The Value of Autofluorescence Bronchoscopy Combined with White Light Bronchoscopy Compared with White Light Alone in the Diagnosis of Intraepithelial Neoplasia and Invasive Lung Cancer

A Meta-Analysis

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Objective: To compare the accuracy of autofluorescence bronchoscopy (AFB) combined with white light bronchoscopy (WLB) versus WLB alone in the diagnosis of lung cancer.

Methods: The Ovid, PubMed, and Google Scholar databases from January 1990 to October 2010 were searched. Two reviewers independently assessed the quality of the trials and extracted data. The relative risk for sensitivity and specificity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia and invasive cancer were pooled by Review Manager.

Results: Twenty-one studies involving 3266 patients were ultimately analyzed. The pool relative sensitivity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia and invasive cancer was 2.04 (95% confidence interval [CI] 1.72–2.42) and 1.15 (95% CI 1.05–1.26), respectively. The pool relative specificity on a per-lesion basis of AFB + WLB versus WLB alone was 0.65 (95% CI 0.59–0.73).

Conclusions: Although the specificity of AFB + WLB is lower than WLB alone, AFB + WLB seems to significantly improve the sensitivity to detect intraepithelial neoplasia. However, this advantage over WLB alone seems much less in detecting invasive lung cancer.

Key Words: Autofluorescence bronchoscopy, White light bronchoscopy, Intraepithelial neoplasia, Invasive lung cancer, Meta-analysis.

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Lung cancer is the leading cause of cancer mortality globally.¹ The Third National inquest case study researched by the Health Ministry of China in 2008 reported that the major incidence of lung cancer increased 465% in the past 30 years in China. Although surgery for early stage lung cancers offers a relatively good prospect of cure, 5-year survival rates for patients with stage IA disease are 73%; however, for those with disease at stages II to IV, the rates range from 46 to 9%.² Currently, only 16% of lung cancers are diagnosed when disease is localized, and fewer lung cancers are diagnosed at stage 0, resulting in a combined 5-year survival rate of only 15%.³ Therefore, more sensitive methods for detecting clinically silent lung cancers at the earlier stages are greatly needed.

White light bronchoscopy (WLB) is a commonly used diagnostic tool for obtaining tissue for the definitive diagnosis of lung cancer. However, WLB is limited in its ability to detect small intraepithelial and microinvasive/preinvasive lesions, which may be only a few cells thick and might only have a surface diameter of a few millimeters. Autofluorescence bronchoscopy (AFB) was developed to address this limitation of WLB.4 AFB has been shown to be a far more sensitive method of detecting microinvasive/preinvasive lesions. However, the literature gives confusing results regarding the sensitivity and specificity of detecting these lesions when AFB + WLB is compared with WLB alone. For the proper use of fluorescence bronchoscopy for the diagnosis of central-type early lung cancer, we systematically reviewed the literature to summarize the evidence for the value of AFB + WLB versus WLB alone in the diagnosis of microinvasive/ preinvasive and invasive lung cancer.

MATERIALS AND METHODS

Search Strategy

We searched for articles comparing the value of AFB + WLB versus WLB alone, using search engines in Ovid, PubMed, and Google Scholar from January 1990 to October 2010. The following key words were used: "AFB" or "fluo-

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rescence bronchoscopy" or "autofluorescence endoscopy" or "fluorescence endoscopy," and "WLB" or "conventional bronchoscopy" or "video bronchoscopy." We compared sources to exclude duplicate references (i.e., the same outcomes reported on the same cohort). Reference lists of included studies and review articles were manually searched.

Study Selection

Inclusion criteria were (a) articles were published in English; (b) AFB and WLB were used in the diagnosis of intraepithelial neoplasia and invasive lung cancer; (c) histopathology analysis was used as the reference standard; (d) for per-lesion statistics, sufficient data were presented to calculate the sensitivity and specificity of intraepithelial neoplasia (moderate/severe dysplasia or carcinoma in situ [CIS]) and invasive lung cancer; and (e) when data or subsets of data were presented in more than one article, the article with most details or the most recent article was chosen.

Data Extraction

Information was extracted from all eligible publications, independently by two reviewers (J.S. and J.Y.), according to the inclusion criteria listed earlier. Disagreement was resolved by discussion between the two reviewers. Relevant studies were further examined with Quality Assessment of Diagnostic Accuracy Studies criteria.⁵ The following data were collected from each study: first author's surname, year of publication, type of AFB, average subject age, sample size, patient characteristics, and outcome. To compare the diagnostic value for lung cancer of the two types of bronchoscopies, we studied the sensitivity and specificity of the two to diagnose intraepithelial neoplasia and invasive cancer, respectively.

Statistical Analysis

The relative risk (RR) for sensitivity and specificity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia or invasive cancer were calculated by Review Manager (RevMan; version 4.2. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration). A statistical test with a p less than 0.05 was considered significant. RR of more than 1 reflects more sensitivity of in AFB + WLB and vice versa. The results were generated using the fixed-effects model. A randomeffect model was employed when there was evidence of significant statistical heterogeneity, generating a more conservative estimate. All p values were two sided. All confidence intervals (CIs) had a two-sided probability coverage of 95%. Subgroup analysis was carried out to look at the diagnostic value of the different types of AFB. An estimate of potential publication bias was carried out using funnel plotting, in which the standard error of log (RR) of each study was plotted against its log (RR). An asymmetric plot suggested a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a well-established linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the RR. The significance of the intercept was determined by the t test suggested by Egger (p < 0.05 was considered

representative of statistically significant publication bias) calculated by using STATA version 10.0 (Stata Corporation, College Station, TX). Linear regression was also calculated by STATA.

