CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Diagnosis and Treatment of Bronchial Intraepithelial Neoplasia and Early Lung Cancer of the Central Airways

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **Bronchial intraepithelial lesions may be precursors of central airway lung carcinomas. Identification and early treatment of these preinvasive lesions might prevent progression to invasive carcinoma.**
Methods: **We systematically reviewed the literature to develop evidence-based recommendations regarding the diagnosis and treatment of intraepithelial lesions.**
Results: **The risk and timeline for progression of bronchial intraepithelial lesions to carcinoma in situ (CIS) or invasive carcinoma are not well understood. Multiple studies show that autofluorescence bronchoscopy (AFB) is more sensitive that white light bronchoscopy (WLB) to identify these lesions. In patients with severe dysplasia or CIS in sputum cytology who have chest imaging studies showing no localizing abnormality, we suggest use of WLB; AFB may be used as an adjunct when available. Patients with known severe dysplasia or CIS of central airways should be followed with WLB or AFB, when available. WLB or AFB is also suggested for patients with early lung cancer who will undergo resection for delineation of tumor margins and assessment of synchronous lesions. However, AFB is not recommended prior to endobronchial therapy for CIS or early central lung cancer. Several endobronchial techniques are recommended for the treatment of patients with superficial limited mucosal lung cancer who are not candidates for resection.**
Conclusion: **Additional information is needed about the natural history and rate of progression of preinvasive central airway lesions. Patients with severe dysplasia or CIS may be treated endobronchially; however, it remains unclear if these therapies are associated with improved patient outcomes.**
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Abbreviations: ACCP = American College of Chest Physicians; AFB = autofluorescence bronchoscopy; BIN = bronchial intraepithelial neoplasia; CIS = carcinoma in situ; CR = complete response; EBBT = endobronchial brachytherapy; NBI = narrow band imaging; PDT = photodynamic therapy; SqCC = squamous cell carcinoma; WLB = white light bronchoscopy

Summary of Recommendations

3.1.1.1. In patients with severe dysplasia or carcinoma in situ (CIS) in sputum cytology who have chest imaging studies showing no localizing abnormality, standard white light bronchoscopy (WLB) is suggested to exclude an endobronchial lesion (Grade 2C)**.**

Remark: Autofluorescence bronchoscopy (AFB) may be used as an adjunct to WLB when available.

3.2.1.1. For patients with known severe dysplasia or CIS in the central airways on biopsy, follow-up WLB is suggested (Grade 2C)**.**

Remark: AFB may be used when available. The timing and duration of follow-up are unknown.

Remark: Physicians and patients should discuss potential risk and benefits of follow-up bronchoscopy.

3.3.3.1. For patients with early lung cancer undergoing resection, WLB is suggested for the delineation of tumor margins and the assessment of synchronous lesions (Grade 2C)**.**

Remark: AFB or narrow band imaging may be used when available.

3.4.1.1. For patients being considered for curative endobronchial therapy to treat CIS or early central lung cancer, WLB is suggested over routine use of AFB (Grade 2C)**.**

4.6.1. For patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection, endobronchial treatment with photodynamic therapy, brachytherapy, cryotherapy, or electrocautery is recommended (Grade 1C)**.**

Most patients with clinically diagnosed lung cancer present at a late stage, when curative resection is not an option.[2] The long-term outcome of these patients is relatively poor, with survival rates < 15% at 5 years after diagnosis.[2] Central airway carcinomas are considered to develop gradually from preinvasive epithelial lesions and may be multifocal.[3] Early identification and treatment of these lesions has been suggested as a strategy to manage central lung carcinomas at an early, minimally invasive stage.

White light bronchoscopy (WLB) is frequently used for diagnosing central airway carcinomas. However, WLB is not sufficiently accurate for the detection of small preinvasive lesions. The development of autofluorescence bronchoscopy (AFB) has allowed for the detection of small central airway lesions even at a stage when they are a few millimeters in diameter. Techniques such as Nd:YAG laser, photodynamic therapy (PDT), electrocautery, cryotherapy, and brachytherapy can be used to ablate intraepithelial lesions before they became invasive.

1.0 Methods

The goal of this study was to update previously published recommendations regarding the diagnosis and management of bronchial intraepithelial neoplasia (BIN).[4] A systematic review of the literature was conducted to identify relevant studies from MEDLINE in the English language published between January 1966 and March 2012. Literature searches used the following key words: "carcinoma in situ," "preinvasive lesions," "non-small cell lung cancer," "squamous cell carcinoma," "photodynamic therapy," "electrocautery," "cryotherapy," "white light bronchoscopy," and "autofluorescence bronchoscopy." We also manually reviewed the reference list of relevant studies.

The following population, intervention, comparator, outcome (PICO) questions were evaluated in this review:

1. Among patients with severe dysplasia or carcinoma in situ (CIS) in sputum cytology but with chest imaging studies showing no localizing abnormality, does bronchoscopy lead to diagnosis of preinvasive lesions or early, localized lung cancers?
2. Among patients with early lung cancer undergoing resection, does bronchoscopy assist in the delineation of tumor margins and the assessment of synchronous lesions?
3. For patients being considered for curative endobronchial therapy to treat CIS or early central lung cancer, does bronchoscopy lead to changes in the clinical management?
4. For patients with known severe dysplasia or CIS in the central airways on biopsy, does bronchoscopy improve identification of progressive lesions?
5. For patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection, does endobronchial treatment with PDT, brachytherapy, cryotherapy, and electrocautery improve outcomes such as response or progression rates?

