all patients received surgery or other biopsy as a reference standard for diagnosis.

Overall, 1037 patients were enrolled in navigation bronchoscopy, whose pooled diagnostic yield was 73.58%. In total, 1094 patients were enrolled in non-navigation bronchoscopy, with a pooled diagnostic yield of 62.80%. When a random effect model was adopted for the test, the overall OR of diagnostic yield of navigation bronchoscopy to non-navigation bronchoscopy was 1.69 (95% confidence interval [CI] 1.32, 2.18), which was statistically significant ($P < 0.001$, Fig 2).

Publication bias and heterogeneity

The existence of publication bias was revealed by the asymmetric funnel plot graphed by Begg's test (Fig 3a, Begg's test, $P > 0.020$). As a result, Duval's trim and filled analysis was applied to correct for bias. By Duval's trim and filled analysis, three estimated potentially unreported studies were automatically included in the analysis, which turned the funnel plot symmetric (Fig 3b) and shifted the value of pooled OR to 1.46 (95% CI 1.12, 1.93, $P = 0.006$), but the pooled OR did not change significantly. The outcome indicated that the previous result of overall OR was stable, despite publication bias. Heterogeneity between studies was evaluated by omitting one specific study at a time and calculating pooled OR changes. No prominent heterogeneity was found in any specific study (Fig S3). Heterogeneity of included studies was further analyzed by meta-regression according to publication year, nationality, protocol design, navigation system and the particular bronchoscopy that navigation system combined. However, none of the across study differences were the major contributors that introduced heterogeneity into the test.

Diagnostic yield by lesion size

Subgroup analysis was adopted to test OR of bronchoscopic diagnostic yield of PPLs by lesion size with or without navigation assistance, and in total nine studies were included in the analysis.[13,19–25,27] Diagnostic yield of navigation bronchoscopy (64.09%) was statistically higher than that of non-navigation bronchoscopy (48.67%) for PPLs ≤ 20 mm (OR 2.09, 95% CI 1.44, 3.03, $P < 0.001$). In PPLs > 20 mm, there was no statistical difference between pooled diagnostic yield of navigation bronchoscopy (79.27%) and non-navigation bronchoscopy (yield 76.42%, OR 1.15, 95% CI 0.74, 1.78, $P = 0.527$) (Fig 4).

Table 1 Basic characteristics of studies

Study	Type	Design	Ration	Bronchoscope	NB	Brand	Other auxiliaries	Biopsy
Bo *et al*. 2019[13]	Prospective	RCT	China	Not mentioned	VBN	DirectPath	EBUS-GS	Forceps
Asano *et al*. 2015[19]	Prospective	RCT	Japan	P260F	VBN	Bf-NAVI	EBUS-GS, X-ray	Forceps, brush, lavage
Asano 2013 *et al*. [20]	Prospective	RCT	Japan	XP260F, XP40	VBN	Bf-NAVI	X-ray	Forceps, brush, lavage
Oshige *et al*. 2011[21]	Prospective	Non-RCT	German	P260F, 1T-260R	VBN	Bf-NAVI	EBUS-GS	Forceps, brush
Diez-Ferrer *et al*. 2019[22]	Ambispective	Case–control	Spain	XP160F, XP190	VBN	LungPoint	X-ray	Forceps, brush, lavage
Kato *et al*. 2018[23]	Prospective	Non-RCT	Japan	P260F	VBN	LungPoint	CT	Forceps, lavage
Xu *et al*. 2019[24]	Prospective	RCT	China	P260F	VBN	DirectPath	EBUS	Forceps
Miyoshi *et al*. 2019[25]	Retrospective	Case–control	Japan	1T260	VBN	SYNAPSE VINCENT	X-ray	Forceps, brush
Matsumoto *et al*. 2017[26]	Retrospective	Case–control	Japan	Varied	VBN	Ziostation	EBUS-GS, X-ray, ROSE	Forceps, brush, TBNA
Eberhardt *et al*. 2007[27]	Prospective	RCT	American, German	1T160	ENB	SuperDimension	EBUS/EBUS-GS	Forceps

CT, computed tomography; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; GS, guided sheath; NB, navigation bronchoscopy; non-RCT, randomized control trial be disturbed; RCT, randomized control trial; ROSE, rapid on-site evaluation; TBNA, transbronchial needle aspiration; VBN, virtual bronchoscopic navigation.