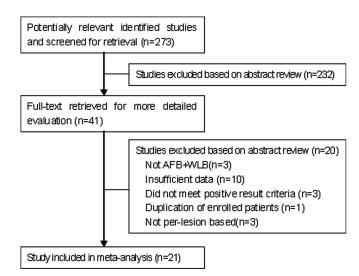
RESULTS

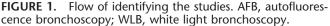
Trial Flow

Two hundred seventy-three reports were originally retrieved after electronic searching, and 41 studies were identified after scanning the titles and abstracts. Twenty studies were excluded for the following reasons: (a) only AFB was performed^{6–8}; (b) sufficient data not presented to calculate sensitivity and specificity^{9–18}; (c) positive result not moderate/severe dysplasia, CIS, or invasive cancer^{19–21}; (d) where data presented in more than one article, article with fewest details was excluded²²; and (e) studies were not per-lesion based^{23–25} (Figure 1).

Characteristics of Included Studies

Twenty-one studies meeting the inclusion criteria were identified.^{26–46} WLB was performed in all studies, whereas different types of AFB were used in different studies. The light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies; Vancouver, BC, Canada) was used in 12 studies. The Storz D-Light system (D-Light, Karl Storz company, Germany) and Pentax SAFE-1000 systems (Pentax, Tokyo, Japan) were performed in three studies each. The Pentax SAFE-3000 system (Pentax), Onco-LIFE device (Xillix Technologies; Richmond), and PDS-2000 (Hamamatsu Photonics K.K., Hamamatsu, Japan) were performed in one study each. Among the 21, 19 studies had sufficient data to analyze the RR for sensitivity of WLB + FLB versus WLB alone to detect intraepithelial neoplasia, whereas 14 studies were used to analyze the RR for sensitivity of WLB + FLB versus WLB alone to detect invasive cancer. Sixteen studies were used to analyze the RR for specificity of WLB + AFB versus WLB





						Preinvasiv	e Lesio	ns		Invasiv	e Cancer	·		
							Sensiti	vity (%)			Sens	itivity	Spec	cificity
Reference	Category of AFB	Average Age (yr)	No. of Subjects	No. of Biopsies	N	Prevalence (%)	WLB	AFB + WLB	N	Prevalence (%)	WLB	AFB + WLB	WLB	AFB + WLB
Edell et al.27	Onco-LIFE	62	170	776	41	5.28	9.76	41.46	35	4.51	91.43	100.00	94.00	75.00
Nakanishi et al.33	PDS-2000	69	71	288	29	10.07	27.59	75.86	16	5.56	75.00	93.75	77.37	52.67
Jang et al.35	D-Light	62	113	283	16	5.65	25.00	93.75		1	NR		93.33	50.00
Lam et al.34	SAFE-1000	60	62	84	11	13.10	54.55	100.00	1	1.19	100.00	100.00	1	NR
Ikeda et al.36	SAFE-3000	68	154	166	48	28.92	66.67	100.00	30	18.07	100.00	100.00	1	NR
Häussinger et al.38	D-Light	59	1173	2907	53	1.82	57.89	82.35		1	NR		62.12	58.38
Chhajed et al.37	LIFE	67	151	343	63	18.37	63.49	96.83	20	5.83	100.00	100.00	53.46	17.69
Moro-Sibilot et al.39	LIFE	60	244	354	42	11.86	35.71	85.71	39	11.02	74.36	76.92	96.34	82.78
van Rens et al.42	LIFE	66	72	88	15	17.05	20.00	100.00	1	1.14	100.00	100.00	1	NR
Shibuya et al.41	LIFE	68	64	212	45	21.23	68.89	91.11	21	9.91	100.00	100.00	65.75	31.51
Hirsch et al.40	LIFE	68	55	391		N	R			1	NR		77.64	29.39
Vermylen et al.43	LIFE	59	34	142	16	11.27	25.00	93.75		1	NR		86.51	20.63
Weigel et al.26	LIFE	65	36	89		N	R			1	NR		86.75	48.19
Ikeda et al.31	LIFE	64	158	262	84	32.06	58.33	100.00	43	16.41	100.00	100.00	62.22	44.44
Venmans et al.32	LIFE	65	95	681	79	11.60	59.49	84.81	21	3.08	100.00	100.00	84.85	60.41
Kakihana et al.29	SAFE-1000	NR	72	147	55	37.41	52.73	100.00	24	16.33	100.00	100.00	1	NR
Häußinger et al.28	D-Light	62	56	264	7	2.65	28.57	71.43	36	13.64	80.56	83.33	93.21	86.43
Horvath et al.30	SAFE-1000	51	60	146	5	3.42	0.00	100.00		1	NR		91.49	76.60
Lam et al.44	LIFE	63	173	700	102	14.57	8.82	55.88	40	5.71	65.00	95.00	90.32	65.95
Ikeda et al.45	LIFE	NR	30	77	28	36.36	35.71	100.00	13	16.88	92.31	100.00	1	NR
Lam et al.46	LIFE	NR	223	451	113	25.06	38.94	84.07		1	NR		91.12	81.36

TABLE 1. Characteristics of Included Studies

alone (Table 1). The size of the cohorts varied from 30 to 1173, with the total number being 3266 patients.