Potentially eligible studies were reviewed by chapter authors based on pre-established criteria, such as patient population, study design, type of bronchoscopy technique used, length of follow-up, and outcomes evaluated. Studies focusing on diagnosis or bronchoscopy management of advanced lung cancer were excluded. The data were assembled into evidence profile tables. The data were further abstracted into the data tables included in this article. From the assembled literature and data tables, recommendations were developed, discussed, refined, and graded according to the level of evidence by the writing committee according to the American College of Chest Physicians (ACCP) Lung

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Cancer Guidelines methodology.[1] The manuscript and recommendations underwent iterative revisions and were then discussed, revised, and approved by the entire ACCP Lung Cancer Guidelines panel as outlined by Lewis et al,[1] "Methodology for Development of Guidelines for Lung Cancer," in the ACCP Lung Cancer Guidelines. The manuscript then underwent a multilevel internal and external review process as described for all of the ACCP Lung Cancer Guidelines articles. Disagreements about recommendations and grading were discussed within the writing committee and resolved by general consensus. The final recommendations were reviewed and approved by the ACCP Guidelines Oversight Committee.

1.1 Data Abstraction

Data were abstracted from each study according to criteria specific to the different types of studies evaluated in the review (ie, natural history, diagnosis, or treatment). Data collected included sociodemographic characteristics of the study population, inclusion and exclusion criteria, intervention(s), and length of follow-up. Relevant outcomes included rates of progression, relative sensitivity, and treatment response for questions evaluating the natural history of preinvasive lesions, the additional accuracy of AFB over WLB, and the effectiveness of different endobronchial therapies, respectively.

1.2 Study Quality

The quality of the studies included in the review was assessed based on criteria developed by the ACCP. These included type of study design, subject selection, explicit descriptions of inclusion and exclusion criteria, length of follow-up, ascertainment of the outcome, statistical analysis, funding, and conflicts of interest. Based on these factors, studies were judged as good, fair, or poor.

1.3 Statistical Analysis

Point estimates with 95% CI (when available) were reported for the different outcomes of interest. No attempt was made to obtain summary estimates given the high degree of heterogeneity across studies and differences in study design, length of follow-up, and definition of outcomes measures.

2.0 Characteristics of Preinvasive Lesions

2.1 Classification of Preinvasive Lesions

Squamous cell carcinoma (SqCC) is the second most frequent type of lung cancer, representing approximately 30% of pulmonary malignancies. In contrast to adenocarcinoma, SqCC is believed to arise in the central airways through a stepwise series of molecular and cellular alterations in which the airway epithelium progresses from normal to hyperplasia, metaplasia, dysplasia (mild, moderate, and severe), and finally CIS.[3] In general, dysplasia (in particular severe forms) and CIS are considered the most important preinvasive lesions for SqCC. According to the World Health Organization classification,[5] mild dysplasia is diagnosed by the presence of mild cellular atypia that is limited to the lower one-third of the airway epithelium. In moderate dysplasia, there are more severe cytologic abnormalities that involve the lower two-thirds of the epithelium. Severe dysplastic lesions display a high degree of cellular atypia and minimal cell maturation. In these cases, cellular changes extend to the entire airway epithelium but without reaching the surface. Lesions that progress to CIS show extreme cytologic aberration (including uneven chromatin, variable nuclear size and shape, dyskaryosis, and other nuclear abnormalities) that extend throughout the airway epithelium but do not infiltrate the basement membrane. Less commonly, an exophytic or polypoid lesion, labeled angiogenic squamous dysplasia, may develop.[6] Although this classification is useful,[7] studies have reported considerable variability in the grading of specific preinvasive lesions, even among highly experienced pulmonary pathologists.[8] The stepwise model of SqCC development is supported by studies using serial sputum cytology examinations as well as animal data.[9,10] However, preinvasive lesions may fluctuate between the different pathologic grades or skip steps as they progress toward CIS or invasive SqCC.[11] Additionally, studies using sputum cytology may have collected samples from different parts of the pulmonary airway, thus not representing the progression of a single precancerous lesion. The concept of "field cancerization" has been proposed as an alternative model to explain progression of sputum atypia to invasive cancer.[12] According to this model, multiple foci of precursor lesions are produced throughout the respiratory epithelium as a consequence of exposure to smoking. SqCC may develop from any of these lesions rather than because of stepwise progression of a single area.

2.2 Diagnosis of BIN and Early Central Lung Cancer

The standard imaging tool for the diagnosis of central airway lung cancer is WLB; however, this technique is limited in its ability to detect small early central cancers and preinvasive lesions of the airway.[13-15] AFB emerged in the early 1990s as an imaging tool to detect these smaller lesions.[16,17] The underlying premise of this technology is that the normal airway tissue autofluorescence is modified by the presence of preinvasive lesions and/or microinvasive tumors. Several commercial devices have been developed and tested since the introduction of AFB. These instruments use different light sources (helium-cadmium laser or xenon lamp) and excitation wavelengths to generate contrasts between normal and abnormal tissue; the color of abnormal areas (brown-red or brown-purple, green, red, or blue) varies according to the specific device. Some devices incorporate WLB and AFB in the same bronchoscope, potentially reducing the time required to complete a procedure.

Several studies and a recent meta-analysis evaluated the diagnostic accuracy of AFB.[16,18-41] Most studies investigated the central airways first with WLB followed by AFB (a single trial randomized the order of the two procedures). More than one-half of the studies were conducted with a sole first-generation device; however, newer bronchoscopes were represented in several studies. In general, areas that appear abnormal under WLB or AFB underwent biopsy; additional biopsy specimens from normally appearing "control" areas were also obtained in most, but not all, studies. WLB and AFB findings were compared against a pathologic gold standard as determined by blinded pathologists. Participants in these studies included individuals at high risk for lung cancer due to extensive smoking history and/or chronic obstructive lung disease, abnormal sputum cytology, or prior history of lung cancer or other smoking-related malignancies. Most studies primarily included a male population. Because the true sensitivity of these tests cannot be determined (as it is not possible to sample the entire central airways), the accuracy of WLB vs AFB was compared in terms of the relative sensitivity index (ie, the ratio of sensitivity of AFB and WLB to the sensitivity of WLB alone).

