Original Article

White light, autofluorescence and narrow-band imaging bronchoscopy for diagnosing airway pre-cancerous and early cancer lesions: a systematic review and meta-analysis

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Background: We aimed to summarize the diagnostic accuracy of white light bronchoscopy (WLB) and advanced techniques for airway pre-cancerous lesions and early cancer, such as autofluorescence bronchoscopy (AFB), AFB combined with WLB (AFB + WLB) and narrow-band imaging (NBI) bronchoscopy.

Methods: We searched for eligible studies in seven electronic databases from their date of inception to Mar 20, 2015. In eligible studies, detected lesions should be confirmed by histopathology. We extracted and calculated the 2×2 data based on the pathological criteria of lung tumor, including high-grade lesions from moderate dysplasia (MOD) to invasive carcinoma (INV). Random-effect model was used to pool sensitivity, specificity, diagnostic odds ratio (DOR) and the area under the receiver-operating characteristic curve (AUC).

Results: In 53 eligible studies (39 WLB, 39 AFB, 17 AFB + WLB, 6 NBI), diagnostic performance for high-grade lesions was analyzed based on twelve studies (10 WLB, 7 AFB, 7 AFB + WLB, 1 NBI), involving with totally 2,880 patients and 8,830 biopsy specimens. The sensitivity, specificity, DOR and AUC of WLB were 51% (95% CI, 34–68%), 86% (95% CI, 73–84%), 6 (95% CI, 3–13) and 77% (95% CI, 73–81%). Those of AFB and AFB + WLB were 93% (95% CI, 77–98%) and 86% (95% CI, 75–97%), 52% (95% CI, 37–67%) and 71% (95% CI, 56–87%), 15 (95% CI, 4–57) and 16 (95% CI, 6–41), and 76% (95% CI, 72–79%) and 82% (95% CI, 78–85%), respectively. NBI presented 100% sensitivity and 43% specificity.

Conclusions: With higher sensitivity, advanced bronchoscopy could be valuable to avoid missed diagnosis. Combining strategy of AFB and WLB may contribute preferable diagnosis rather than their alone use for high-grade lesions. Studies of NBI warrants further investigation for precancerous lesions.

Keywords: Advanced bronchoscopy; lung cancer; white light bronchoscopy (WLB); autofluorescence bronchoscopy (AFB); narrow-band imaging bronchoscopy

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Introduction

Lung cancer is one of the leading causes of cancer mortality worldwide (1), mainly attributed to its biologically aggressive nature and late stage at the time of diagnosis. However, the 5-year survival rate of patients stage IA could be up to 74.6% (2), indicating patients with longer life expectancy after diagnosis and treatment in early stage. A long-term follow-up (12.5 years) surveillance study found 34% lung-cancer detection rate in patients harboring endobronchial pre-invasive lesions after median 16.5 months (3), suggesting these patients at high risk of primary or secondary cancer. Therefore, diagnosis of precancerous lesions and early-stage lung cancer is crucial.

Currently, conventional white light bronchoscopy (WLB) is the most common tool for the detection of central-airway lung precancerous and cancerous lesions. In some cases, these lesions may be too thin or diminutive to be detected under the WLB. In order to address this limitation, advanced techniques such as autofluorescence bronchoscopy (AFB) and narrow-band imaging (NBI) bronchoscopy have been developed. AFB is the technique that emits fluorescent light containing green (520 nm peak) and red spectrum (>630 nm peak) (4), normal mucosa reflects this fluorescent light and presents a green-color image, while precancerous and cancerous lesions (even a few millimeters in diameter) absorb the green spectrum, and the reflected light turns magenta. NBI, another new-developed technique, only presents two narrow-bands of light (400–430 and 525–550 nm respectively) that can be absorbed by hemoglobin, in order to demonstrate a detailed image of the surface structure of lesions and superficial mucosal capillaries (5).

Though the superior diagnostic performance of AFB, AFB combined with WLB (AFB + WLB) and NBI (versus WLB) has been investigated for lung cancer in several comparison meta-analyses (6-9), all these available bronchoscopic techniques have not been overviewed for precancerous and cancer lesions [including high-grade lesions from moderate dysplasia (MOD) to INV] by single-arm synthesis in one article yet.

In this systematic review and meta-analysis, we primarily summarized the diagnostic accuracy of each technique based on eligible studies (single-arm synthesis), and secondly, we conducted an exploratory comparison between advanced techniques versus WLB directly only based on comparison studies (direct comparison). During above processes, techniques' performance for different lesions was investigated, including their performance for high-grade lesions.

Methods

This meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (10). We performed an independent double-blind quality assessment (with J Zhang, blind to J Wu) and data extraction (with J Zhang blind to J Wu, Z Xu, Y Yang, and Z Liang). Any discrepancies were resolved by the discussion with W Liang.