Publication Bias and Heterogeneity

Publication bias was found according to funnel plot in the articles enrolled in the analysis of RR for sensitivity detection of intraepithelial neoplasia (Figure 2; Begg's test,

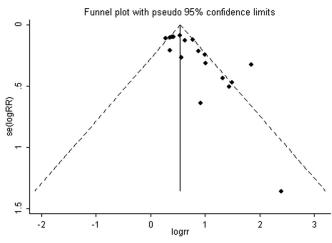


FIGURE 2. Funnel plot of 19 studies included in the analysis of relative risk (RR) for sensitivity of autofluorescence bronchoscopy + white light bronchoscopy (WLB) versus WLB to detect intraepithelial neoplasia.

p = 0.039; Egger's test, p = 0.000). Heterogeneity was both found in sensitivity to detect intraepithelial neoplasia and specificity (p < 0.05). Therefore, a random effect model was used for the meta-analysis to obtain a summary estimate for sensitivity and specificity with 95% CI. To explore the possible source of heterogeneity, subgroup analyses were applied. Heterogeneity was also found in the LIFE subgroup.

Relationship between Prevalence and Sensitivity

Linear regression suggested that the sensitivity correlated with the prevalence of intraepithelial neoplasia, both for WLB($r^2 = 0.208$, p = 0.049) and AFB + WLB($r^2 = 0.214$, p = 0.046), but not correlated with the prevalence of invasive cancer ($r^2 = 0.004$, p = 0.821; $r^2 = 0.016$, p = 0.664).

Meta-Analysis Results

Relative Sensitivity to Detect Intraepithelial Neoplasia

The pool sensitivity on a per-lesion basis of AFB + WLB and WLB to detect intraepithelial neoplasia was 84.63 and 42.54%, respectively. The pool relative sensitivity of AFB + WLB versus WLB was 2.04 (95% CI 1.72–2.42) and was statistically significant (p < 0.00001).^{27–39,41–46} Onco-LIFE had the highest RR (4.25; 95% CI, 1.56–11.55), but only one study was included. The analysis in the subgroups whose enrolled studies were more than one showed that the

highest RR was 2.16 in D -Light (95% CI 1.06–4.39). SAFE-1000 was the lowest at 1.88 (95% CI 1.50–2.36), and the LIFE RR was 2.10 (95% CI 1.66–2.66). The RR of the other subgroups was as follows: SAFE-3000, 1.49 (95% CI

AFB+WLB&WLB (sub-group) 01 AFB+WLB&WLB

Review:

Comparison:

1.22–1.83) and PDS-2000, 2.75 (95% CI 1.47–5.13). The test of heterogeneity for the 19 studies was significant (p < 0.00001). Thus, RR was calculated using a random-effect model (Figure 3).

udy sub-category	AFB+WLB n/N	WLB n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
I LIFE					
hhajed 2005	61/63	40/63	-	8.40	1.53 [1.26, 1.85]
loro-sibilot 2002	36/42	15/42	_ _	5.95	2.40 [1.57, 3.67]
ens 2001	15/15	3/15		2.48	4.43 [1.75, 11.23]
hibuya 2001	41/45	31/45		8.17	1.32 [1.07, 1.64]
eda 1999	84/84	49/84		8.51	1.71 [1.42, 2.05]
enmans 1999	67/79	47/79		8.29	1.43 [1.16, 1.75]
ermylen 1999	15/16	4/16		2.78	3.75 [1.59, 8.84]
Lam 1998	57/102	9/102		→ 3.99	6.33 [3.32, 12.10]
eda 1997	28/28	10/28		5.34	2.71 [1.67, 4.41]
Lam 1994	95/113	44/113		7.89	2.16 [1.69, 2.76]
ototal (95% Cl) al events: 499 (AFB+WLB),	587 252 (WLB)	587	•	61.81	2.10 [1.66, 2.66]
st for heterogeneity: Chi ² = 5 st for overall effect: Z = 6.12	2.78, df = 9 (P < 0.00001), I ²	= 82.9%			
D-Light					
ng 2006	15/16	4/16		2.78	3.75 [1.59, 8.84]
auBinger 2005	28/34	11/19	⊢ ∎—	6.06	1.42 [0.94, 2.15]
auBinger 1999	5/7	2/7	_ 	1.53	2.50 [0.71, 8.83]
ototal (95% CI)	57	42		10.37	2.16 [1.06, 4.39]
al events: 48 (AFB+WLB), 1	7 (WLB)				
st for heterogeneity: Chi ² = 4 st for overall effect: Z = 2.13		0%			
SAFE-1000					
Lam 2006	11/11	6/11		4.90	1.77 [1.04, 3.02]
rvath 1999	5/5	0/5		0.39	11.00 [0.77, 158.01]
kihana 1999	55/55	29/55		7.83	1.88 [1.47, 2.41]
ototal (95% CI)	71	71	•	13.12	1.88 [1.50, 2.36]
al events: 71 (AFB+WLB), 3	5 (WLB)		-		
st for heterogeneity: Chi ² =1 st for overall effect: Z = 5.52					
SAFE-3000					
:da 2006	48/48	32/48		8.32	1.49 [1.22, 1.83]
ototal (95% Cl)	48	48	•	8.32	1.49 [1.22, 1.83]
tal events: 48 (AFB+WLB), 3	2 (WLB)				
st for heterogeneity: not appl st for overall effect: Z = 3.89					
Onco-LIFE					
lell 2009	17/41	4/41		2.22	4.25 [1.56, 11.55]
btotal (95% Cl)	41	41		2.22	4.25 [1.56, 11.55]
tal events: 17 (AFB+WLB), 4			1		
st for heterogeneity: not appl st for overall effect: Z = 2.84					
PDS-2000					
kanishi 2007	22/29	8/29		- 4.16	2.75 [1.47, 5.13]
itotal (95% Cl)	22/29	29		- 4.16 - 4.16	-
al events: 22 (AFB+WLB), 8		23		4.10	2.75 [1.47, 5.13]
t for heterogeneity: not appl t for overall effect: Z = 3.18	licable				
tal (95% CI)	833	818	•	100.00	2.04 [1.72, 2.42]
al events: 705 (AFB+WLB), st for heterogeneity: Chi ² = 7 st for overall effect: Z = 8.20	348 (WLB) 0.26, df = 18 (P < 0.00001), l	0		200100	