The results of studies evaluating the accuracy of AFB and WLB are shown in Fig 1. Overall, most studies showed that AFB combined with WLB improves the detection of preinvasive lesions/CIS compared with WLB alone. The sensitivity of WLB combined with AFB ranged from 43% to 100% compared with 0% to 85% for WLB alone. Similarly, the meta-analysis by Sun et al[18] reported a pooled sensitivity on a per-lesion basis to detect preinvasive lesions/CIS of 85% for WLB combined with AFB compared with 43% for WLB alone; the overall relative sensitivity was 2.04 (95% CI, 1.56-11.55). However, the pooled sensitivity of WLB combined with AFB vs WLB alone for invasive SqCC was only marginally improved (95% vs 89%, respectively; relative sensitivity, 1.15; 95% CI, 1.05-1.26). Conversely, the specificity of WLB combined with AFB was consistently lower than for WLB alone. The range of estimated specificities for WLB combined with AFB was 4% to 94% compared with 36% to 94% for WLB alone. The meta-analyses reported a pooled specificity of 61% for combined WLB and AFB and 80% for WLB alone.

Although several studies have consistently demonstrated an increased sensitivity of AFB compared with WLB alone for detection of preinvasive lesions, there are some limitations worth noting. The majority of studies cited above were conducted in tertiary-care centers. Additionally, most studies evaluated the

FIGURE 1. [Section 2.2] Yield of white light and autofluorescence bronchoscopy for the detection of preinvasive airway epithelium lesions.

First Author	Year	No. of Patients	No. of Lesions	Sensitivity		Relative Sensitivity	Specificity	
				WLB	WLB +AFB		WLB	WLB +AFB
Haussinger[21]	2005	1173	34	58	82	**1.4**	62	58
Ernst[38]	2005	300	85	11	66	**6.2**	95	73
Lam[27]	1994	223	113	39	84	**2.2**	91	81
Lam[26]	1998	173	102	9	56	**6.3**	90	66
Edell[31]	2009	170	41	10	44	**4.3**	94	75
Ikeda[40]	1999	155	84	51	95	**1.6**	62	66
Ikeda[39]	2006	154	48	65	90	**1.4**	49	47
Chhajed[22]	2005	151	83	72	96	**1.3**	53	23
Lam[16]	1993	94	77	48	73	**1.5**	94	94
Van Rens[41]	2001	72	15	20	100	**5**	51	4
Kakihana[35]	1999	72	55	51	88	**1.6**	54	56
Kusunoki[30]	2000	65	74	61	90	**1.5**	85	78
Hirsch[23]	2001	55	78	18	73	**4.4**	78	46
Sato[28]	2001	50	28	85	94	**1.1**	36	38
Kurie[24]	1998	39	60	-	43	**-**	-	43
Venmans[37]	1998	33	9	78	100	**1.3**	88	60
Weigel[19]	1999	36	3	0	67	**-**	87	48
Vermylen[29]	1999	34	16	25	94	**3.8**	87	21
Venmans[25]	1999	33	79	59	85	**1.4**	85	60
Chiyo[34]	2005	32	30	53	98	**1.8**	50	37
Ueno[32]	2007	31	14	53	77	**1.5**	94	77
Yokomise[36]	1997	30	14	65	90	**1.4**	71	77

Inclusion criteria: studies comparing detection of airway abnormalities by white light and autofluorescence bronchoscopy through 2012. AFB = autofluorescence bronchoscopy; WLB = white light bronchoscopy.

sensitivity of AFB based on case series or relatively small cohorts of highly selected individuals. These factors limit the generalizability of the study findings. The sensitivity and specificity of WLB and AFB were estimated based on the evaluation of biopsy samples obtained from sites that revealed abnormalities during bronchoscopy. However, a study that conducted AFB prior to lobectomy and then compared the number of preinvasive lesions identified by AFB vs those diagnosed on the dissected bronchial tree obtained during surgery showed that AFB missed approximately one-half of the preinvasive lesions.[33] Additionally, these studies were subject to verification bias (ie, the gold standard was differentially applied based on results of WLB and AFB), with estimates of diagnostic accuracy likely influenced by the ratio of biopsy samples from abnormal vs normal "control" sites, a factor that was determined by study design. The specificity of AFB combined with WLB was considerably lower than for WLB alone. However, a study found that some lesions identified as abnormal by AFB but found to be negative on pathology (ie, false-positive findings) had chromosomal abnormalities similar to preinvasive lesions or invasive carcinoma.[42] These findings suggest that these lesions may represent abnormal epithelium with the potential for malignant progression.

Different AFB systems were used across published studies, creating difficulties to assess if technical factors may impact the accuracy of AFB. However, a limited number of studies comparing different devices found equivalent results.[43,44] Variability in inclusion and exclusion criteria in the studies evaluated likely generated heterogeneity in the population studied, a factor that could influence the prevalence of preinvasive lesions and the performance of AFB. These differences translated into substantial variability in the accuracy of AFB vs WLB across studies limiting data pooling.[18]

More recently, narrow band imaging (NBI) and optical coherence tomography have been introduced as new endoscopic imaging techniques to assess the airway mucosa.[45,46] NBI allows visualization the mucosal surface structure and adjacent blood vessels by the use of optical imaging enhancing technology (using a light source with a short wavelength). Few studies suggest that NBI may have similar sensitivity but greater specificity than WLB and AFB for detection of preinvasive lesions.[47,48] Optical coherence tomography is an imaging method that uses reflected light waves to generate high-resolution images of cellular and extracellular structures. Initial studies suggest that this technique may also be useful to identify airway preinvasive lesions.[49] Further studies are needed to determine potential clinical indications for these imaging modalities.

In summary, AFB combined with WLB is more sensitive, improving the detection of preinvasive lesions (although not necessarily of invasive cancers) among individuals at high risk for lung cancer, compared with WLB alone. However, this higher sensitivity is achieved at the expense of a lower specificity. Thus, use of AFB may also result in a higher number of unnecessary biopsies.

2.3 The Natural History of BIN

The natural history of preinvasive lesions and CIS has been evaluated in several relatively small longitudinal studies (Fig 2).[11,50-63] In general, these studies primarily included male individuals at high risk for lung cancer due to extensive smoking exposure, history

FIGURE 2. [Section 2.3] Percent of patients showing progression to a higher-grade lesion according to the initial class of the preinvasive airway lesion.