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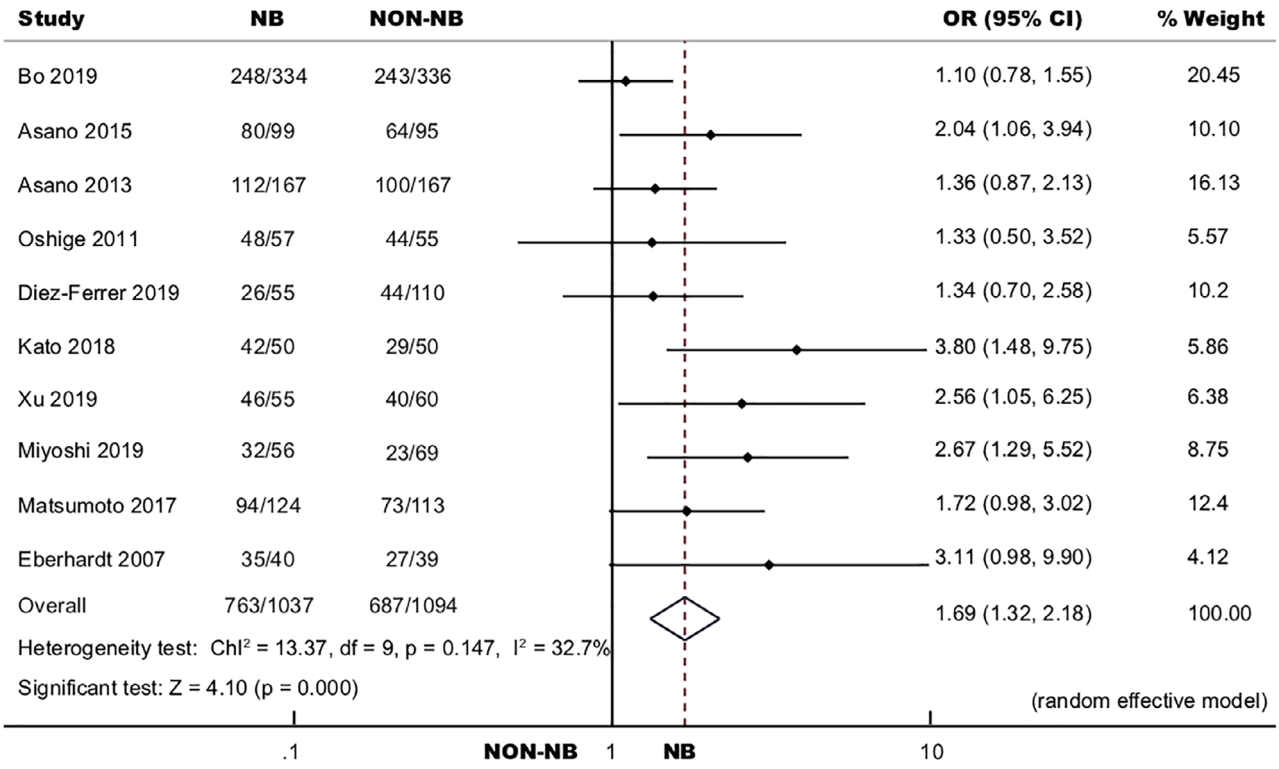

Figure 2 Forest plot of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy. CI, confidence interval; NB, navigation bronchoscopy; NON-NB, non-navigation bronchoscopy; OR, odds ratio.

Diagnostic yield by lobe location of the lesion

Six studies provided information on bronchoscopic diagnostic yield according to the pulmonary lobe containing the lesion.[13,19,20,24,25,27] Whilst five studies grouped PPLs by different pulmonary lobes, Miyoshi *et al.* classified PPLs in the right middle lobe (RML) and left lingula lobe of the lung into the same group, and this study was therefore excluded from the analysis.[25] Pooled diagnostic yield of navigation bronchoscopy and non-navigation bronchoscopy for PPLs at bilateral upper lobes (BULs), RML and bilateral lower lobes (BLLs) was 75.56%, 89.23%, 70.74% and 67.28%, 82.46%, 65.90%, respectively. Diagnostic yield of navigation bronchoscopy was statistically better than non-navigation bronchoscopy at BULs