FIGURE 3. Forest plot of relative risk for subgroup and overall sensitivity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB to detect intraepithelial neoplasia. CI, confidence interval.

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Review:

Relative Sensitivity to Detect Invasive Cancer

AFB+WLB&WLB (sub-group)

The pool sensitivity on a per-lesion basis of AFB + WLB versus WLB to detect invasive cancer was 94.71 and 88.53%, respectively. The pool relative sensitivity of AFB + WLB versus WLB was 1.15 (95% CI 1.05–1.26) and was statistically significant (p = 0.003).^{27–29,31–34,36,37,39,41,42,44,45} Only the RR of LIFE was statistically significant (p = 0.01), with a value of 1.21 (95% CI 1.04–1.40) among the sub-

groups. The RR of other subgroups was not statistically significant (p > 0.05). PDS-2000 had the highest RR (1.25, 95% CI 0.92–1.70), but only one study was enrolled. The RR of the other subgroups was as follows: D-Light, 1.03 (95% CI 0.83–1.29) and Onco-LIFE, 1.09 (95% CI 0.97–1.22). The RR of both SAFE-1000 and SAFE-3000 were 1. The test of heterogeneity for the 14 studies was not significant (p = 0.23). Thus, the RR was calculated using a fixed-effect model (Figure 4).

tudy	AFB+WLB	WLB	RR (fixed)	Weight	RR (fixed)
udy sub-category	n/N	n/N	95% Cl	vveight %	95% Cl
FE					
nhajed 2005	20/20	20/20			Not estimable
oro-sibilot 2002	30/39	29/39	-+-	20.57	1.03 [0.80, 1.33]
nibuya 2001	21/21	21/21			Not estimable
ens 2001	1/1	1/1			Not estimable
eda 1999	43/43	43/43			Not estimable
enmans 1999	21/21	21/21			Not estimable
Lam 1998	38/40	26/40		18.44	1.46 [1.15, 1.85]
da 1997	13/13	12/13		8.87	1.08 [0.88, 1.33]
ototal (95% Cl)	198	198	•	47.87	1.21 [1.04, 1.40]
al events: 187 (AFB+WLB), 173 (V		201			
t for heterogeneity: Chi ² = 5.02, df t for overall effect: Z = 2.52 (P = 0		2%			
D-Light					
auBinger 1999	30/36	29/36		20.57	1.03 [0.83, 1.29]
btotal (95% Cl)	36	36		20.57	1.03 [0.83, 1.29]
tal events: 30 (AFB+WLB), 29 (WL			Т		
st for heterogeneity: not applicable					
st for overall effect: Z = 0.31 (P = 0					
SAFE-1000					
Lam 2006	1/1	1/1			Not estimable
akihana 1999	24/24	24/24			Not estimable
btotal (95% Cl)	25	25			Not estimable
al events: 0 (AFB+WLB), 0 (WLB)					
st for heterogeneity: not applicable					
st for overall effect: not applicable					
SAFE-3000					
da 2006	30/30	30/30			Not estimable
btotal (95% CI)	30	30			Not estimable
al events: 0 (AFB+WLB), 0 (WLB)					
t for heterogeneity: not applicable t for overall effect: not applicable					
Onco-LIFE					
dell 2009	35/35	32/35	L	23.05	1.09 [0.97, 1.22]
ibtotal (95% Cl)	35/35	32/33	E	23.05	1.09 [0.97, 1.22]
tal events: 35 (AFB+WLB), 32 (WL			•	20.00	1.05 [0.57, 1.22]
st for heterogeneity: not applicable					
st for overall effect: Z = 1.52 (P = 0					
PDS-2000					
akanishi 2007	15/16	12/16	+	8.51	1.25 [0.92, 1.70]
ototal (95% Cl)	16	16		8.51	1.25 [0.92, 1.70]
al events: 15 (AFB+WLB), 12 (WL					
for heterogeneity: not applicable					
t for overall effect: Z = 1.41 (P = 0	0.16)				
tal (95% Cl)	340	340	•	100.00	1.15 [1.05, 1.26]
tal events: 322 (AFB+WLB), 301 (V					
st for heterogeneity: Chi ² = 6.86, df		2%			
st for overall effect: Z = 2.97 (P = 0).003)				