First Author	Year	No. of Patients	No. of Lesions	Eligibility Criteria				F/U (mo)	% Progression[a] (by initial lesion grade)		
				Pk-yrs Smoking	COPD	Cancer History	Other		Mod Dyspl	Severe Dyspl	CIS
Salaun[57]	2008	37	54	>30	-	Aerodig	Asbestos exp	102-114	-	**4**	**55**
Van Boerdonk[61]	2011	474	451	>20	Yes	Aerodig		43	-	-	-
Jeanmart[62]	2003	48	80	-	-	-	Sputum dyspl	18-36	**57**	**66**	-
Moro-Sibilot[52]	2004	27	31	-	-	-	High risk	25	-	**33**	**39**
Bota[51]	2001	104	416	>20	-	Aerodig	Asbestos exp	24	-	**37**	**69**
Venmans[55]	2000	9	9	-	-	-	CIS	22	-	-	**56**
Alaa[50]	2011	124	98	-	-	-	Sputum dyspl	20	**14**	**28**	-
Breuer[63]	2005	52	483	-	-	Lung	Sputum dyspl	11-21	-	**32**	-
George[56]	2007	22	53	-	-	-	Sputum dyspl	4-17	-	**17**	-
Hoshino[54]	2004	50	99	-	-	-	Sputum dyspl	7		**18**	
Lam[60]	2004	106	399	-	-	-	Sputum dyspl	6	**0**	**0**	-
Lam[58]	2002	51	114	>30	-	-	>40 years old	6	**0**	**0**	-
Kennedy[59]	2004	79	-	>30	Yes	-	Sputum dyspl	-	**15**	-	-

Inclusion criteria: studies reporting rate of progression over time of central airway lesions through 2012.
Aerodig = aerodigestive; CIS = carcinoma in situ; dyspl = dysplasia; exp = exposure; F/U = follow-up.
[a]Indicates progression to higher grade or carcinoma.

of lung or upper airway cancer, or abnormal sputum cytology. Follow-up was variable across studies but in general short in duration in relation to the relatively slow suspected progression of most preinvasive lesions. The type of preinvasive lesions and the definition of progression varied across studies, making pooling of results difficult.

The rate of progression of CIS to invasive SqCC was evaluated in four different studies and found to range from 39% to 69%, depending on the patient population and length of follow-up. In one of the larger studies, Bota et al[51] evaluated 416 preinvasive lesions in 104 subjects who were treated for lung or upper airway cancer, had occupational exposures, or were heavy smokers. Approximately 69% of the CIS progressed or required treatment because of lack of regression after 3 months of observation. Conversely, 37% of the lesions showing severe dysplasia and only 3.5% of the lesions showing mild to moderate dysplasia at baseline progressed during the observation period. Salaün et al[57] performed AFB in 37 individuals with at least 30 pack-years smoking history, exposure to asbestos, or a prior carcinoma of the upper airways who were then observed for >12 years. The rate of progression in this study was 55% for CIS compared with 4.3% for severe dysplasia. In a study of 27 patients with synchronous or previously treated lung or upper airway cancer followed with serial WLB and AFB, patients with CIS or persistent severe dysplasia were treated with endobronchial therapy.[52] Overall, 39% of CIS and 33% of severe dysplasia lesions progressed (several after treatment) over a median follow-up period of approximately 2 years. Finally, a study of nine patients with CIS treated with endobronchial therapy and then followed for a median of <2 years reported that 56% of the lesions progressed to carcinoma.[55]

Other studies evaluated rates of progression to a higher grade or CIS among the different grades of dysplastic preinvasive lesions.[11,50,53,54,56,58,60] A series published by Alaa et al[50] reported rates of progression to CIS or cancer among 124 patients with abnormal sputum cytology or past aerodigestive cancer followed with serial AFB for a median of 2 years. Rates of progression to CIS were 14% and 28% for lesions showing moderate or severe dysplasia, respectively. Lam et al[58,60] reported the rate of progression of premalignant lesions identified among subjects on the placebo arm of two randomized controlled trials testing chemopreventive lung cancer drugs. The population of both studies consisted of smokers recruited from the community who were found to have sputum atypia. In the first study, the investigators reported that 2.3% of the lesions showing mild dysplasia and none of the showing moderate to severe dysplasia progressed to a higher grade over a relatively short, 6-month follow-up period. The second study showed that after 6 months of follow-up, all severe and moderately dysplastic lesions regressed to a lower grade; none of the lesions showing mild dysplasia progressed.

Breuer et al[11] reported the outcome of 134 preinvasive lesions in a cohort of 52 individuals at high risk of lung cancer. Overall, 32% of lesions showing severe dysplasia and 9% of lesions with mild/moderate dysplasia progressed to CIS or SqCC when followed for a range of 11 to 21 months; regression was observed in 54% of the preinvasive lesions. In a case series reported by Hoshino et al,[54] 50 subjects with suspicious or positive sputum cytology or with history of lung cancer were followed with AFB for a mean of 7 months. Of the 11 lesions showing severe dysplasia, 18% progressed to SqCC compared with only 2% of the 56 lesions showing moderate dysplasia. Higher rates of progression to CIS or invasive carcinoma (approximately 60%) were reported in a case series of 48 former smokers (almost one-half with previous history of resected lung cancer) who had at least one area of metaplasia or more severe dysplasia on initial evaluation.[53] Finally, the outcomes of 22 patients with 53 preinvasive lesions followed for a median of 23 months (range, 12-85 months) was reported by George et al.[56] Progression to cancer was observed in 17% of patients with severe dysplasia or CIS; none of the lesions showing mild or moderate dysplasia progressed to invasive carcinoma during the observation period.

Several factors complicate the evaluation of the natural history of preinvasive airway lesions. Despite recent efforts to standardize the classification of these lesions,[5] differentiating the various degrees of dysplasia or distinguishing severe dysplasia vs CIS can be difficult. Classification of lesions is particularly problematic for biopsy samples obtained via bronchoscope, a procedure known to distort the histologic features of pathologic samples. Despite this potential problem, most of the studies cited above did not report the quality of the biopsy samples or the agreement between study pathologists evaluating the histologic specimens. Another inherent challenge in the evaluation of the natural history of preinvasive lesions is related to the need for biopsy and histopathologic analysis to determine the degree of atypia and grade of the lesions being evaluated. However, most preinvasive lesions are quite small, and, thus, the biopsy procedure can significantly disrupt or even completely remove entire areas of dysplasia. Therefore, the observed rates of progression in these studies may not represent the true aggressiveness of undisrupted preinvasive lesions.