Search strategy and study selection

Scopus, Embase, Web of Science, PubMed, ProQuest (scholarly journals), the Cochrane Library and Ovid (all EBM review) databases were searched from their date of inception to Mar 20, 2015. The retrieval formula was: [(fluorescence or autofluorescence or autofluorescence imaging) or (narrow band or narrow-band imaging)] and bronchoscopy (all field) (English). Duplicate articles were removed, and articles with inappropriate publication types were excluded, including reviews, systematic reviews, meta-analysis, case reports, letters, correspondences, comments, editorials, conference abstracts, erratum, short surveys, books or book chapters, and notes. In eligible studies, these advanced techniques should be investigated for diagnosing early lung cancer in the range of hyperplasia, metaplasia, dysplasia (mild/moderate/severe), carcinoma in situ (CIS) and INV, confirmed by histopathology. Sufficient data for constructing 2×2 contingency tables should be given in eligible studies.

Quality assessment

The quality of all included studies was assessed according to the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) (11). Question 3 in domain 4 "*Were all patients included in the analysis?*" was revised as "*Were all patients or biopsy specimens included in the analysis?*", since there were two types of analysis for 2×2 data construction (patient- or biopsy-based). The risk of bias and concern regarding applicability were scored as "high", "low" and "unclear" according to the answers of questions. Based on these scores in each domain of the tool, we rated the quality for each study (high quality: "low risk" and "low concern" in all domains; low quality: at least one "high risk" or "high concern"; moderate quality: at least one "unclear risk" or "unclear concern", without "high risk" or "high concern").

Data extraction

The following characteristics of each study were extracted: author, year, type of analysis, total number of patients, and pathological results of biopsy specimens. During this process, the extracted data only reflected the data in the final statistical analysis of each included study, for example, if the number of patients enrolled in a study was not equal to the number of patients finally included in analysis, we would extract the data belonging to the final analysis.

2×2 contingency tables of true positive, false positive, false negative and true negative were constructed based on relevant calculation formula and given data from studies, such as sensitivity, specificity, positive predictive value and negative predictive value (12,13). We calculated the 2×2 data in two sets: the first set was based on the original pathological diagnostic criteria of lung tumor, within the range from hyperplasia to INV; the second set was based on the criteria from MOD to INV, which was regarded as high-graded lesions. During the above process, if we found the results of two techniques were lacking sufficient comparability in comparison studies, e.g., both positive results (true positive plus false negative) were not equal, their 2×2 data were only used for our single-arm synthesis, not for direct comparison.

Statistical analysis

We estimated the pooled sensitivity, specificity, diagnostic odds ratio (DOR), and the area under the receiver-operating characteristic curve (AUC), the index considering the pooled sensitivity and specificity together. Hierarchical summary receiver operating characteristic (HSROC) curves were plotted for the overall performance of each technique.

The test of heterogeneity with the value of I^2 in meta-analysis is lack of sufficient reliability, due to the correlation between sensitivity and specificity-the variation of sensitivity would be mutually influenced by the variation of specificity (14). However, random-effect model was used to attenuate the effect of heterogeneity because we assumed its existence during the process of data synthesis. Moreover, we conducted a meta-regression to assess the effects of study period, quality (based on QUADAS-2) and type of analysis on the heterogeneity.

For bivariate model has taken the relation between sensitivity and specificity into account for the threshold effect (15), and there is no existing test perfectly matching our meta-analysis (14), we did not respectively estimate the threshold effect and publication bias.

Statistic procedures were conducted using STATA 13.0 (StataCorp, College Station, US). When there were only three corresponding studies in a group, the pooled sensitivity, specificity, DOR and AUC with 95% CI were calculated using Meta-DiSc 1.4 (XI Cochrane Colloquium, Barcelona, Spain). For direct comparison, we used Z test to estimate whether significant difference was indicated ($P<0.05$), which was completed in Excel 2011 (Microsoft, Seattle, US).

Results

Study identification, characteristics and quality assessment

The details of study identification are shown in *Figure 1*. Three thousand one hundred and ninety-four articles were identified from electronic databases, of which 53 studies (39 WLB, 39 AFB, 17 AFB + WLB, 6 NBI) were finally included, involving a total of 6,543 patients and 18,458 biopsy specimens. Among these 53 included studies, twelve studies (10 WLB, 7 AFB, 7 AFB + WLB, 1 NBI) were within the data for the diagnosis of MOD to INV, involving 2,880 patients and 8,830 biopsy specimens. The characteristics of included studies are presented in *Table 1*, and detailed results of quality assessment are shown in *Table S1*.