FIGURE 4. Forest plot of relative risk (RR) for subgroup and overall sensitivity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB to detect invasive cancer. CI, confidence interval.

Relative Specificity

The pool specificity on a per-lesion basis of AFB + WLB versus WLB was 60.94 and 79.70%, respectively. The pool relative specificity on a per-lesion basis of AFB + WLB versus WLB was 0.65 (95% CI 0.59–0.73) and was statistically significant (p < 0.00001).^{26–28,30–33,35,37–41,43,44,46} The RR of the subgroups were as follows: LIFE, 0.56 (95% CI 0.47–0.68); D-Light, 0.78 (95% CI 0.62–0.99); SAFE-1000, 0.84 (95% CI 0.75–0.93); Onco-LIFE, 0.80 (95% CI 0.76–0.84); and PDS-2000, 0.68 (95% CI 0.59–0.78). The test of heterogeneity for the 16 studies was significant (p < 0.0000)

Review:	AFB+WLB&WLB (sub-group)
Comparison:	01 AFB+WLB&WLB
Outcome:	04 specificity

0.00001). Thus, the RR was calculated using a random-effect model (Figure 5).

Adverse Effects

Adverse effects were reported in two studies. In one study,²⁷ reported adverse effects were seen in nine patients. All adverse effects were commensurate with bronchoscopy, with none being attributable to the AFB devices. Serious complications include fever and hypoxia, resulting in hospitalization in four patients. Ikeda et al.³⁶ reported only minor adverse effects such as faint blood-tinged sputum and mild

01 LIFE Chhajed 2005 46 Moro-sibilot 2002 226 Hirsch 2001 92 Shibuya 2001 46 Ikeda 1999 60 Vermylen 1999 26 Weigel 1999 40 S.Lam 1998 366 S.Lam 1994 275 Subtotal (95% CI) 101 Total events: 1530 (AFB+WLB), 2311 (WLE 10000 02 D-Light 103 Jang 2006 105 HauBinger 1999 191 Subtotal (95% CI) 101 Total events: 1530 (AFB+WLB), 1245 (WLE) Jang 2006 105 HauBinger 1999 193 Subtotal (95% CI) 104 Total events: 1170 (AFB+WLB), 1245 (WLE) Test for overall effect: Z = 2.00 (P = 0.05) 03 SAFE-1000 106 Horvath 1999 108 Subtotal (95% CI) 105 Total events: 108 (AFB+WLB), 129 (WLB) 108 Subtotal (95% CI) 105 Total events: 108 (AFB+WLB), 129 (WLB) 108 Dest for heterogeneity: not applicable 25	9 (P < 0.00001), I	n/N 139/260 263/273 243/313 96/146 84/135 493/581 109/126 72/83 504/558 308/338 2813 1 ² = 96.8%		% 4.81 7.09 6.01 5.03 5.45 7.00 4.12 5.35 7.05 7.08 58.99	95% Cl 0.33 [0.25, 0.44] 0.86 [0.81, 0.91] 0.38 [0.32, 0.45] 0.48 [0.37, 0.63] 0.71 [0.57, 0.90] 0.71 [0.66, 0.77] 0.24 [0.17, 0.34] 0.56 [0.44, 0.71] 0.73 [0.68, 0.78] 0.89 [0.84, 0.95] 0.56 [0.47, 0.68]
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akanishi 2007 128	01)				
istatal (05%, CI)	8/243	188/243	-	6.48	0.68 [0.59, 0.78]
bibiai (35% Ci)	243	243	◆	6.48	0.68 [0.59, 0.78]
tal events: 128 (AFB+WLB), 188 (WLB)					
st for heterogeneity: not applicable					
st for overall effect: Z = 5.49 (P < 0.0000	01)				
tal (95% Cl)	5825	5685	◆	100.00	0.65 [0.59, 0.73]
tal events: 3461 (AFB+WLB), 4531 (WLE		.2			
st for heterogeneity: Chi ² = 336.10, df = 1		, 1~= 95.5%			
st for overall effect: Z = 7.71 (P < 0.0000	15 (P < 0.00001),				

FIGURE 5. Forest plot of relative risk (RR) for subgroup and overall specificity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB. CI, confidence interval.

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cough, commonly associated with routine bronchoscopic examination, with there being no specific relation to the AFB examination.