The majority of participants in the series reviewed above were highly selected and not representative of traditional high-risk smokers. Several studies recruited

high numbers of subjects who, in addition to smoking, had prior lung or aerodigestive cancer or a history of potentially carcinogenic occupational exposure. Furthermore, there was considerable heterogeneity across studies in inclusion and exclusion criteria, frequency of surveillance bronchoscopies, length of follow-up, study end points, and the definition of progression. Moreover, the protocol for management of severe dysplastic lesions and/or CIS varied across studies. The protocol of several studies mandated immediate treatment of CIS at the time of diagnosis or following a short observation period. Thus, there is limited information about the rate of progression of these lesions. This design assumes that CIS will invariably transform into invasive SqCC; however, CIS lesions and even some early invasive carcinoma may regress even if untreated.[64]

Most studies reported the absolute percentage of patients or lesions that progressed and how progression rates depended on histologic grade. However, the probability of progression is expected to increase with a longer observation period, a factor that was not considered in the analyses; progression rates (ie, percent progression per year of follow-up) would be a better indicator of malignant risk of preinvasive lesions. Additionally, most studies did not provide CIs for the estimates of progression or control for the correlated nature of the data arising from the fact that some participants had multiple preinvasive lesions.

3.0 Proposed Indications for WLB and AFB

3.1 Evaluation of Patients With Sputum Atypia

Patients with sputum atypia are at increased risk for lung cancer. Prior studies evaluating the role of sputum cytology for early identification of lung cancer have shown that abnormalities in sputum cytology are associated with a risk of lung cancer.[10,65-68] In a study of 2,006 smokers with airway obstruction, Prindiville et al[65] reported an incidence of lung cancer per 100 person-years of 1.3, 1.6, 2.2, and 23.1 for individuals with normal, mild, moderate, and worse than moderate atypia, respectively, on the baseline sputum cytology sample. An earlier study of sputum cytopathologic monitoring in the workplace showed that 11% of workers with moderate dysplasia and 46% of those with severe dysplasia in sputum samples developed SqCC.[10] Similarly, data from the Johns Hopkins Lung Project showed that 14% of subjects with moderate sputum atypia or worse progressed to lung cancer compared with only 3% of those without atypia.[67] Overall, these data suggest that individuals with sputum atypia should be further evaluated with WLB or AFB to identify radiologically occult carcinomas and high-risk preinvasive lesions.

Few studies reported findings of AFB performed among high-risk smokers with abnormal sputum cytology (Fig 3).[21-23,28,69-72] In a study evaluating the yield of AFB in a cohort of 309 smokers (≥ 30 pack-years) with sputum atypia who were recruited from the community, McWilliams et al[72] found that 48% of participants had dysplasia or CIS; the number of invasive cancers was not reported. Chhajed et al[22] found 20 cancers and three CIS among 151 high-risk smokers with moderate dysplasia or worse in sputum cytology mass screening who underwent AFB. Similarly, a study of 79 subjects with moderate sputum atypia and chest radiographs that were not read as suspicious of lung cancer revealed that 4% harbored a lung cancer, and an additional 4% had CIS on AFB.[70] Furthermore, 9% of participants were found to have lesions classified as severe dysplasia. Other smaller studies reported rates of CIS and/or cancer between 7% and 29% among subjects with abnormal sputum cytology that were evaluated with AFB.[21,23,71,73] The results of these studies show that, in high-risk individuals with sputum atypia, AFB can identify a number of subjects with preinvasive lesions or early lung cancer. However, sputum cytology is seldom used in clinical practice, and current guidelines[74] recommend against the use of sputum cytology for lung cancer screening. Thus, individuals with sputum atypia are rarely encountered in clinical practice. Prior studies have also shown that one-half of preinvasive lesions may

Figure 3. [Section 3.1] Yield of bronchoscopy in patients with severe dysplasia or carcinoma in situ on sputum cytology.

First Author	Year	No. of Patients	Eligibility Criteria	Findings (No. of lesions)	
				Dysplasia/CIS	Carcinoma
Chhajed[22]	2005	151	Abnormal sputum cytology in screening program	**60**	**23**
Lam[71]	2009	85	Abnormal sputum cytology	**-**	**7**
Kennedy[70]	2005	79	Abnormal cytology and normal radiology	**39**	**3**
Hirsch[23]	2001	55	Suspicious of abnormal cytology or positive radiology	**28**	**4**
Sato[28]	2001	50	Suspicious or abnormal cytology	**39**	**28**

Inclusion criteria: studies reporting findings on bronchoscopy in patients with abnormal sputum cytology through 2012. See Figure 2 legend for expansion of abbreviations.

be missed by bronchoscopy. Consequently, it is possible that AFB may identify and lead to treatment of lesions that will not transform into invasive carcinoma. Moreover, there are no trials showing that use of WLB or AFB and/or early treatment of preinvasive lesions or CIS leads to improved outcomes among subjects with sputum atypia. Thus, additional studies are necessary to assess whether WLB or AFB should be routinely used to evaluate high-risk smokers with abnormal sputum cytology but no radiologic abnormalities.

3.1.1 Recommendation

3.1.1.1. In patients with severe dysplasia or CIS in sputum cytology who have chest imaging studies showing no localizing abnormality, standard WLB is suggested to exclude an endobronchial lesion (Grade 2C)**.**

Remark: AFB may be used as an adjunct to WLB when available.

3.2 Follow-up of High-Grade BIN

Longitudinal data regarding rates of progression of preinvasive lesions among patients followed with serial AFB have been reviewed previously. Although rates of progression varied across these relatively heterogeneous studies, in general, most reports showed that preinvasive lesions with severe dysplasia or CIS are more likely to progress than lesions showing lower degrees of atypia. However, a considerable proportion of lesions can regress without intervention, and there are not validated methods to distinguish lesions that are more likely to progress if left untreated.