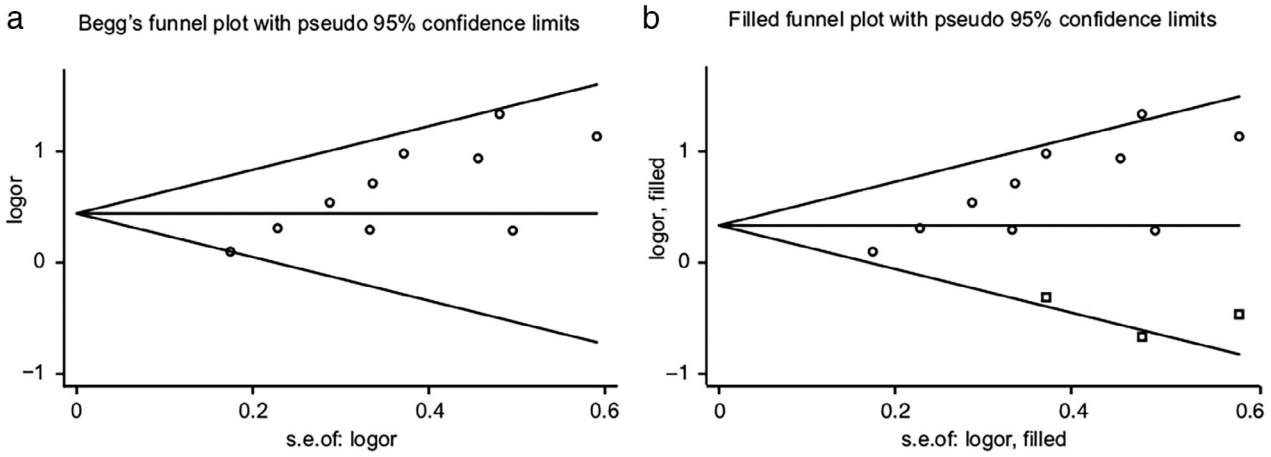

Figure 3 Funnel plot. (**a**) Funnel plot of 10 studies included in analysis of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy graphed by Begg's test. (**b**) Funnel plot adjusted by Duval's trim and filled test. (○) Included studies and (□) filled studies.

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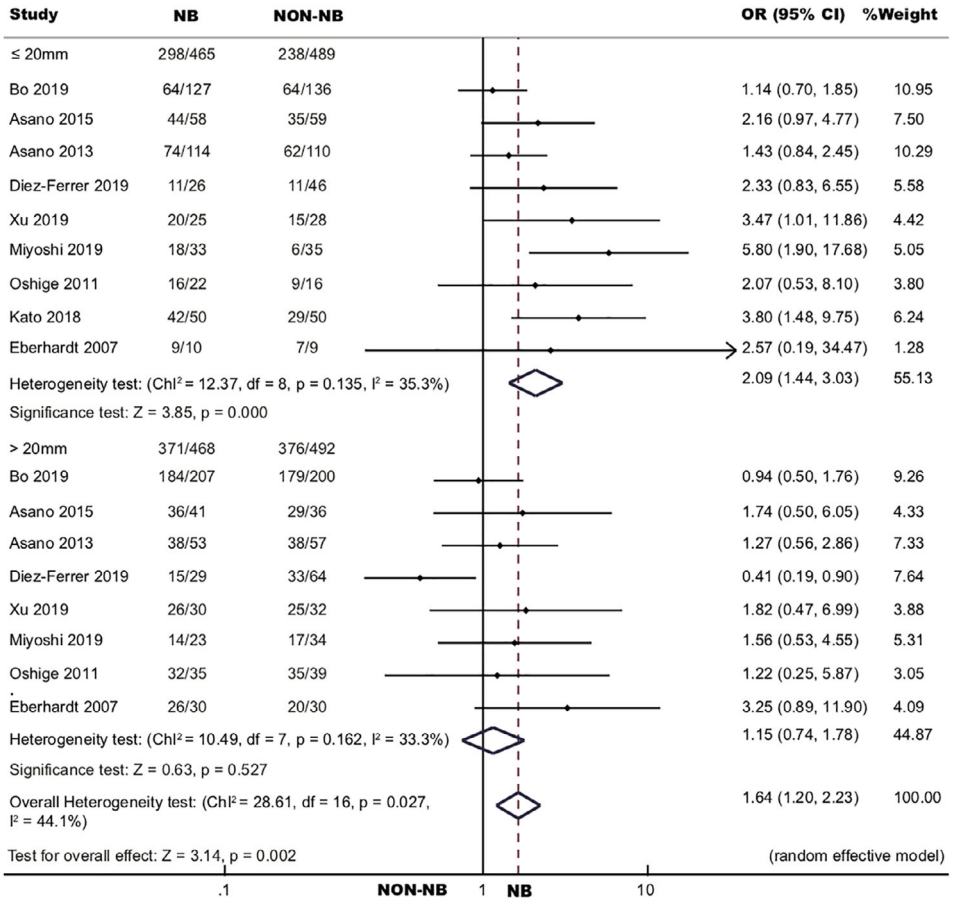

Figure 4 Forest plot of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy by lesion size.

(OR 1.50, 95% CI 1.09, 2.08, $P = 0.014$). However, the diagnostic difference of bronchoscopy with and without navigation was not statistically significant at RML (OR 1.73, 95% CI 0.61, 4.95, $P = 0.303$) or BULs (OR 1.21, 95% CI 0.84, 1.75, $P = 0.313$) (Fig 5).

Diagnostic yield by distance from the hilum

Location of lesions were classified into center, intermediate, and peripheral third according to the distance from the hilum.[28] In this analysis, PPLs in the center and intermediate third lung were included in one group and compared with PPLs in the peripheral third. Four studies were adopted for this analysis.[19,20,22,23] Navigation bronchoscopy yielded 70.59% and was statistically better than non-navigation bronchoscopy which yielded 50.36% in the peripheral third lung (OR 2.26, 95% CI 1.48, 5.92, $P < 0.001$). When PPLs were located at the center and intermediate thirds, diagnostic yield of navigation bronchoscopy (68.97%) and non-navigation bronchoscopy (67.36%) did not differ statistically (OR 0.93, 95% CI 0.34, 2.54, $P = 0.890$) (Fig 6).