DISCUSSION

Detection of cancers at an early stage, followed by complete surgical resection, is the only curative treatment approach currently available for the majority of lung cancer patients. Advances in bronchoscopy⁴⁷ and the use of sputum cytology have helped to increase the detection of central-type early lung cancer. WLB is usually used in the detection of lung cancer. Nevertheless, although this type of bronchoscopy can detect early lung cancer, the detection of preinvasive lesions is difficult even for experienced bronchoscopists. One study⁴⁸ showed that only 29% of CIS lesions were visible to experienced bronchoscopists using WLB.

According to our meta-analysis, AFB + WLB can effectively and significantly improve the sensitivity to detect only intraepithelial neoplasia compared with WLB alone, the pool relative sensitivity of AFB + WLB versus WLB to detect intraepithelial neoplasia is 2.04. It has been reported in Bronchial Intraepithelial Neoplasia/Early Central Airways Lung Cancer, ACCP Evidence-Based Clinical Practice Guidelines (2nd edition) that the pool sensitivity on a perlesion basis of AFB + WLB and WLB to detect intraepithelial neoplasia was 80 and 40%, respectively; the pool specificity was 60 and 81%, respectively; and the pool relative sensitivity of AFB + WLB versus WLB was 2.49 Although the literatures enrolled in our meta-analysis were 38.9% same to this guideline for the different enrollment standard and the results of the guideline were not obtained by meta-analysis, our conclusions were surprisingly similar. Thus, we believe that our results are credible.

Although the sensitivity of AFB combined with WLB to detect invasive cancer was improved, its RR was only 1.15, which is much lower than the RR for sensitivity to detect intraepithelial neoplasia. If one is screening for invasive cancer, then, perhaps only WLB is needed. It is less expensive, easier to perform, and can be done in more centers and used more widely in populations whose chest radiology evidences are suspicious of central airways lesion. Thus, using WLB alone would seem to be cost effective.

The disadvantage of AFB is the lower specificity compared with WLB. The specificities of AFB + WLB in this meta-analysis were all decreased, compared with WLB alone, and the specificity of AFB + WLB was only 65% of WLB alone. The reason for the low specificity is that AFB has difficulty in distinguishing between preinvasive lesions and other benign epithelial changes such as bronchitis, which is frequently present in patients whose sputum cytology is suspicious or positive for malignancy.⁴¹ Some anthropic factors, such as severe coughing during AFB examination or AFB, were performed in patients after brushing or biopsy by recent WLB; all can result in false positive. The low specificity of AFB is also problematic because more biopsies are needed, resulting in greater cost and potential patient harm.

Bronchoscopic devices subsequent to LIFE have made many improvements. SAFE 1000 system uses a xenon lamp,

instead of the laser used in the LIFE system. A new version (SAFE-3000), incorporating single action image switching and simultaneous display, is now available. Storz D-light and Onco-LIFE systems combine autofluorescence and reflected light. AFI (Olympus Medical System Corp., Tokyo, Japan) has developed a display of a composite image, integrating three signals: an autofluorescence signal plus reflected green (G) and red (R) light signals. AFI will display a light green image for normal epithelium and blue or magenta for an abnormal fluorescence, depending on the condition of abnormal epithelium. This may be more objective than the LIFE system, under which normal areas appear as green, whereas areas suspicious for moderate dysplasia or greater have a definite brown or brownish-red color. In one study, the AFI system had better sensitivity (80%) and specificity (83%) than the LIFE system.8 Also, some studies reported that AFI has a higher sensitivity and specificity than WLB.7,17 However, these studies were not enrolled in our analysis because they did not match our inclusion criteria. In addition to equipment upgrades, quantitative methods have also been reported to improve the sensitivity and specificity for diagnosing lung cancer. One study reported about AFB (PDS-2000) images that were analyzed using Photoshop 6.0 (Adobe Systems Inc., San Jose, CA). Normal and abnormal bronchial parts were defined. Color histograms for red, green, and blue were generated in each area, using a histogram tool. Then the R:G ratio was calculated.33

Our findings are limited because of data heterogeneity. Possible reasons are as follows: (1) studies enrolled in the meta-analysis were over a long time span 1994 to 2009; (2) use of different types of AFB, but mainly LIFE (57.14%); studies of other types of AFB were few or not match our enrollment standard; (3) study populations were different in many articles, with some having patients with known or suspected lung cancer, whereas others had patients only with high risk of lung cancer, resulting in different prevalence of lesions. Linear regression suggested that the sensitivity correlated with the prevalence of intraepithelial neoplasia, both for WLB and AFB + WLB. Therefore, an important issue is to define a population recommended for AFB examination. Thoracic computed tomography is a sensitive method for detecting early lung cancer but has a high false-positive rate and is not as sensitive for detecting central preinvasive and microinvasive cancers. Conventional sputum cytology is hampered by a low sensitivity, but this can be improved by using DNA analyses of sputum slides, using automated sputum cytology, but with a modest reduction of specificity.50-53 Thus, patients with positive automated sputum cytology, but with chest imaging studies showing no localizing abnormality, may be a defined population recommended for having an AFB examination for detection of early lung cancer. The efficiency of AFB in detecting early lung cancer may thereby be enhanced in the setting of such dual screening.