No observational or randomized controlled trials have compared outcomes of smokers with preinvasive lesions who are either followed with serial WLB or AFB or only evaluated if they develop lung cancer symptoms. Thus, there is no direct evidence that early detection of progression followed by treatment improves the outcomes of high-risk individuals. Although close observation seems prudent given the relatively poor outcomes of patients with central lung cancers who are diagnosed based on clinical symptoms, there are potential risks (including mortality) associated with endobronchial treatment of preinvasive lesions. Given that a subset of preinvasive lesions may regress, overtreatment will be expected. Finally, the best timing and duration of follow-up are unknown, although the interval between studies should probably be >6 months based on the low progression rates reported in prior studies using shorter observation periods.[60] Physicians should carefully discuss the potential benefits and risks of follow-up bronchoscopy in subjects with preinvasive lesions.

3.2.1 Recommendation

3.2.1.1. For patients with known severe dysplasia or CIS in the central airways on biopsy, follow-up WLB is suggested (Grade 2C)**.**

Remark: AFB may be used when available.

Remark: The timing and duration of follow-up are unknown. Physicians and patients should discuss potential risk and benefits of follow-up bronchoscopy.

3.3 Evaluation of Patients Prior to Lung Cancer Surgery

3.3.1 Synchronous Lesions: Several reports from small case series reported on the potential usefulness of AFB for identifying synchronous lesions in patients with early lung cancer who are being evaluated for curative surgical resection (Fig 4).[16,27,41,55,75-77] These studies found occult synchronous CIS in 9% of individuals with known lung cancer during preoperative evaluation.[41] Rates of moderate dysplasia or higher-grade lesions have been found in 14% to 44% of these patients.[41,55,75]

3.3.2 Surgical Margins: Presurgical AFB may also play a role in determining the size and delineating the margins of early central carcinomas.[4,78] More recently,

FIGURE 4. [Section 3.3] Percent of patients with a synchronous lesion identified by bronchoscopy (white light or autofluorescence) prior to lung cancer surgery.

Frist Author	Year	No. of Patients	No. of Lesions	Intervention	Eligibility Criteria	% with Synchronous Lesions
Lam[77]	1994	223	-	AFB, WLB	Lung or aerodigestive cancer	**15-22**
Lam[16]	1993	94	328	AFB, WLB	Lung cancer	**15**
van Rens[41]	2001	69	-	AFB, WLB	Lung cancer or suspected lesions	**9**
Pierrard[76]	2000	43	-	AFB	Lung cancer	**9**
Pierrard[75]	2004	26	28	AFB, WLB	radiologically occult lung cancer	**23**
Venmans[55]	2000	9	-	AFB	Suspected CIS	**44**

Inclusion criteria: studies reporting the presence of additional airway abnormalities on bronchoscopy in patients with lung cancer through 2012. See Figure 1 and 2 legends for expansion of abbreviations.

NBI has been introduced as an alternative technique for the endobronchial assessment of these early carcinomas.[45,79] The addition of NBI to AFB and WLB in the evaluation of endobronchial tumors seems to increase specificity without compromising sensitivity. Zaric et al[80] performed WLB, AFB, and NBI on 118 patients with lung cancer not limited to early intramucosal lesions. The aim of the study was to determine sensitivity and specificity of each technique and their combination in detection of lung cancer extension. Both NBI and AFB alone or in combination improved the sensitivity and specificity of WLB. NBI and AFB had similar diagnostic accuracy. The combination of both techniques slightly improved the sensitivity of AFB alone from 89% to 94% ($P = .03$) but not its specificity (86% vs 78%). The authors conclude that NBI and AFB show higher sensitivity and specificity than WLB in evaluating lung cancer extension.[80] In a prior study comparing NBI with WLB, Zaric et al[81] performed both techniques on 106 individuals with lung cancer. In 20 patients (19%), NBI examination revealed greater tumor extension, and in 14 (13%) that greater extension led to change in the therapeutic decision. These studies suggest that WBL, AFB, and NBI may help identify synchronous lesions and/or determine surgical margins of lesions and may lead to changes in the management of some patients being evaluated for surgical resection. Further studies should evaluate if the addition of these techniques improves patient outcomes.

3.3.3 Recommendation

3.3.3.1. For patients with early lung cancer undergoing resection, WLB is suggested for the delineation of tumor margins and the assessment of synchronous lesions (Grade 2C)**.**

Remark: AFB or NBI may be used when available.

3.4 Evaluation of Patients With Early Central Lung Cancer Prior to Curative Endobronchial Therapy

Patients with CIS or early invasive carcinoma of the central airways who are not considered candidates for resection may be treated with endobronchial therapy with a curative intent. AFB has been proposed as a tool to evaluate the size of the lesion, determine if all margins can be visualized, and identify additional lesions. These factors may help predict if endobronchial therapy will be successful and identify patients who may require surgery to completely remove the lesion.

Sutedja et al[78] studied 23 consecutive patients with a diagnosis of radiographically occult lung cancer determined by WLB who were referred for endobronchial treatment with curative intent. Of these, four patients were found to have locally advanced cancers on CT scan of the chest. AFB showed that only 32% of the remaining 19 patients had small cancers with visible distal margins that were adequate candidates for endobronchial therapy; other patients were referred for surgery or radiotherapy. Thus, AFB findings affected the type of therapy recommended in almost 70% of the patients in the study.

Although these results suggest a potential role for AFB to evaluate patients considered for endobronchial therapy of early central lung cancers, there are some limitations of this study that should be noted. The population enrolled was highly selected, with more than one-half of the cases (58%) having second primary cancer or synchronous lung cancers. Almost 20% of the subjects were not considered eligible for endobronchial therapy prior to AFB, based on the results of the initial CT scan. Of the 13 patients referred for resection based on AFB findings, 53% were not considered candidates for surgery; thus, the impact of AFB on the management of these patients was limited. More importantly, these findings are based on a very small sample of patients recruited from a single referral center. Additionally, the study did not include a control arm of patients evaluated with WLB alone to assess if the addition of AFB and the subsequent changes in management lead to improved clinical outcomes. Thus, these results need to be validated in larger samples and prospectively compared with the current standard of care before AFB is adopted in clinical practice prior to endobronchial therapy.