Meta-analysis

The performance of all techniques by single-arm synthesis was shown in *Table 2*. Based on original pathological criteria

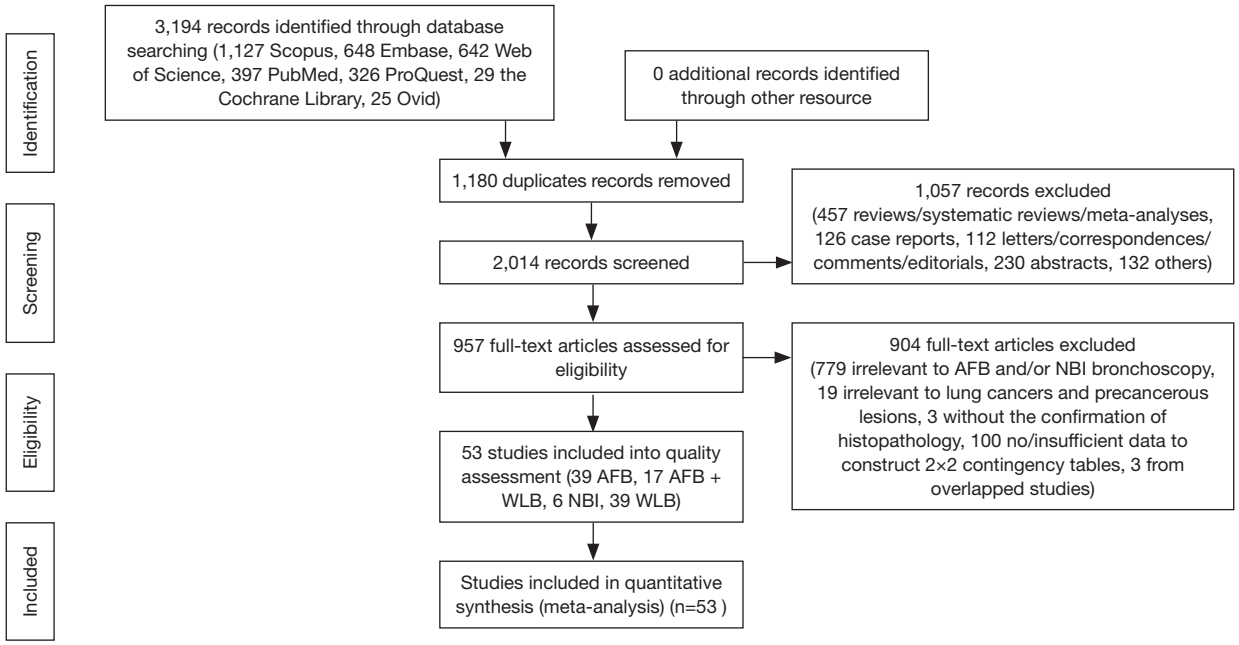

Figure 1 Flowchart of study selection. Three thousand one hundred and ninety-four studies were firstly identified. Finally, a total of 53 eligible studies were included in this meta-analysis. From: Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097. For more information, visit www.prisma-statement.org.

of different lung tumor, the sensitivity, specificity, DOR and AUC of WLB were 54% (95% CI, 46–61%), 79% (95% CI, 73–84%), 4 (95% CI, 3–6) and 72% (95% CI, 68–76%). The performance of AFB and AFB + WLB were close: 87% (95% CI, 82–90%) and 88% (95% CI, 82–93%) sensitivity, 60% (95% CI, 58–72%) and 59% (95% CI, 48–68%) specificity, 13 (95% CI, 8–19) and 11 (95% CI, 6–19) DOR, and 85% (95% CI, 81–87%) and 82% (95% CI, 78–85%) AUC. NBI presented remarkable diagnostic performance: 96% (95% CI, 78–99%) sensitivity, 84% (95% CI, 70–92%) specificity, 131 (95% CI, 35–490) DOR and 94% (95% CI, 91–96%) AUC. The HSROC of each technique were showed in *Figure 2*.

Based on the criteria of MOD to INV, majorities of diagnostic outcome were similar to the outcome based on original pathological criteria, except the specificity of AFB + WLB increased to 71% (56–87%), the AUC of AFB decreased to 76% (72–79%), and the specificity of NBI decreased to 43% (*Table 2*).

In the secondary part, we conducted an exploratory comparison between WLB and advanced bronchoscopies (*Table 3*). Based on original pathological criteria, though significant higher specificity of WLB was shown (P<0.05), its sensitivity (P<0.001), DOR (versus AFB: P<0.001; versus AFB + WLB: P=0.126; versus NBI: P=0.008) and AUC (versus AFB: P<0.001; versus AFB + WLB: P=0.083; versus NBI: P<0.030) were lower than those of three advanced techniques.

