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-

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 random-effect 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 excluded[22]; 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

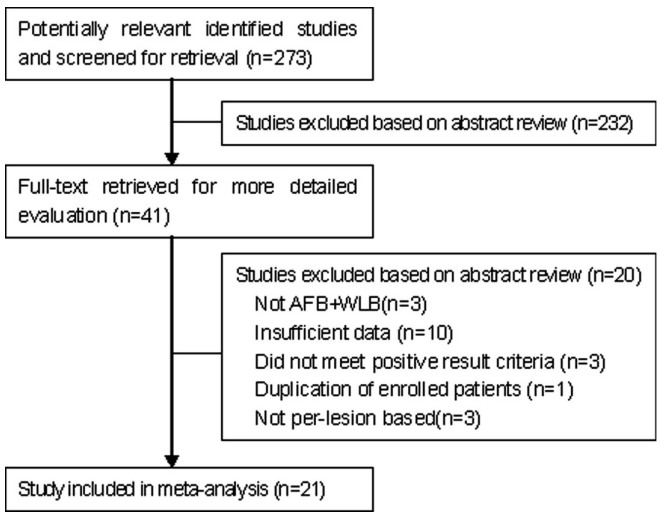

FIGURE 1. Flow of identifying the studies. AFB, autofluorescence bronchoscopy; WLB, white light bronchoscopy.