In conclusion, compared with application of WLB alone, AFB + WLB seems to significantly improve the sensitivity and ability to detect intraepithelial neoplasia. However, this advantage over WLB alone seems much less in detecting invasive lung cancer. Although the specificity of

AFB is lower than WLB, the development of newer instruments of AFB and the application of quantitation methods might improve the specificity of AFB, which would shorten examination time, reduce biopsy site size, and decrease risk and cost.

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REFERENCES

- Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
- Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714.
- 3. Cancer Facts & Figures 2005. Atlanta, GA: American Cancer Society, 2005.
- Moghissi K, Dixon K, Stringer MR. Current indications and future perspective of fluorescence bronchoscopy: a review study. *Photodiagnosis Photodyn Ther* 2008;5:238–246.
- Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUA-DAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.
- Lee P, Brokx HA, Postmus PE, et al. Dual digital video-autofluorescence imaging for detection of pre-neoplastic lesions. *Lung Cancer* 2007;58: 44–49.
- Ueno K, Kusunoki Y, Imamura F, et al. Clinical experience with autofluorescence imaging system in patients with lung cancers and precancerous lesions. *Respiration* 2007;74:304–308.
- Chiyo M, Shibuya K, Hoshino H, et al. Effective detection of bronchial preinvasive lesions by a new autofluorescence imaging bronchovideoscope system. *Lung Cancer* 2005;48:307–313.
- Divisi D, Di Tommaso S, De Vico A, et al. Early diagnosis of lung cancer using a SAFE- 3000 autofluorescence bronchoscopy. *Interact Cardiovasc Thorac Surg* 2010;11:740–744.
- Lee P, van den Berg RM, Lam S, et al. Color fluorescence ratio for detection of bronchial dysplasia and carcinoma in situ. *Clin Cancer Res* 2009;15:4700–4705.
- Beamis JF Jr, Ernst A, Simoff M, et al. A multicenter study comparing autofluorescence bronchoscopy to white light bronchoscopy using a non-laser light stimulation system. *Chest* 2004;125:148S–149S.
- Herth FJ, Ernst A, Becker HD. Autofluorescence bronchoscopy—a comparison of two systems (LIFE and DLight). *Respiration* 2003;70: 395–398.
- Venmans BJ, van Boxem TJ, Smit EF, et al. Bronchial intraepithelial neoplastic lesions in head and neck cancer patients: results of autofluorescence bronchoscopy. *Ann Otol Rhinol Laryngol* 2001;110:635–638.
- Sato M, Sakurada A, Sagawa M, et al. Diagnostic results before and after introduction of autofluorescence bronchoscopy in patients suspected of having lung cancer detected by sputum cytology in lung cancer mass screening. *Lung Cancer* 2001;32:247–253.
- Lam S, MacAulay C, Hung J, et al. Detection of dysplasia and carcinoma in situ with a lung imaging fluorescence endoscope device. *J Thorac Cardiovasc Surg* 1993;105:1035–1040.
- Lam S, Hung JY, Kennedy SM, et al. Detection of dysplasia and carcinoma in situ by ratio fluorometry. *Am Rev Respir Dis* 1992;146: 1458–1461.
- Zaric B, Canak V, Stojanovic G, et al. Autofluorescence videobronchoscopy (AFI) for the assessment extension in lung cancer. *Technol Cancer Res Treat* 2009;8:79–84.
- Weigel TL, Yousem S, Dacic S, et al. Fluorescence bronchoscopic surveillance after curative surgical resection for non-small-cell lung cancer. *Ann Surg Oncol* 2000;7:176–180.
- Zaric B, Becker HD, Perin B, et al. Autofluorescence imaging videobronchoscopy improves assessment of tumor margins and affects therapeutic strategy in central lung cancer. *Jpn J Clin Oncol* 2010;40:139– 145.