Moreover, though AUC of WLB was non-inferior to that of AFB (75% versus 76%, P=0.271), even superior to the AFB + WLB (89% versus 81%, P<0.001), WLB still presented lower sensitivity and DOR for these high-graded lesions. Regarding NBI, we were limited to calculate the DOR and AUC based on the data from only one study (*Table 3*).

Meta-regression indicated there was no strong effect of study period and quality on the heterogeneity according to the data of single-arm synthesis with original criteria. Types of analysis (biopsy- versus patient-based) may be the source based on the I^2 value, even if the P value of heterogeneity was not lower than 0.05 (*Table 4*).

Discussion

In this systematic review and meta-analysis, we primarily performed single-arm synthesis of conventional WLB and advanced bronchoscopies for diagnosing early lung cancer in one article. Besides, we also conducted an exploratory direct comparison of these techniques. Based on original

Table 1 Characteristics of included studies

Author	Study quality	Type of analysis	Patient (n)	Biopsy (n)	Positive result of pathological criteria*								
					2×2 data	Total	HYP	MET	MIL	MOD	SEV	CIS	INV
Kurie 1998 (16)	Moderate	Biopsy-based	39	234	Original[&]	42	–		42			–	–
Moro-Sibilot 2002 (17)	Moderate	Biopsy-based	244	315	Original	42	–	–	–	23		19	–
Herth 2003 (18)	Moderate	Patient-based	74	Unclear	Original	34	–	–	–	–	–	34	
Lee 2007 (19)	High	Biopsy-based	48	126	Original	22	–	–	–	5	13	4	–
Moghissi 2008 (20)	Moderate	Patient-based	93	Unclear	Original	20	–	20	–	–	–	–	–
Lee 2009 (21)	High	Biopsy-based	738	3,292	Original	278	–	–	–	87	99	92	–
Zaric 2009 (22)	Moderate	Biopsy-based	27	108	Original	40	–	–	4	–	–	36	
Zaric 2010 (23)	High	Biopsy-based	104	624	Original	309	–	–	–	–	–	309	
Lam 1992 (24)	Moderate	Biopsy-based	82	238	Original	37	–	–	16	12	6	3	–
Lam 1993 (25)	Moderate	Biopsy-based	94	264	Original	77	–	–	–	33	15	29	–
Lam 1994 (26)	Moderate	Biopsy-based	223	451	Original	113	–	–	–	78		35	–
Yokomise 1997 (27)	Moderate	Biopsy-based	30	51	Original	20	–	–		4		16	
Horvath 1999 (28)	High	Biopsy-based	56	146	Original	19	2	3	9	5	–	–	–
Kakihana 1999 (29)	Moderate	Biopsy-based	72	147	Original	79	–	–		51		28	
Ikeda 1999 (30)	High	Biopsy-based	133	262	Original	127	–	–		72		55	
Weigel 1999 (31)	Moderate	Biopsy-based	34	89	Original	6	–	–			3		3
Weigel 2000 (32)	Moderate	Biopsy-based	25	71	Original	4	–	–	–		3	0	1
Shibuya 2001 (33)	Moderate	Biopsy-based	64	191	Original	45	–	–		42		3	–
Furukawa 2000 (34)	Moderate	Biopsy-based	108	234	Original	131	–	–		87		44	
Means-Markwell 2003 (35)	Moderate	Biopsy-based	28	70	Original	2	–	–	–	1	0	1	–
Lang 2005 (36)	High	Biopsy-based	36	71	Original	26	–	5		2		0	19
Chhajed 2005 (37)	High	Biopsy-based	151	343	Original	83	–	–	–	52	8	3	20
Chiyo 2005 (38)	Moderate	Biopsy-based	32	60	Original	30	–	–	6	22	2	–	–
Lam 2006 (39)	Moderate	Biopsy-based	62	84	Original	12	–	–	–	5	4	2	1
Ikeda 2006 (40)	Moderate	Biopsy-based	154	166	Original	78	–	–	4	24	1	19	30
Ueno 2007 (41)	High	Biopsy-based	31	64	Original	30	–	–	–	11	2	1	16
Nakanishi 2007 (42)	High	Biopsy-based	71	288	Original	37	–	–	–	–	14	23	
Gabrecht 2007 (43)	High	Biopsy-based	21	41	Original	11	–	–	1	3	4		3
Li 2010 (44)	Moderate	Biopsy-based	136	241	Original	76	–	–	–	–	3	0	73
Ali 2011 (45)	High	Biopsy-based	13	47	Original	13	–	4		2		7	
Cetınkaya 2011 (46)	Moderate	Patient-based	30	27	Original	7	–	–		6		1	
Venmans 1999 (47)	Moderate	Biopsy-based	95	660	Original	79	–	–	–	31	39	9	–
Kusunoki 2000 (48)	Moderate	Biopsy-based	65	216	Original	49	–	–	–	–	21	9	19