Diagnostic yield by bronchus sign

Bronchus sign was evaluated by CT to describe the positional relationship of a PPL relative to the nearby bronchus.[29] No bronchus found near the PPL was termed as bronchus sign negative. If a bronchus was found adjacent to, or within, the PPL, it was defined as bronchus sign positive. Five studies were included in our analysis.[19,20,22,23,25] In the bronchus sign positive subgroup, overall OR of diagnostic yield of navigation bronchoscopy (75.00%) to non-navigation bronchoscopy (59.73%) was 2.26, 95% CI (1.21, 4.26), which was statistically significant ($P = 0.011$). In the bronchus sign negative subgroup, pooled diagnostic yield of navigation bronchoscopy (39.24%) was similar to non-navigation bronchoscopy (31.03%), and the overall OR was 1.49 (95% CI 0.77, 2.98, $P = 0.234$) (Fig 7).

Diagnostic yield by nature of the lesion

Seven studies were included in the analysis.[13,20–22,24,25,27] In total, 498 malignant PPLs detected by navigation bronchoscopy yielded 77.91%, and 596 malignant PPLs, detected by non-navigation bronchoscopy, yielded 65.94%.

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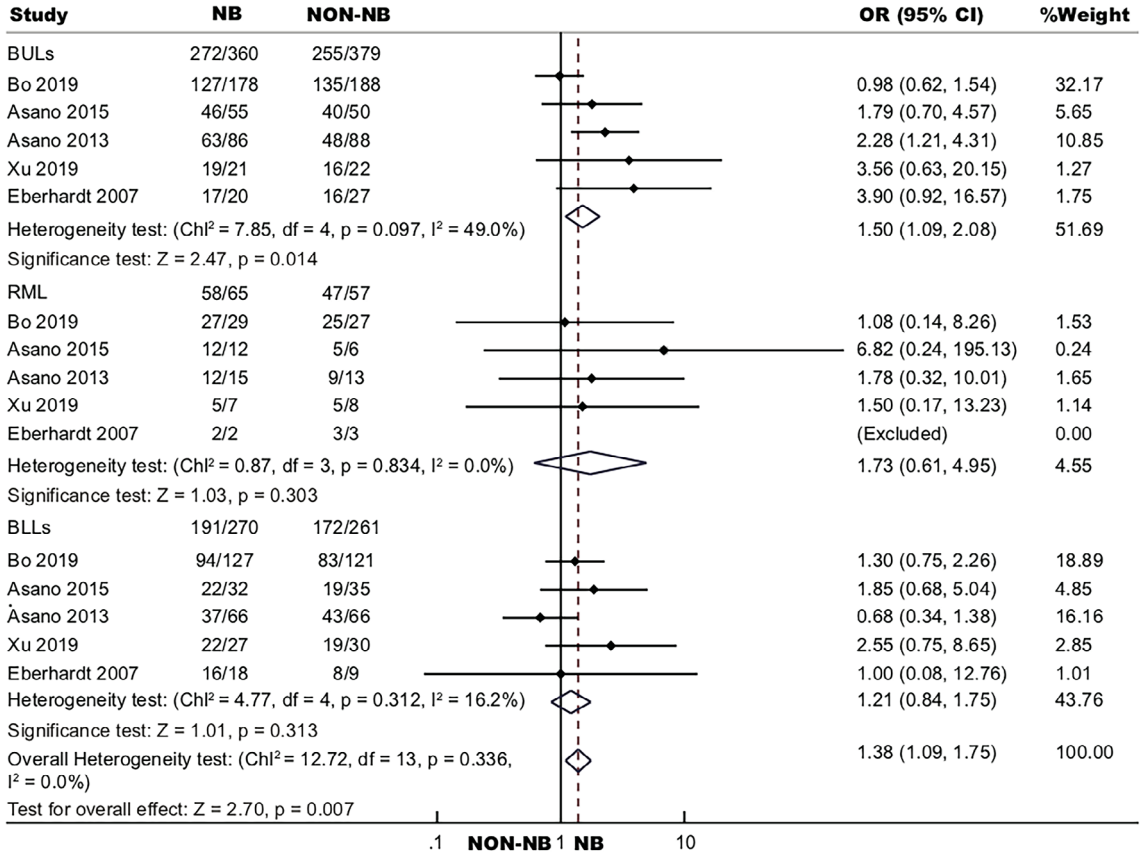

Figure 5 Forest plot of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy by the lobe location of the lesion. BLLs, bilateral lower lobes; BULs, bilateral upper lobes; RML, right middle lobe.

The pooled OR was 1.67 (95% CI 1.26, 2.22, $P < 0.001$). Pooled diagnostic yield of navigation bronchoscopy for benign PPLs was 63.10% (159/252), Diagnostic yield of non-navigation bronchoscopy for benign PPLs was 55.17% (128/232), and the pooled OR was 1.40 (95% CI 0.97, 2.03, $P = 0.075$) (Fig 8).

