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Bronchial Intraepithelial Neoplasia/Early Central Airways Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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**Background:** An evidence-based approach is necessary for the localization and management of intraepithelial and microinvasive non-small cell lung cancer in the central airways.

**Methods:** Material appropriate to this topic was obtained by literature search of a computerized database. Recommendations were developed by the writing committee and then reviewed by the entire guidelines panel. The final recommendations were made by the Chair and were voted on by the entire committee.

**Results:** White light bronchoscopy has diagnostic limitations in the detection of microinvasive lesions. Autofluorescence bronchoscopy (AFB) is a technique that has been shown to be a sensitive method for detecting these lesions. In patients with moderate dysplasia or worse on sputum cytology and normal chest radiographic findings, bronchoscopy should be performed. If moderate/severe dysplasia or carcinoma in situ (CIS) is detected in the central airways, then bronchoscopic surveillance is recommended. The use of AFB is preferred if available. In a patient being considered for curative endobronchial therapy to treat microinvasive lesions, AFB is useful. A number of endobronchial techniques as therapeutic options are available for the management of CIS and can be recommended to patients with inoperable disease. In patients with operable disease, surgery remains the mainstay of treatment, although patients may be counseled about these techniques.

**Conclusions:** AFB is a useful tool for the localization of microinvasive neoplasia. A number of endobronchial techniques available for the curative treatment can be considered first-line therapy in inoperable cases. For operable cases, the techniques may be considered and discussed with the patients.

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**Key words:** angiogenic squamous dysplasia; autofluorescence bronchoscopy; carcinoma in situ; fiberoptic bronchoscopy; Nd-YAG; photodynamic therapy; radiographically occult lung cancer

**Abbreviations:** AFB = autofluorescence bronchoscopy; ASD = angiogenic squamous dysplasia; CCD = charged-couple device; CIS = carcinoma in situ; FVB = flexible videobronchoscopy; LIFE = light-induced fluorescence endoscopy; NBI = narrow band imaging; NSCLC = non-small cell lung cancer; PDT = photodynamic therapy; SqCC = squamous cell carcinoma; WLB = white light bronchoscopy

The majority of lung cancer cases are diagnosed in a late stage, when nonspecific symptoms such as cough, dyspnea, and hemoptysis are present. Fewer than 15% of patients with invasive lung cancer survive 5 years after treatment. Advances in early diagnostic and treatment options have the potential to manage lung carcinoma while still in an intraepithelial and microinvasive or minimally invasive stage.

White light bronchoscopy (WLB) is one of the most commonly used diagnostic tools for obtaining a 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 by WLB in detecting intraepithelial and microinvasive or preinvasive lung cancer lesions. AFB is now an established technique that has been shown to be a far more sensitive method of detecting these lesions than WLB.

In addition to the development of AFB for the
early diagnosis of intraepithelial and microinvasive or minimally invasive lung carcinoma, there are five techniques available being used to ablate intraepithelial malignant and microinvasive endobronchial malignant lesions without surgical excision. These modalities include Nd-YAG laser therapy, photodynamic therapy (PDT), electrocautery, cryotherapy, and high-dose rate brachytherapy. These may be particularly appropriate treatment options in patients with limited cardiopulmonary reserve.

MATERIALS AND METHODS

To update previous recommendations on bronchial intraepithelial neoplasia/early central airways lung cancer, guidelines on lung cancer diagnosis and management were identified by a systematic review of the literature (see “Methodology for Lung Cancer Evidence Review and Guideline Development” chapter). Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and review of the Thoracic Oncology Network reference lists of relevant articles. Recommendations were developed by the section editor and writing committee, graded by a standardized method (see “Methodology for Lung Cancer Evidence Review and Guideline Development” chapter), and then reviewed by the entire guidelines panel, including the Chair and the Vice Chair. The final recommendations were developed by the Chair and were voted on by the entire committee. All members of the lung cancer panel approved the chapter before approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) in the English language from January 1966 to January 2006, and review of the relevant articles. The search words that were used were as follows: “carcinoma in situ” (CIS), “angiogenic squamous dysplasia” (ASD), “radiographically occult lung cancer,” “neodinium yttrium-aluminum-garnet,” “photodynamic therapy,” “electrocautery,” “cryotherapy,” “non-small cell lung cancer” (NSCLC), “light-induced fluorescence endoscopy,” “white light bronchoscopy,” (WLB) “autofluorescence bronchoscopy,” (AFB) “flexible videobronchoscopy” (FVB), and “narrow band imaging” (NBI).