Table 1 (*continued*)

Table 1 (*continued*)

Author	Study quality	Type of analysis	Patient (n)	Biopsy (n)	Positive result of pathological criteria*								
					2×2 data	Total	HYP	MET	MIL	MOD	SEV	CIS	INV
Hirsch 2001 (49)	High	Biopsy-based	55	391	Original	71	–	–		71 (ASD)		–	–
Fuso 2005 (50)	High	Biopsy-based	166	166	Original	93	–	–	–	13		80	
Ernst 2005 (51)	Moderate	Biopsy-based	293	821	Original	85	–	–	–		85		
Divisi 2010 (52)	Moderate	Biopsy-based	168	388	Original	328	–	–	–		328		
Lam 1998 (53)	High	Biopsy-based	173	700	Original	142	–	–	–	93		9	40
Vermylen 1999 (54)	Moderate	Biopsy-based	34	142	Original	16	–	–	–	7	3	6	–
Häußinger 1999 (55)	Moderate	Biopsy-based	60	264	Original	48	–	–	5	6		1	36
					Extra[#]	43	–	–	–	6		1	36
Venmans 2000 (56)	Moderate	Biopsy-based	59	267	Original	22	–	–	–	10	9	3	–
Sato 2001 (57)	Moderate	Biopsy-based	50	123	Original	67	–		39			28	
Häußinger 2005 (58)	Moderate	Biopsy-based	1,173	2,907	Original	53	–	–	–		19+34		–
Hanibuchi 2007 (59)	Moderate	Biopsy-based	123	282	Original	93	–	37		10		3	43
Edell 2009 (60)	Moderate	Biopsy-based	170	776	Original	76	–	–	–	33	6	2	35
Xing 2005 (61)	Moderate	Biopsy-based	95	200	Original	13	–	–	–	6	3	2	2
Reinders 2009 (62)	Moderate	Biopsy-based	367	749	Original	92	–	–	–	–		92	
Shibuya 2003 (63)	Moderate	Biopsy-based	48	67	Original	15	–	–		15 (ASD)		–	–
Bojan 2009 (64)	Moderate	Biopsy-based	36	132	Original	92	–	2	–	–	–	90	
Zaric 2009 (65)	High	Biopsy-based	106	636	Original	281	–	–	–	–	–	281	
Vincent 2007 (66)	High	Biopsy-based	22	64	Original	13	–	–	–	1	3	9	
Nguyen 2013 (67)	Moderate	Biopsy-based	70	64	Original	18	–	–	–	12	6	–	–
Herth 2009 (68)	Moderate	Patient-based	62	98	Original	17	–	–	–		17		–

*, the data we extracted would be only responsible for the final statistical analysis of each individual study; [&], 2×2 data based on original pathological criteria used in included studies; [#], 2×2 data based on pathological criteria from moderate dysplasia to invasive carcinoma, not used in included study. HYP, hyperplasia; MET, metaplasia; MIL, mild dysplasia; MOD, moderate dysplasia; SEV, severe dysplasia; CIS, carcinoma in situ; INV, invasive carcinoma; ASD, angiogenic squamous dysplasia.

pathological criteria used in included studies, our findings indicated the sensitivity and overall diagnostic performance (DOR and AUC) of advanced bronchoscopies (AFB, AFB + WLB and NBI) were superior to those of WLB. Based on the pathological criteria from MOD to INV, higher sensitivity and DOR of AFB and AFB + WLB could still be found.

Findings of interest were that, based on the original pathological criteria from hyperplasia to INV, both over 80% sensitivity and specificity were indicated in NBI bronchoscopy in single-arm synthesis, as well as the significantly superior DOR and AUC of NBI were shown when compared with those of WLB (in direct comparison). This outcome could be a result of both the color change and characteristics of submucosa vessels seen with the use of NBI; such characteristics could help practitioners effectively recognize and distinguish malignant lesions from benign lesions (5,9).