- Hanibuchi M, Yano S, Nishioka Y, et al. Autofluorescence bronchoscopy, a novel modality for the early detection of bronchial premalignant and malignant lesions. *J Med Invest* 2007;54:261–266.
- Kusunoki Y, Imamura F, Uda H, et al. Early detection of lung cancer with laser-induced fluorescence endoscopy and spectrofluorometry. *Chest* 2000;118:1776–1782.
- Venmans BJ, van der Linden H, van Boxem TJ, et al. Early detection of preinvasive lesions in high-risk patients: a comparison of conventional flexible and fluorescence bronchoscopy. *J Bronchol* 1998;5:280–283.
- Stringer MR, Moghissi K, Dixon K. Autofluorescence bronchoscopy in volunteer asymptomatic smokers. *Photodiagnosis Photodyn Ther* 2008; 5:148–152.
- Baba M, Iyoda A, Nomoto Y, et al. Cytological findings of pre-invasive bronchial lesions detected by light-induced fluorescence endoscopy in a lung cancer screening system. *Oncol Rep* 2007;17:579–583.
- Fuso L, Pagliari G, Boniello V, et al. Autofluorescence bronchoscopy to identify pre-cancerous bronchial lesions. *Monaldi Arch Chest Dis* 2005; 63:124–128.
- Weigel TL, Kosco PJ, Dacic S, et al. Fluorescence bronchoscopic surveillance in patients with a history of nonsmall cell lung cancer. *Diagn Ther Endosc* 1999;6:1–7.
- Edell E, Lam S, Pass H, et al. Detection and localization of intraepithelial neoplasia and invasive carcinoma using fluorescence-reflectance bronchoscopy: an international, multicenter clinical trial. J Thorac Oncol 2009;4:49–54.
- Häußinger K, Stanzel F, Huber RM, et al. Autofluorescence detection of bronchial tumors with the D-Light/AF. *Diagn Ther Endosc* 1999;5:105– 112.
- Kakihana M, Il KK, Okunaka T, et al. Early detection of bronchial lesions using system of autofluorescence endoscopy (SAFE) 1000. *Diagn Ther Endosc* 1999;5:99–104.
- Horvath T, Horvathova M, Salajka F, et al. Detection of bronchial neoplasia in uranium miners by autofluorescence endoscopy (SAFE-1000). *Diagn Ther Endosc* 1999;5:91–98.
- Ikeda N, Honda H, Katsumi T, et al. Early detection of bronchial lesions using lung imaging fluorescence endoscope. *Diagn Ther Endosc* 1999; 5:85–90.
- Venmans BJ, Van Boxem TJ, Smit EF, et al. Results of two years experience with of preinvasive bronchial neoplasia. *Diagn Ther Endosc* 1999;5:77–84.
- Nakanishi K, Ohsaki Y, Kurihara M, et al. Color auto-fluorescence from cancer lesions: improved detection of central type lung cancer. *Lung Cancer* 2007;58:214–219.
- Lam B, Wong MP, Fung SL, et al. The clinical value of autofluorescence bronchoscopy for the diagnosis of lung cancer. *Eur Respir J* 2006;28: 915–919.
- Jang TW, Oak CH, Chun BK, et al. Detection of pre-invasive endobronchial tumors with D-light/autofluorescence system. J Korean Med Sci 2006;21:242–246.
- Ikeda N, Honda H, Hayashi A, et al. Early detection of bronchial lesions using newly developed videoendoscopy-based autofluorescence bronchoscopy. *Lung Cancer* 2006;52:21–27.
- Chhajed PN, Shibuya K, Hoshino H, et al. A comparison of video and autofluorescence bronchoscopy in patients at high risk of lung cancer. *Eur Respir J* 2005;25:951–955.
- 38. Häussinger K, Becker H, Stanzel F, et al. Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomised controlled multicentre trial. *Thorax* 2005;60:496–503.
- Moro-Sibilot D, Jeanmart M, Lantuejoul S, et al. Cigarette smoking, preinvasive bronchial lesions, and autofluorescence bronchoscopy. *Chest* 2002;122:1902–1908.
- Hirsch FR, Prindiville SA, Miller YE, et al. Fluorescence versus whitelight bronchoscopy for detection of preneoplastic lesions: a randomized study. J Natl Cancer Inst 2001;93:1385–1391.
- Shibuya K, Fujisawa T, Hoshino H, et al. Fluorescence bronchoscopy in the detection of preinvasive bronchial lesions in patients with sputum cytology suspicious or positive for malignancy. *Lung Cancer* 2001;32: 19–25.
- van Rens MT, Schramel FM, Elbers JR, et al. The clinical value of lung imaging fluorescence endoscopy for detecting synchronous lung cancer. *Lung Cancer* 2001;32:13–18.

- 43. Vermylen P, Pierard P, Roufosse C, et al. Detection of bronchial preneoplastic lesions and early lung cancer with fluorescence bronchoscopy: a study about its ambulatory feasibility under local anaesthesis. *Lung Cancer* 1999;25:161–168.
- Lam S, Kennedy T, Unger M, et al. Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. *Chest* 1998; 113:696–702.
- Ikeda N, Kim K, Okunaka T, et al. Early localization of bronchogenic cancerous/precancerous lesions with lung imaging fluorescence endoscope. *Diagn Ther Endosc* 1997;3:197–201.
- Lam S, Macaulay C, Leriche JC, et al. Early localization of bronchogenic carcinoma. *Diagn Ther Endosc* 1994;1:75–78.
- Kato H, Horai T. A color atlas of endoscopic diagnosis in early stage lung cancer. Aylesbury, England: Wolfe, 1992. Pp. 35.
- 48. Woolner LB, Fontana RS, Cortese DA, et al. Roentgenographically

occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period. *Mayo Clin Proc* 1984;59:453–466.

- Kennedy TC, McWilliams A, Edell E, et al. Bronchial intraepithelial neoplasia/early central airways lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:221S–233S.
- Xing S, Khanavkar B, Nakhosteen JA, et al. RIDTELC Lung Study Group. Predictive value of image cytometry for diagnosis of lung cancer in heavy smokers. *Eur Respir J* 2005;25:956–963.
- Palcic B, Garner DM, Beveridge J, et al. Increase of sensitivity of sputum cytology using high-resolution image cytometry: field study results. *Cytometry* 2002;50:168–176.
- Kemp RA, Reinders DM, Turic B. Detection of lung cancer by automated sputum cytometry. J Thorac Oncol 2007;2:993–1000.
- McWilliams A, Mayo J, MacDonald S, et al. Lung cancer screening: a different paradigm. Am J Respir Crit Care Med 2003;168:1167–1173.