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REFERENCES

For the purposes of this chapter, the reviewed literature was limited to diagnostic and treatment approaches to early stage lung cancer. The definition of an early stage cancer is a roentgenographically occult squamous cell carcinoma (SqCC) that is < 2 cm in surface area, appears superficial endoscopically, has clearly visible margins, and demonstrates no invasion beyond the bronchial cartilage assessed either by histopathology or by available imaging including high-resolution CT or endobronchial ultrasound. Although there is an extensive literature on the detection and treatment of early stage lung cancer, the reported studies consist of small to moderate-size case series. Clinical outcomes in these studies were defined as response to treatment and included complete, partial, or no response. Complete response was defined as no evidence of disease visually as well as on histology and cytology examination. Some studies also included time to tumor recurrence. Relative sensitivity is commonly used in these reports to express the additional value of AFB over WLB when, as in most reports, WLB was performed before AFB by the same observer and the actual prevalence of lesions was unknown. Relative sensitivity is defined as the ratio of the sensitivity of WLB alone or WLB combined with AFB divided by the sensitivity of WLB alone.

DIAGNOSIS OF EARLY STAGE LUNG CANCER

AFB

Imaging of the central airway mucosa with AFB was developed in the early 1990s at the British Columbia Cancer Research Centre in Vancouver, BC, and proposed as a method to localize high-grade dysplasia (moderate and severe dysplasia), CIS, and minimally invasive SqCC.1–4 The underlying premise of this technology was that the large area of the tracheobronchial mucosa comprises the substantial site of the origin of SqCC and early disease in the central airways might not be detected by WLB. This is an important issue because SqCC comprises 17 to 29% of all lung cancers.5 Previous efforts at imaging these lesions used porphyrin products, which, while allowing better imaging, was limited by skin photosensitivity reactions and did not gain significant acceptance by clinicians.6

After Lam et al7 introduced AFB in 1992, the light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies; Vancouver, BC, Canada) became commercially available in 1998. This system used a helium-cadmium laser to illuminate the bronchial mucosa with 442-nm light. The red and green autofluorescence emitted light was captured by a photomultiplier camera, and a pseudocolor image of the relative red-green intensity in an area is generated in real time by computer. The image was displayed green in normal areas and red-brown in abnormal areas, because of reduced green autofluorescence in abnormal and preneoplastic mucosal lesions.