However, based on the pathological criteria from MOD to INV, the specificity of NBI decreased to 43% (66). Regarding above findings, one consideration should be taken: the objective of the included studies was to investigate the

Table 2 Single-arm synthesis

Group	Study (n)	Patient (n)	Biopsy (n)	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	DOR	AUC (%)
Original pathological criteria							
WLB	39	4,356	11,587	54 [46–61]	79 [73–84]	4 [3–6]	72 [68–76]
AFB	39	4,027	11,149	87 [82–90]	65 [58–72]	13 [8–19]	85 [81–87]
AFB + WLB	17	3,208	9,150	88 [82–93]	59 [48–68]	11 [6–19]	82 [78–85]
NBI	6	344	1,061	96 [78–99]	84 [70–92]	131 [35–490]	94 [91–96]
Moderate dysplasia, severe dysplasia, CIS and invasive carcinoma							
WLB	10	1,153	3,353	51 [34–68]	86 [75–93]	6 [3–13]	77 [73–81]
AFB	7	896	1,937	93 [77–98]	52 [37–67]	15 [4–57]	76 [72–79]
AFB + WLB	7	1,125	3,315	86 [75–97]	71 [56–87]	16 [6–41]	82 [78–85]
NBI	1	22	64	100	43	–	–

Data in parentheses are 95% CIs. WLB, white light bronchoscopy; AFB, autofluorescence bronchoscopy; AFB + WLB, AFB combined with WLB; NBI, narrow-band imaging; DOR, diagnostic odds ratio; AUC, area under the receiver-operating characteristic curve; CIS, carcinoma in situ.

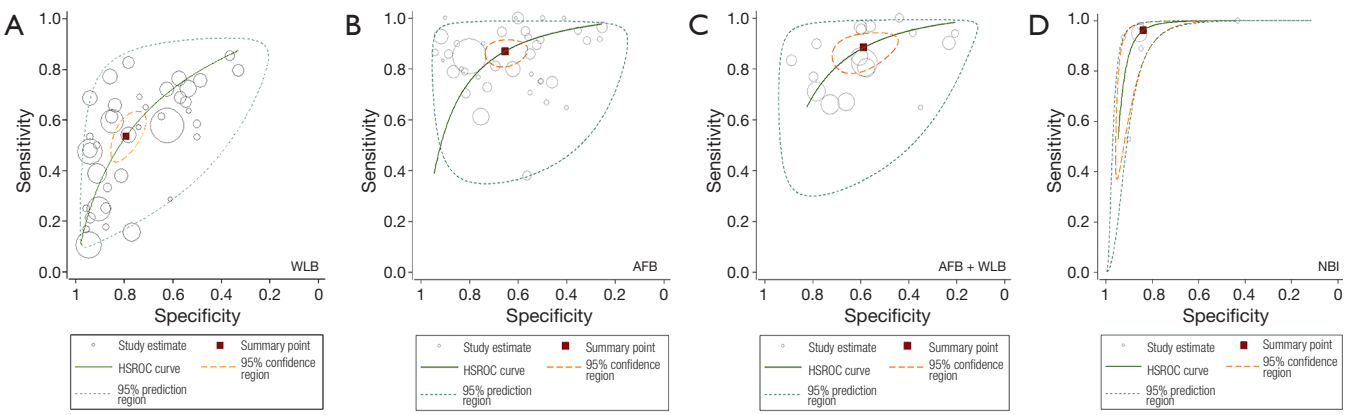

Figure 2 HSROC curve of WLB, AFB, AFB + WLB and NBI. The performance of NBI is remarkable, that of AFB and AFB + WLB is close. WLB showed the worse performance in single-arm synthesis. HSROC, hierarchical summary receiver operating characteristic; WLB, white light bronchoscopy; AFB, autofluorescence bronchoscopy; AFB + WLB, AFB combined with WLB; NBI, narrow-band imaging.

performance of NBI for diagnosing lung cancer (cancerous lesions). Accordingly, among the lesions under positive criteria of pathology, the percentage of cancerous lesions was far larger than the percentage of precancerous lesions (63-68). Therefore, during statistical calculation, we assumed that the large percentage of cancerous lesions in positive lesions may account for the remarkably high sensitivity and specificity of NBI in our research. A question that whether this technique still present such high diagnostic performance for precancerous lesions in the central airway, still warranted more studies to answer.

Autofluorescence technique was reported with more advantages for early lung cancer than white light technique in three published meta-analyses (6-8). In our research, we analyzed their performance based on original pathological criteria in included studies and found the similar outcome—higher sensitivity, DOR and AUC of AFB and AFB + WLB than those of WLB. When we used the criteria from MOD to INV, we found difference: AFB and AFB + WLB did not present superior enough AUC to WLB. This finding