3.4.1 Recommendation

3.4.1.1. For patients being considered for curative endobronchial therapy to treat CIS or early central lung cancer, WLB is suggested over routine use of AFB (Grade 2C)**.**

3.5 Endobronchial Treatment of Early-Stage Lung Cancer for Patients Who Are Not Candidates for Surgery

For patients who are not candidates for surgery, several techniques for endobronchial treatment of early central lung cancers have been developed. These include PDT,[77] brachytherapy,[82] electrocautery,[83] cryotherapy,[84] and Nd:YAG laser therapy (Fig 5).[85-98] Information about the extension and depth of invasion of a lesion may be important before using these therapies.[101] Konaka et al[101] showed that the size and the appearance of endobronchial cancers correlates with its depth of penetration. Small ($\leq$ 10 mm in diameter) and hypertrophic (superficial thickening of the

FIGURE 5. [Section 3.5] Outcomes of endobronchial treatment of early-stage lung cancer.

First Author	Year	No. of Patients	No. of lesions	Intervention	Eligibility Criteria	Outcome (%)	
						CR	PR
Miyazu[86]	2002	12	18	PDT	Central early lung cancer	**100**	-
Kato[87]	1996	-	95	PDT	Central early lung cancer	**83**	-
Cortese[88]	1997	21	23	PDT	Central early lung cancer	**71**	-
Kato[89]	2006	204	264	PDT	Central early lung cancer	**85**	**15**
Moghissi[90]	2007	21	23	PDT	Central early lung cancer	**100**	-
Furuse[91]	1993	54	64	PDT	Central early lung cancer	**85**	**10**
Patelli[92]	1999	23	26	PDT	Central early lung cancer	**62**	**39**
Sutedja[93]	1992	26	-	PDT	Inoperable lung cancer	**91**	-
Radu[94]	1999	64	101	PDT	Aerodigestive cancer	**78**	-
Cortese[95]	1984	19	20	PDT	Lung Cancer	**32**	-
Edell[96]	1987	38	40	PDT	Lung Cancer	**34**	-
Edell[97]	1992	13	14	PDT	Central early lung cancer	**93**	-
Kato[98]	2003	41	46	PDT	Central early lung cancer	**85**	-
Hennequin[99]	2007	106	-	Brachytherapy	Central early lung cancer	**59**	**22**
Marsiglia[100]	2000	34	-	Brachytherapy	Lung cancer	**94**	-
Perol[82]	1997	19	-	Brachytherapy	Small endobronchial tumor	**83**	-
van Boxem[83]	1998	13	15	Electrocautery	Radiologically occult	**77**	**23**
Deygas[84]	2001	35	41	Cryotherapy	Central early lung cancer	**91**	-

Inclusion criteria: studies reporting results after endobronchial treatment of early airway cancers through 2012. CR = complete response; PDT = photodynamic therapy; PR = partial response.

epithelium) tumors only invade beyond the cartilage in 5% of the cases. Conversely, nodular (elevation of the mucosa ≥ 2 mm with a large base) and polyploid (pedunculated) lesions invade beyond the cartilage in 18% and 27% of the cases, respectively.[101] Fujimura et al[102] and Nakamura et al[103] also reported that the larger the dimensions of an endobronchial tumor, the greater the risk of deeper mural invasion and lymph node involvement. Since laser beams used for endobronchial treatments such as PDT cannot penetrate the exterior wall of cartilage, tumors with extracartilaginous invasion and/or with lymph node involvement are not amenable to curative endobronchial therapy. A newer technique, endobronchial ultrasound, has been shown to be quite accurate in determining the depth of endobronchial tumors.[86,104]

4.0 Techniques of Endobronchial Therapy

4.1 Photodynamic Therapy

The first endoscopic PDT treatment of lung cancer was performed in 1980, and since then this technique has been frequently used to treat early central lung carcinoma.[87-89,105,106] PDT works through the generation of singlet oxygen and other cytotoxic species when a photosensitizing drug (photofrin or the newer generation, mono-L-aspartyl chlorine e6 [NPe6]) is activated by light of a certain wavelength.[90] Furuse et al[91] conducted a phase 2 study on PDT using photofrin II, a hematoporphyrin derivative, as a photosensitizer. Forty-nine patients with 59 early central squamous carcinomas were treated and assessed for response. Overall, 85% of the cancers had a complete response (CR) to PDT, 10% had a partial response, and 5% showed no change.[91] The median duration of CR was 14 months (range, 2-32 months). Of the 50 cancers that had a CR, 10% had a local recurrence outside the photoradiated field within 18 months after treatment. The rate of CR was higher for smaller tumors; 100% of the cancers < 5 mm in longitudinal length had CR compared with only 38% of tumors with lengths > 20 mm.[91] Kato et al[89] treated 204 patients with 264 centrally located early-stage lung cancers between 1980 and 2005. More than 97% of the lesions were SqCCs of clinical stage 0 (70%) or I (30%). In terms of types of tumors, 80% were of the hypertrophic type, 16% were nodular, and the remaining 5% were pedunculated. The maximum tumor dimension was < 10 mm in 68% of lesions, 10 to 20 mm in 19%, and > 20 mm in the remaining 13%. PDT was performed with two different photosensitizers; the great majority were treated with photofrin, however, and mono-L-aspartyl chlorine e6 (NPe6) was used in 15% of the lesions treated since 2004.[89] Complete and partial responses were obtained in 85% and 15% of the cancers, respectively. Recurrence occurred in 12% of cancers that had an initial CR. Based on size, CR was obtained for 95% of cancers with a longitudinal length of < 5 mm, 94% of those 5 to 9 mm, 80% of those 10 to 20 mm, and only 44% of tumors > 20 mm.[89] In a subgroup analysis of 83 lesions < 10 mm in longitudinal length, the rate of CR was 93%, but the 5-year overall survival was only 58%. The authors attribute this discrepancy to the fact that most of the patients were elderly, with low cardiopulmonary

function.[89] Smaller series from the United States, Canada, and Europe reported CR rates to PDT in 62% to 100%.[90,92-97,107]