We further analyzed bronchoscopic diagnostic yield by different characteristics of the lesions (size, lobe location, distance from the hilum, bronchus sign and nature). Results of the diagnostic OR covariant by navigation bronchoscopy and non-navigation bronchoscopy were as follows: overall bronchoscopic diagnostic yield for PPLs > 20 mm was statistically higher than PPLs ≤ 20 mm (OR 2.55, 95% CI 1.59, 4.10, $P < 0.001$). Non-navigation bronchoscopy had better performance at the inner two thirds of the lung compared to the peripheral third (OR 2.52, 95% CI 1.42, 4.46, $P = 0.002$). Overall, bronchoscopic diagnostic yield for PPLs at BULs was almost the same as PPLs at the RML and BLLs (OR 1.06, 95% CI 0.74, 1.50, $P = 0.763$). Bronchosopic diagnostic yield of bronchus sign positive PPLs was greater than bronchus sign negative PPLs (OR 4.22, 95% CI 2.62, 6.81, $P < 0.001$), irrespective of whether they were navigation assisted or not. Diagnostic yield of malignant lesions was statistically higher than benign lesions, both in the navigation group (OR 2.57, 95% CI 1.76, 3.74, $P < 0.001$) and non-navigation group (OR 2.63, 95% CI 1.82, 3.81, $P < 0.001$) (Table 2).

Complications

A total of seven studies included in the analysis reported complications.[13,19,20,23,24,26,27] Prevalence of complications reported in navigation bronchoscopy and non-navigation bronchoscopy was 3.22% and 2.67%, respectively. There was no significant difference between onset of complications of the above two groups (OR 1.28, 95% CI 0.73, 2.25, $P = 0.397$). Pneumothorax and hemorrhage were the most common complications reported. There was 1.73% pneumothorax, 1.38% hemorrhage, 0.11% others happened in the navigation group, and 1.51% pneumothorax, 0.93% hemorrhage, 0.23% others happened in the non-navigation group.

Discussion

Diagnostic yield of bronchoscopy for pulmonary lesions is affected by multiple factors, such as prevalence of malignancy,[28,30] lesion size,[8,14,31] localization[14] and bronchus

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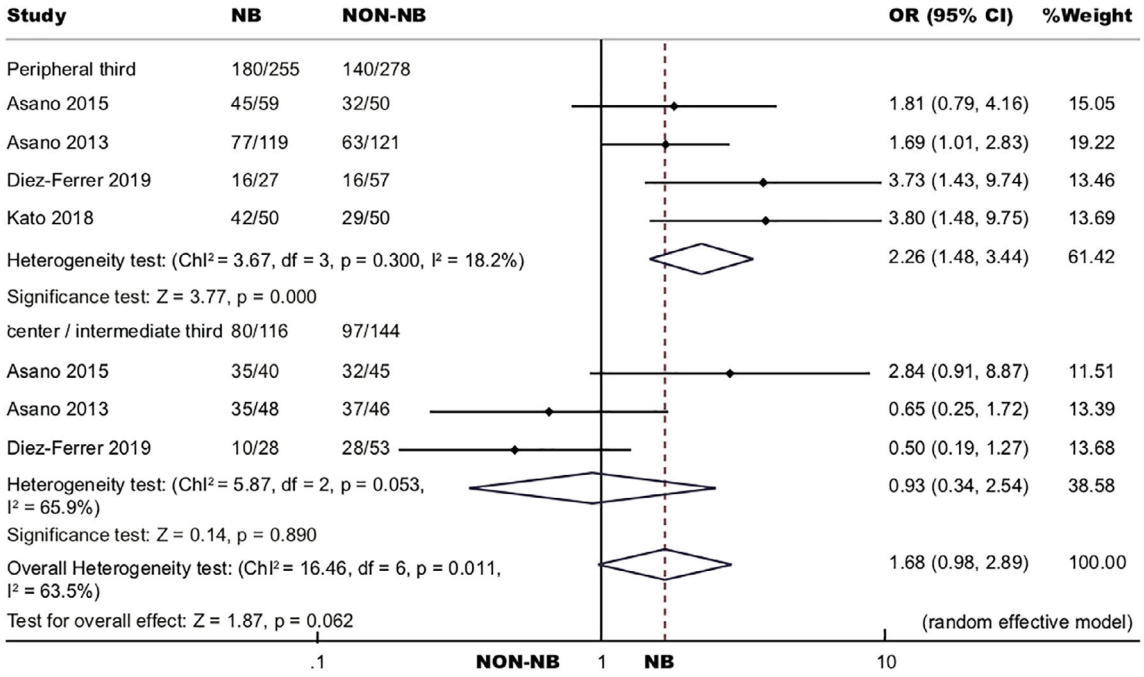

Figure 6 Forest plot of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy by distance from the lesion to the hilum.