Table 3 Direct comparison

Group	Study (n)	Patient (n)	Biopsy (n)	Technique	Sensitivity (95% CI) (%)	P	Specificity (95% CI) (%)	P	DOR (95% CI)	P	AUC (95% CI) (%)	P
Original pathological criteria												
WLB versus AFB	30	2,492	6,062	WLB	51 [42–60]	<0.001	79 [72–85]	0.002	4 [3–5]	<0.001	71 [67–75]	<0.001
				AFB	86 [82–90]		62 [54–70]		10 [7–15]		84 [81–87]	
WLB versus AFB + WLB	14	2,578	7,813	WLB	51 [35–66]	<0.001	83 [75–89]	<0.001	5 [3–9]	0.126	77 [74–81]	0.083
				AFB + WLB	88 [80–93]		57 [45–68]		10 [5–19]		82 [78–85]	
WLB versus NBI	3	154	226	WLB	29 [17–44]	<0.001	82 [74–88]	0.043	2 [1–6]	0.008	66 [47–85]	0.030
				NBI	79 [65–90]		71 [62–78]		19 [7–52]		89 [82–96]	
Moderate dysplasia, severe dysplasia, CIS and invasive carcinoma												
WLB versus AFB	6	728	1,549	WLB	50 [25–75]	0.009	83 [64–93]	0.009	5 [2–12]	0.393	75 [71–79]	0.271
				AFB	88 [74–95]		50 [33–66]		7 [4–12]		76 [72–80]	
WLB versus AFB + WLB	5	862	2,727	WLB	46 [20–73]	0.062	91 [87–94]	<0.001	9 [3–24]	0.413	89 [86–92]	<0.001
				AFB + WLB	85 [54–97]		71 [57–82]		14 [4–51]		81 [77–84]	
WLB versus NBI	1	22	64	WLB	62	–	65	–	–	–	–	–
				NBI	100		43		–		–	

WLB, white light bronchoscopy; AFB, autofluorescence bronchoscopy; AFB + WLB, AFB combined with WLB; NBI, narrow-band imaging; DOR, diagnostic odds ratio; AUC, area under the receiver-operating characteristic curve; CIS, carcinoma in situ.

Table 4 Meta-regression for source of heterogeneity

Source of heterogeneity	WLB		AFB		AFB + WLB		NBI	
	P*	I^2 (95% CI) (%)	P*	I^2 (95% CI) (%)	P*	I^2 (95% CI) (%)	P*	I^2 (95% CI) (%)
Median year: past versus current	0.57	0 [0–100]	0.21	37 [0–100]	0.85	0 [0–100]	0.30	18 [0–100]
Quality: high versus moderate	0.84	0 [0–100]	0.10	56 [1–100]	0.37	0 [0–100]	0.19	39 [0–100]
Analysis: biopsy- versus patient-based	0.10	57 [3–100]	0.17	44 [0–100]	0.09	58 [6–100]	0.03	71 [37–100]

*, P value was based on the joint model, considering the sensitivity and specificity together; P value <0.05, indicated the factors could be the source of heterogeneity during data synthesis. WLB, white light bronchoscopy; AFB, autofluorescence bronchoscopy; AFB + WLB, AFB combined with WLB; NBI, narrow-band imaging.

has been not yet reported in previous meta-analyses (6-8). We assume, the comparable diagnostic accuracy of WLB for higher-degree lesions, especially INV, contributed the non-superiority of AFB and AFB + WLB regarding the AUC: in Sun *et al.* meta-analysis (6), the pooled sensitivity of WLB was 88.53% for invasive lesions, and 42.54% for intraepithelial neoplasm including moderate/severe dysplasia (SEV) and CIS. Regardless of the AUC of AFB and AFB + WLB versus WLB, their another overall index, DOR, paralleled with their sensitivity, were still higher than

those of WLB.

Besides, in both single-arm synthesis and direct comparison, we also surprisingly found the specificity of AFB + WLB was over 70% for MOD to INV. Considering all diagnostic indexes (sensitivity, specificity, DOR and AUC) among AFB, AFB + WLB and WLB, the combination strategy of autofluorescence and white light techniques may be more useful to diagnose these range of lesions rather than their alone use. Based on this assumption, another meta-analysis comparing AFB and AFB + WLB directly is needed.

Considering the superior sensitivity and DOR of all advanced techniques we studied for different lesions (from hyperplasia to INV), comprehensive strategy could be further explored for patients. In current stage, for the low prevalence of invasive and high-grade lesions, we understand that using these techniques even in addition to computed tomography (CT) for screening lung cancer in high-risk population is still out of sufficient evidence (69). However, due to the potential property of pre-invasive lesions progressing as worse lesions, as well as the controversy that early intervention could be applied to treat these lesions, advanced bronchoscopies may be considered for the surveillance or follow-up when these lesions exist in airway (3,70,71). Furthermore, combined with genetic and epigenetic analysis, these advanced techniques may be useful to provide more evidence of diagnosis, chemoprevention and early endobronchial intervention for pre-invasive lesions in future studies (72-75).