In the aforementioned study by Kato et al,[98] the authors included a case series from a phase 2 PDT study using mono-L-aspartyl chlorine e6 (talaporfin sodium, NPe6), a new-generation photosensitizer. A total of 45 central early-stage lung cancers in 40 patients were treated. CR was obtained in 85% of the lesions (83% of patients). Rates of skin photosensitivity were considerably lower than with photofrin, an older photosensitizer. Moreover, the disappearance of skin photosensitivity was faster, having resolved in 85% of the patients within 2 weeks of administration.[98]

In summary, PDT appears to be an effective therapeutic modality for small early-stage centrally located lung cancers, the majority of which are SqCCs. CR rates have been achieved in 32% to 100% of cancers, with the longitudinal length of the cancer being an important predictor of response. However, some patients experience local recurrences, and long-term outcomes remain suboptimal. NPe6, a newer-generation photosensitizer, appears to be as effective but better tolerated than older agents. However, these data have only been reported by one group and need to be validated in larger number of patients.

4.2 Brachytherapy

Endobronchial brachytherapy (EBBT) using a high-dose-rate iridium source is recognized as an effective palliative treatment of endobronchial obstruction caused by central tumors.[99] Hennequin et al[99] reported one of the largest series available on the treatment of limited endobronchial carcinomas with EBBT. The study included 106 patients with carcinoma of the central airways accessible to bronchoscopy, not visible on CT scan or < 10 mm in thickness, and lack of lymph node involvement or distant metastasis. The patients were not candidates for surgery or for external beam radiotherapy because of medical contraindications. On reevaluation 1 to 2 months after EBBT, 59% had achieved complete histologic response, 22% complete macroscopic response, 9% partial response, and 8% no response or progression.[99] Patients with a CR had a significantly shorter mean endobronchial tumor length (16 vs 25 mm, $P = .006$). Similarly, patients with tumors that were not visible on CT scan, and thus more likely to be true BIN, achieved a CR more frequently (66% vs 31%, $P = .01$). Median overall survival was 21 months, and the 2- and 5-year survival rates were 47% and 24%, respectively.[99] Five percent of patients died of causes directly attributed to EBBT (massive hemoptysis or necrosis of the bronchial wall). Additionally, 9% and 4% of patients had grade 2 or 3 radiation bronchitis, respectively.[99] In two smaller studies, CR rates with brachytherapy were reported in 83% to 85% of patients.[82,100]

4.3 Electrocautery

Bronchoscopic electrocautery causes tissue destruction by the use of a high-frequency, heat-generating electrical current. There is only one report of a very small series of 13 patients with 15 cancers treated with this modality.[83] CR was achieved in 10 patients with 12 cancers (80% of the tumors). Three patients with CR died of causes unrelated to the cancers. The remaining seven patients with a CR continued in CR after a median follow-up of 22 months (range 13-40 months). Further studies are needed to recommend the routine use of this technique.

4.4 Cryotherapy

Cryotherapy is a technique that uses freezing as a mechanism to destroy cancerous lesions. Similarly to electrocautery, only one report on a small series of 35 patients with 41 cancers evaluated the efficacy of this technology for the treatment of central airway cancers.[84] This study showed a 91% CR rate. Two-year follow-up was available for 32 of these patients, 20 of whom (63%) were still alive. Eleven patients (50%) of 22 for whom 4-year follow-up was available were still alive and considered long-term survivors. However, these results need to be validated in additional studies.

4.5 Nd:YAG Laser Therapy

Nd:Yag laser therapy is extensively used for palliative treatment of severe airway obstruction caused by airway tumors. However, there are no data on the use of this technique for early centrally located tumors.[4]

In summary, these studies show that endobronchial therapy is associated with CR in a considerable percentage of patients with early central SqCC. However, long-term outcomes remain relatively poor. No trial has compared clinical outcomes of patients treated with endobronchial therapy vs a control arm. Given the limited data regarding the natural history of early SqCC, the potential complications of many techniques, and the limited life expectancy of some patients with contraindications for surgery, additional information is necessary to determine the impact of endobronchial treatments on patient outcomes.

4.6 Recommendation

4.6.1. For patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection, endobronchial treatment with PDT, brachytherapy,

cryotherapy, or electrocautery is recommended (Grade 1C).

5.0 Conclusions

Current evidence suggests that intraepithelial lesions of the bronchial mucosa may be precursors of central airway SqCC. However, the natural history of these lesions and the risk of progression to CIS or invasive carcinoma have only been evaluated in a small number of studies conducted among highly selected individuals and, thus, are not well understood. AFB and NBI are more sensitive than WLB to detect and assess preinvasive lesions. Potential clinical applications of these technologies include the evaluation of patients with severe dysplasia or CIS in sputum cytology who have chest imaging studies showing no localizing abnormality, the follow-up of patients with known severe dysplasia or CIS of central airways, and the assessment of patients with early lung cancer who will undergo resection for delineation of tumor margins and assessment of synchronous lesions. However, AFB should not be used prior to endobronchial therapy for CIS or early central SqCC. Additional studies are needed to further evaluate the impact of WLB, AFB, and NBI in the outcomes of these patients.

Several endobronchial techniques are recommended for the treatment of patients with CIS or superficial limited mucosal SqCC who are not candidates for resection. PDT is the technique that has been evaluated most extensively; other options for the endobronchial treatment of these lesions include brachytherapy, electrocautery, cryotherapy, and Nd:YAG laser. However, studies evaluating the efficacy of these techniques were not randomized and included a limited number of selected patients.

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Dr Yung: contributed to critical revision of the article.
Dr Mathur: contributed to critical revision of the article.
Dr Zulueta: contributed to review of literature, preparation of evidence tables, and drafting of the recommendations and the article.
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