A multiinstitutional trial7 of 173 subjects with a total of 700 lesions showed that AFB with the LIFE device identified more abnormalities than WLB. It
was established that AFB provided a 2.71 increase in relative sensitivity compared to WLB alone for localization of moderate dysplasia, severe dysplasia, CIS, and invasive carcinoma. The final World Health Organization classifications of these lesions have been reviewed by a panel of pathologists. When lesions of invasive carcinoma were excluded, the relative sensitivity increased to 6.2. Based on this study, the LIFE device was approved for clinical use by the Food and Drug Administration in 1998 and was subsequently widely used in the United States, Canada, Europe, and Japan (Table 1). Kurie et al reported no benefit of AFB for the localization of metaplasia or mild dysplasia in a population with relatively low prevalence for high-grade dysplastic lesions or lung cancer. However, many other groups confirmed that AFB provides a significantly increased relative sensitivity for localizing moderate dysplasia, severe dysplasia, and CIS (Table 1). This system is no longer commercially available in the United States. Lam and McWilliams summarized the different methods of inducing and imaging autofluorescence by the current commercially available products. The populations studied with AFB included patients with symptoms of lung cancer (hemoptysis, cough, chest pain); patients with radiologic evidence of lung cancer; preoperative patients with lung cancer; postoperative patients with no recurrence of tumor after 2 years; patients with postoperative head and neck cancer; and patients with abnormal sputum cytology, or abnormal DNA content based on automated microscopy. The patients examined by AFB because of abnormal sputum tended to have the highest yield of high-grade dysplasia (moderate or severe dysplasia) or CIS, ranging from 19 to 39% of the biopsy specimens.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No.</th>
<th>Lesions, No.</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al</td>
<td>94</td>
<td>77</td>
<td>48</td>
<td>73</td>
</tr>
<tr>
<td>Lam et al</td>
<td>223</td>
<td>113</td>
<td>39</td>
<td>79</td>
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<tr>
<td>Lam et al</td>
<td>173</td>
<td>102</td>
<td>9</td>
<td>56</td>
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<tr>
<td>Weigal et al</td>
<td>36</td>
<td>3</td>
<td>0</td>
<td>67</td>
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<tr>
<td>Kurie et al</td>
<td>39</td>
<td>60</td>
<td>9</td>
<td>43</td>
</tr>
<tr>
<td>Kennedy et al</td>
<td>55</td>
<td>77</td>
<td>21</td>
<td>76</td>
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<td>Vennmans et al</td>
<td>33</td>
<td>9</td>
<td>78</td>
<td>100</td>
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<td>Vennmans et al</td>
<td>95</td>
<td>40</td>
<td>70</td>
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</tr>
<tr>
<td>Khanshikar et al</td>
<td>243</td>
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<tr>
<td>Metwalli et al</td>
<td>87</td>
<td>14</td>
<td>50</td>
<td>86</td>
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<tr>
<td>Thulerville et al</td>
<td>138</td>
<td>76</td>
<td>57</td>
<td>84</td>
</tr>
<tr>
<td>van Rens et al</td>
<td>72</td>
<td>15</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Yokomise et al</td>
<td>30</td>
<td>14</td>
<td>65</td>
<td>90</td>
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<tr>
<td>Ikeda et al</td>
<td>158</td>
<td>84</td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>Shibuya et al</td>
<td>64</td>
<td>45</td>
<td>69</td>
<td>91</td>
</tr>
<tr>
<td>Sato et al</td>
<td>63</td>
<td>46</td>
<td>61</td>
<td>89</td>
</tr>
<tr>
<td>Lee et al</td>
<td>62</td>
<td>17</td>
<td>41</td>
<td>100</td>
</tr>
<tr>
<td>Overall</td>
<td>1,699</td>
<td>858</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 2—North American Commercially Available Autofluorescence Imaging Systems

<table>
<thead>
<tr>
<th>Device</th>
<th>Excitation Light, nm</th>
<th>Detection Range, nm</th>
<th>Image Composition</th>
<th>Suspicious Mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onco-LIFE</td>
<td>395–445</td>
<td>470–710</td>
<td>Green fluorescence, red reflectance</td>
<td>Brown-red against green background</td>
</tr>
<tr>
<td>Storz D-light</td>
<td>380–410</td>
<td>475–800</td>
<td>Dual fluorescence, blue reflectance</td>
<td>Blue-brown against green background</td>
</tr>
<tr>
<td>SAFE 1000</td>
<td>420–450</td>
<td>490–590</td>
<td>Green fluorescence</td>
<td>Dark green against lighter green background</td>
</tr>
</tbody>
</table>
tissues. Using reflected red light as a reference has the theoretical advantage over reflected blue light in that it is less absorbed by hemoglobin and, hence, is less influenced by changes in vascularity associated with inflammation. The Storz D-Light system consists of a charged-coupled device (CCD) camera and a filtered Xe lamp (380 to 440 nm). It combines a fluorescence image with a blue reflectance image. The lesions appear purple against a blue-green background. Frame averaging is used to amplify the weak autofluorescence. This system appeared to have similar results to the LIFE system in a comparison study. The Pentax SAFE-1000 system uses a filtered Xe lamp in the 420- to 450-nm range to produce the excitation light, but only detects fluorescence in the green spectrum (490 to 590 nm) using a single image-intensified CCD sensor. Two systems not yet commercially available in the United States include the Pentax SAFE-3000 system (Pentax Medical Co.; Lincoln Park, NJ) and the Wolf system (Richard Wolf Medical Instruments Corp.; Vernon Hills, IL).