Some limitations existed in our research. Firstly, there was no united standard of the inclusion criteria of study selection about which types or range of pathology should be regarded as the positive results. For example, one study regarded the range from metaplasia to SEV as the positive standard (17), but the range from MOD to CIS was used as the positive pathological result in another study (18). Accordingly, except the original criteria used in our included studies, we also conducted our analysis based on the specific range, from MOD to INV, which may hopefully address this issue and show the exact performance of these techniques when diagnosing. Secondly, the nature of our research limited us to consider other factors regarding the details of study procedure in all included researches for further analysis, such as single or independent diagnosis among bronchoscopists or pathologists, experience level of practitioners, random biopsy, etc. Moreover, our included studies of NBI were still lack of sufficiency. Considering its possibly high sensitivity and specificity, we expect more NBI studies not only for diagnosing lung cancer, but also precancerous lesions.

In conclusion, with remarkable sensitivity, we believe potential lesions of pre-cancerous and cancerous lesions could be covered by advanced techniques, especially precancerous lesions, almost invisible and easily missed by WLB. Combining strategy of AFB and WLB may contribute preferably rather than their alone use for detecting high-grade lesions from MOD to INV. NBI for airway precancerous lesions warrants further investigation.

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Footnote

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Supplementary

Table S1 Quality assessment of diagnostic accuracy studies-2 (QUADAS-2)

Author	Risk of bias														Applicability concerns		
	D1Q1	D1Q2	D1Q3	D1	D2Q1	D2Q2	D2	D3Q1	D3Q2	D3	D4Q1	D4Q2	D4Q3	D4	D1	D2	D3
Kurie 1998	Y	Y	Y	L	Y	Y	L	Y	U	L	U	Y	N	U	L	L	L
Moro-Sibilot 2002	Y	Y	U	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Herth 2003	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	N	U	L	L	L
Lee 2007	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Moghissi 2008	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	N	U	L	L	L
Lee 2009	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Zaric 2009	N	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	U	U	L	L	L
Zaric 2010	N	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Lam 1992	U	Y	U	U	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Lam 1993	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	N	U	L	L	L
Lam 1994	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Yokomise 1997	U	Y	U	U	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Horvath 1999	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Kakihana 1999	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Ikeda 1999	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Weigel 1999	N	Y	U	U	Y	Y	L	Y	Y	L	U	Y	Y	L	U	L	L
Weigel 2000	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Shibuya 2001	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	N	U	U	L	L
Furukawa 2000	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Means-Markwell 2003	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Lang 2005	Y	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Chhajed 2005	Y	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Chiyo 2005	U	Y	U	U	Y	Y	L	Y	Y	L	U	Y	N	U	U	L	L
Lam 2006	Y	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Ikeda 2006	Y	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Ueno 2007	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Nakanishi 2007	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Gabrecht 2007	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Li 2010	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Ali 2011	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Cetınkaya 2011	U	Y	Y	L	Y	Y	L	Y	U	L	U	N	Y	U	L	L	L
Venmans 1999	U	Y	U	U	Y	U	L	Y	U	L	U	Y	Y	L	U	L	L
Kusunoki 2000	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Hirsch 2001	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Fuso 2005	Y	Y	U	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Ernst 2005	N	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Divisi 2010	U	Y	U	U	Y	Y	L	Y	U	L	U	N	Y	U	U	L	L
Lam 1998	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Vermylen 1999	Y	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Häußinger 1999	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Venmans 2000	U	Y	U	U	Y	Y	L	Y	Y	L	U	Y	N	U	U	L	L
Sato 2001	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Häußinger 2005	Y	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Hanibuchi 2007	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Edell 2009	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Xing 2005	U	Y	Y	L	Y	U	L	Y	U	L	U	N	N	U	L	L	L
Reinders 2009	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Shibuya 2003	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Bojan 2009	N	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	U	U	L	L	L
Zaric 2009	N	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Vincent 2007	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Nguyen 2013	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	N	U	L	L	L
Herth 2009	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L

Y, yes; N, no; U, unclear; L, low; H, high; risk of bias: D1, domain 1, patient selection; D2, domain 2, index test; D3, domain 3, reference standard; D4, domain 4, flow and timing; D1Q1, was a consecutive or random sample of patients enrolled? D1Q2, was a case-control design avoided? D1Q3, did the study avoid inappropriate exclusions? D2Q1, were the index test results interpreted without knowledge of the results of the reference standard? D2Q2, if a threshold was used, was it prespecified? D3Q1, is the reference standard likely to correctly classify the target condition? D3Q2, were the reference standard results interpreted without knowledge of the results of the index test? D4Q1, was there an appropriate interval between the index test and reference standard? D4Q2, did all patients receive the same reference standard? D4Q3, were all patients or biopsy specimens included in the analysis? Applicability concern: D1, domain 1, are there concerns that the included patients and setting do not match the review question? D2, domain 2, are there concerns that the index test, its conduct, or its interpretation differ from the review question? D3, domain 3, are there concerns that the target condition as defined by the reference standard does not match the question?