sign.[32,33] Other than all the variations, such as experienced bronchoscopist,[34] different bronchoscopes,[7] auxiliary instruments,[35,36] and sampling technics,[37] all these factors will have some influence on transbronchial lung biopsy. After sampling of the lesions, rapid on-site evaluation (ROSE) and histological staining to confirm the diagnosis

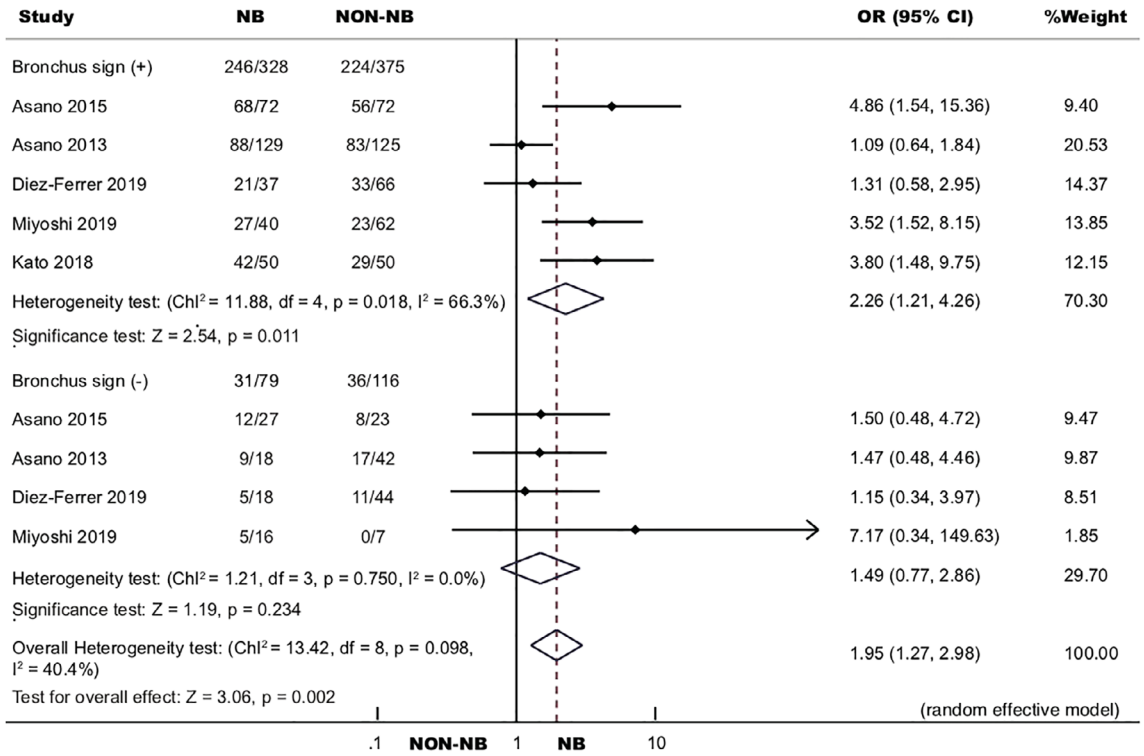

Figure 7 Forest plot of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy by bronchus sign.

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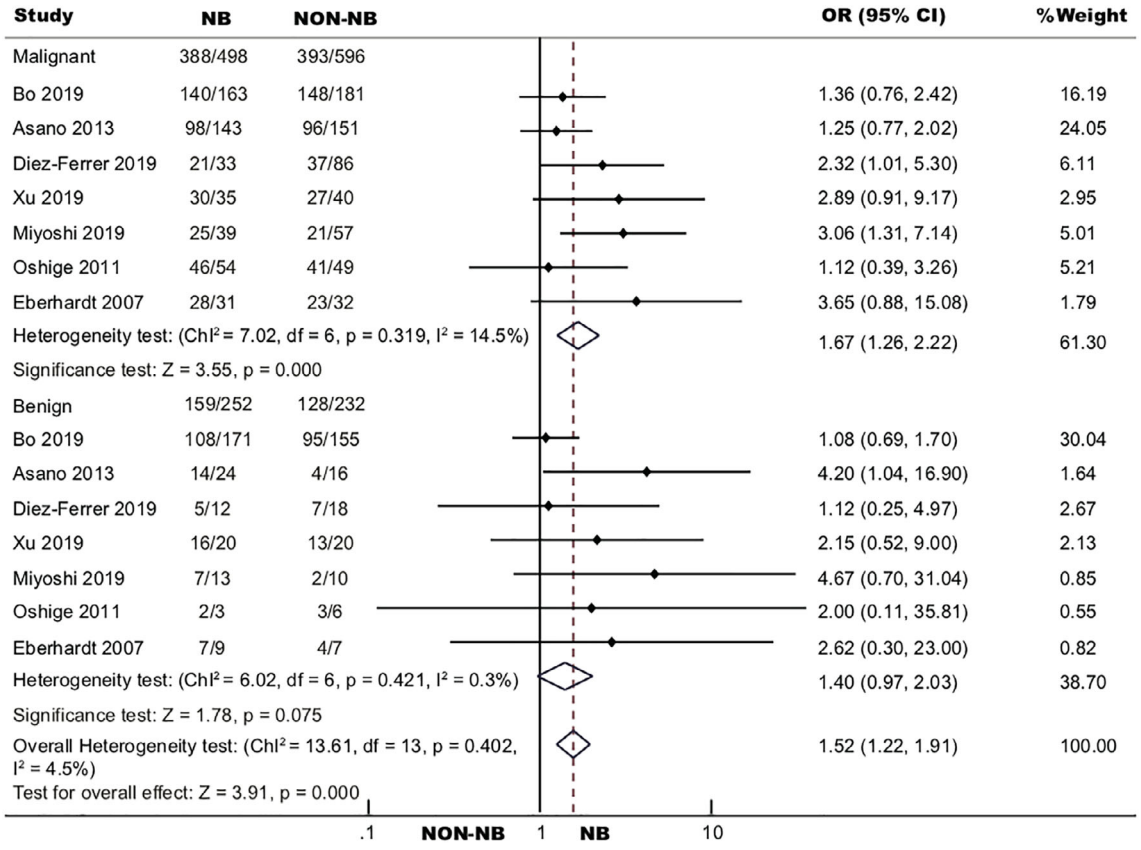