The Pentax SAFE-3000 system uses a semiconductor laser diode that emits 408-nm wavelength light for excitation of bronchial mucosa and detects autofluorescence using a single high-sensitivity CCD sensor in the fluorescence spectrum 430 to 700 nm. The Wolf system is similar to the Xillix LIFE-Lung system, with a filtered 300-W Xe lamp in the violet-blue range (390 to 460 nm) and slightly different band-pass filters for detection being 500 to 590 nm (green region) and 600 to 700 nm (red region). Most of the published data regarding autofluorescence bronchoscopy are with the use of the LIFE-Lung device. However, a large, randomized, controlled, multicenter trial in Europe using the Storz device was recently published, in which subjects were enrolled who were current smokers and had either symptoms concerning for lung carcinoma (new cough, hemoptysis, or new dyspnea) or radiologic suspicion for carcinoma. The study randomized 1,173 subjects to WLB only, or to WLB plus AFB examination. The authors reported a low overall yield of high-grade dysplasia or CIS (3.9%) but reaffirmed the increased relative sensitivity of AFB with WLB (5.1%) compared to WLB alone (2.7%) [Tables 3, 4]. The sensitivity for localizing CIS, however, only increased by a factor of 1.24 (p = 0.75) with AFB, and only 12 of 2,907 biopsies (0.4%) performed revealed CIS. These highly experienced bronchoscopists likely were able to detect CIS fairly well with WLB. Possible reasons for the low yield may have been the relatively low smoking histories and younger age limit of the patients included, as well as pathology interpretation and quality control by a panel of pathologists, which were not specified.

All studies appear to show a lower specificity with AFB compared to WLB at the expense of higher sensitivity. Although low specificity is seen for most screening technologies, such as mammography and prostate-specific antigen, lower specificity with AFB is somewhat problematic because it might result in more biopsy specimens with AFB and there is a greater cost with AFB than with a minimally invasive screening diagnostic procedure. However, data regarding lesions that are positive on autofluorescence but negative on pathology (false-positive findings) suggest that these lesions may have potential for progression and therefore may not truly be benign lesions (Tables 3, 4). The presence of multiple areas of abnormal autofluorescence, notwithstanding the histopathology grade, appears to be a risk factor for subsequent development of lung cancer. Pasic et al evaluated a group of 46 subjects with either previous aerodigestive cancer or sputum atypia and reported that the presence of two areas of abnormal autofluorescence increased the risk of subsequent lung cancer over the next 4 years compared to subjects with only one suspicious area (50% vs 8%). Therefore, the presence of autofluorescence abnormalities alone may be an indicator of cancer risk and field carcinogenesis.

Videobronchoscopy

The use of AFB and incorporation of the technique into routine clinical practice may improve recognition of bronchial pathology under white light examination. The development of improved white

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**Table 3—Comparison of WLB vs Combined White Light and Storz D-Light Bronchoscopy for the Detection of Moderate/Severe Dysplasia and CIS in the Same Patient Group**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No.</th>
<th>Lesions, No.</th>
<th>Sensitivity, %</th>
<th>Relative Sensitivity</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>WLB</td>
<td>WLB + AFB</td>
<td>WLB</td>
</tr>
<tr>
<td>Haussinger et al</td>
<td>589</td>
<td>34</td>
<td>70</td>
<td>82</td>
<td>1.2</td>
</tr>
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</table>
There have been further advances in endoscopic imaging technology with the incorporation of optical zoom or magnifying lenses to enhance the examination of the bronchial mucosa. The ability to provide a fourfold-magnified view up to 110 times compared with conventional FVB enabled investigators to better visualize and characterize mucosal vascular patterns that may be secondary to early lung cancer angiogenesis. Shibuya et al performed sequential examinations using WLB and AFB followed by high-magnification FVB in 31 subjects at high risk with an average of 62-pack-year smoking history who presented with dysplasia or carcinoma in their sputum. In biopsies of 43 sites with abnormal AFB findings, a tortuous vascular pattern and high vascular area ratio distinguished between dysplasia in 15 of 21 sites vs bronchitis inflammation in 20 of 22 sites with less tortuous vascular pattern and a lower vascular area ratio.