Figure 8 Forest plot of diagnostic OR of navigation bronchoscopy to non-navigation bronchoscopy by nature of the lesion.

will also divert diagnostic yield.[38,39] It is a very difficult task to determine whether navigation bronchoscopy improved diagnostic accuracy when compared to non-navigation bronchoscopy according to the results of different studies. Therefore, in our meta-analysis, we adjusted navigational bronchoscopy and non-navigational bronchoscopy performance under the same condition to make the diagnostic yield comparable.

According to our meta-analysis, diagnostic yield of navigation bronchoscopy for PPLs was 1.69 times higher than that of non-navigation bronchoscopy. The value of OR did not vary between publication year, nationality, design, navigation system and particular bronchoscopes combined with navigation system. The reason why navigation bronchoscopy accumulated diagnostic yield may be because the navigation system enabled a bronchoscopist to find a precise bronchial route to access the PPLs, thus increasing the possibility of achieving proper samples.[25]

Bronchoscopic diagnostic yield was prominently elevated by the navigation system in the peripheral third lung, but not in the inner two thirds. Lesions in the peripheral third lung challenged the precise direction because it needed to pass several generations of bronchi to reach the intended lesions, which made the biopsy route become a complex labyrinth. As a result, navigation assistance was of great importance in these circumstances.[20] Some researchers have defined PPLs as lesions located in the peripheral third of the lung without bronchoscopic evidence of endobronchial abnormalities, and this narrowed definition may make navigation bronchoscopy superior in the diagnosis of PPLs.[25,40]

In accordance with previous records, both navigation bronchoscopy and non-navigation bronchoscopy had a relatively higher diagnostic yield for bronchus sign positive PPLs than bronchus sign negative PPLs,[8,29,32,41,42] yet navigation bronchoscopy still yielded higher than non-navigation bronchoscopy when the bronchus sign was presented. The improvement in diagnostic yield was attributed to the improved precision in arriving at the intended bronchi. What is more, the fact that bronchoscopy was poor at diagnosing bronchus sign negative PPLs, irrespective of whether it was navigation-assisted or not, may indicated that TTNA or surgery should be applied in this case.[29,43]

Diagnostic yield of navigation bronchoscopy was statistically higher than non-navigation bronchoscopy for PPLs ≤ 20 mm, but the elevation did not reach statistical significance for PPLs > 20 mm. It should be noted that the number of subjects enrolled in the two groups were parallel, providing evidence that navigation bronchoscopy is more superior than non-navigation bronchoscopy in the diagnosis of smaller lesions. Previous research proved

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Table 2 Pooled OR of bronchoscopic diagnostic yield listing navigation bronchoscopy subgroup, non-navigation bronchoscopy subgroup and overall

Group	Yield[a]	Yield[b]	OR	95% CI	*P*-value
PPLs >20 mm[a]/PPLs <20 mm[b]					
NB	79.27% (371/468)	61.69% (256/415)	1.89	(0.88, 4.06)	0.105
Non-NB	76.42% (376/492)	47.61% (209/439)	3.36	(1.82, 6.18)	<0.001*
Overall	77.81% (747/960)	54.45% (465/854)	2.55	(1.59, 4.10)	<0.001*
Center and intermediate thirds[a]/peripheral third[b]					
NB	68.97% (80/116)	67.32% (138/205)	1.10	(0.43, 2.80)	0.850
Non-NB	67.36% (97/144)	48.68% (111/228)	2.52	(1.42, 4.46)	0.002*
Overall	65.6% (177/270)	57.51% (249/433)	1.70	(0.95, 3.05)	0.075
BULs[a]/RML and BLLs[b]					
NB	75.56% (272/360)	74.44% (249/335)	1.19	(0.70, 2.00)	0.524
Non-NB	67.28% (255/379)	68.87% (219/318)	0.95	(0.55, 1.66)	0.863
Overall	71.31% (527/739)	71.67% (468/653)	1.06	(0.74, 1.50)	0.763
Bronchus sign positive[a]/negative[b]					
NB	73.38% (204/278)	39.24% (31/79)	4.96	(1.89, 13.05)	0.001*
Non-NB	60.00% (195/325)	31.03% (36/116)	3.61	(2.24, 5.80)	<0.001*
Overall	66.17% (399/603)	34.36% (67/195)	4.22	(2.62, 6.81)	<0.001*
Malignant[a]/benign[b]					
NB	77.91% (388/498)	63.10% (159/252)	2.57	(1.76, 3.74)	<0.001*
Non-NB	65.94% (393/596)	55.17% (128/232)	2.44	(1.70,3.50)	<0.001*
Overall	71.39% (781/1094)	59.30% (287/484)	2.50	(1.93,3.24)	<0.001*

*$P < 0.05$. BLLs, bilateral lower lobes; BULs, bilateral upper lobes; CI, confident index; NB, navigation bronchoscopy; Non-NB, non-navigation bronchoscopy; OR, odds ratio; PPLs, peripheral pulmonary lesions; RML, right middle lobe; yield[a], diagnostic yield of group[a]; yield[b], diagnostic yield of group[b].

endobronchial pathway selection to the lesion to be a major possible error in detecting a peripheral lesion.[44] In contrast with large lesions, which could have several right routes reaching out to intended lesions, it is much more difficult to find a proper biopsy pathway for a small nodule, so navigation assistance in this instance is essential.

Navigation bronchoscopy elevated diagnostic yield when lesions were malignant. Benign lesions were much more difficult to distinguish than malignant diseases, since the biopsy specimens were usually nonspecific.[45] Navigation bronchoscopy was found to enhance the diagnostic yield of PPLs at BULs, but not at RML and BLLs, because navigation bronchoscopy makes it possible for bronchoscopists to arrange the best biopsy route so as to avoid sharp angles and the complex structures of the upper lobes.[27] Bronchi in the upper lobe, seldom affected by respiratory motion and heart beats, further facilitated virtual image formation.[20] However, the constant movement in lesion position with respiratory motion during biopsy disturbed the performance of ENB at BLLs.[46]

Historical rate of complications reported for bronchoscopy was 0%–5%,[8,27,47] and the outcome of our meta-analysis coincides with previous studies. Combined navigation bronchoscopy accumulated diagnostic yield without increasing the risk of complications, confirming that it was a safe and effective approach.

There are several limitations in our study. First, both case-control studies and studies that were not fully randomized were included in the analysis, and would therefore introduce selection bias. Second, only one study included in the analysis evaluated efficacy of ENB, so its representativeness for ENB may be open to doubt. Third, some subgroup analysis was not very convincing due to limited sample size. When analyzing diagnostic yield by size, some studies did not group lesions by PPLs ≤ 20 mm and PPLs >20 mm, and therefore different classification of lesions on the edge of 20 mm may affect the results. Fourth, in this article, diagnostic yield of navigation bronchoscopy affected by characteristic of the lesions itself (size, lobe location, distance from the hilum, bronchus sign and nature) were the main considerations. However, changes caused by different bronchoscopy and biopsy methods (forceps, brush, lavage) were neglected, and require further study.

In conclusion, navigation bronchoscopy is a safe and effective approach that improves diagnostic accuracy without increasing incidence of complications. It accumulates diagnostic yield of PPLs in the peripheral third lung, PPLs being bronchus sign positive, PPLs ≤ 20 mm, malignant PPLs and PPLs in the bilateral upper lobes. A series of multicenter, large-scale studies are needed to further confirm the results of our study.

Acknowledgments

This work was supported by National Key R&D Program of China (grant number 2017YFC0112700), Shanghai Municipal Health and Medical Talents Training Program (grant number 2018BR09), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support

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(grant number 20181815). The authors thank Dr Sakae Homma from the Department of Respiratory Medicine, Toho University Graduate School of Medicine (Tokyo, Japan) and Dr Liyan Bo from the Department of Respiratory and Critical Care Medicine, Tangdu Hospital. Air Force Medical University (Xi'an, China) provided further explanation of their articles for the analysis.

Disclosure

The authors have no conflicts of interest to declare.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1 Risk of bias and applicability concerns graph: review authors' judgments about each domain for each included study.

Figure S2 Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies.

Figure S3 Sensitive analysis by omitting given named study from the overall analysis and estimating diagnostic odds ratio (OR) of navigation bronchoscopy to non-navigation bronchoscopy for peripheral pulmonary lesions (PPLs).

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