In a follow-up study by the same group involving an additional 48 subjects at high risk with sputum suspicious or diagnostic for malignancy, NBI with selective spectral filtering was added to high-magnification FVB in sequential WLB-AFB, high-magnification FVB, and high-magnification FVB-NBI examinations. NBI conferred additional visual information in the detection of capillary blood vessels seen in ASD. In 67 biopsy samples taken from AFB abnormal sites, a specific “dot” vascular pattern seen under high-magnification FVB-NBI identified ASD with a 78% sensitivity in 18 ASD lesions. Collectively, these studies suggest that improvement in optical and digital imaging by the incorporation of high magnification and selective bandwidth filtering of white light may be complementary to AFB. These techniques may help to identify specific subsets of high-risk preinvasive early lung cancer lesions such as ASD. The introduction of ever higher resolution CCD chips will further enhance the resolution of airway mucosal details.

There may be considerable interobserver variation in the reporting of pathology of these early stage lesions and, despite advancement in molecular biology techniques, as yet there are no accurate predictors of risk of malignant progression. The value of localizing intraepithelial neoplasia is related to the natural history of these lesions, with the possibility of their presence being a marker of malignant risk and the potential for cure by local intervention when malignancy is detected at the earliest possible stage.

**PROPOSED INDICATIONS FOR AFB**

*Evaluation of Patients with High-Grade Sputum Atypia*

Moderate dysplasia, severe dysplasia, CIS, and invasive carcinoma grades in sputum cytology have commonly been used as indicators for AFB examination. Historical studies on sputum cytology showed that 11% of subjects with moderate dysplasia and 19 to 46% with severe dysplasia in sputum progressed to SqCC. Patients with high-grade dysplasia or worse have a high prevalence of preneoplasia and/or neoplasia found with AFB examination. The yield of invasive malignancy is positively related to the cytology grade. There is no controversy that a sputum cytology reading of either invasive cancer or CIS requires further investigation, usually with WLB and CT. Sato et al reported a marked improvement in survival of patients who had a sputum diagnosis of SqCC but who had no radiographic abnormalities. One group was treated with surgical resection (n = 207), and another group with the same diagnosis declined treatment (n = 44). The treated group had a 94.9% survival at 10 years, and the untreated group had a 33.5% survival in the same time period. Severe dysplasia has also been reported to portend a high likelihood of impending clinical cancer. Prindiville et al reported that
adjusted risks of lung cancer development for increasing grades of cytologic atypia were 1.0 (normal), 1.10 (mild atypia), 1.68 (moderate atypia), 3.18 (moderate atypia or worse), and 31.4 (worse than moderate atypia). Moderate dysplasia has been associated with increased risk of subsequent cancer in the National Cancer Institute studies. Kennedy et al reported that 79 consecutive subjects with no evidence of malignancy on chest radiograph but moderate dysplasia in sputum who had AFB examination showed lung cancer in 5 subjects (6.3%), with 3 subjects having invasive SqCC and 2 subjects with CIS. An additional seven subjects (8.9%) were found to have severe dysplasia. McWilliams et al reported finding seven cases of CT occult central SqCC in four subjects (CIS, n = 6; microinvasive, n = 1; 1.3%), and a significant yield of high-grade dysplasia (5.7%) with AFB in asymptomatic smokers whose sputum had epithelial cells with an elevated DNA index (> 1.2) when evaluated by quantitative image cytometry.

**Recommendation**

1. For patients with severe dysplasia, CIS, or carcinoma in sputum cytology but with chest imaging studies showing no localizing abnormality, standard WLB is recommended. AFB should be used when available. Grade of recommendation, 1B

**Evaluation of Patients with Suspected, Known or Previous Lung Cancer**

AFB can play a useful role in both the delineation of tumor margins and the assessment of the presence of synchronous lesions in patients with early lung cancer who are being evaluated for curative surgical resection. Synchronous cancer can be found on AFB in up to 17% of these patients, and up to 44% of patients may also have other moderate/severe dysplastic lesions that will require bronchoscopic follow-up.

Lam et al reported that at least one synchronous site of CIS was detected in 15% of 53 subjects with known lung cancer. Vennans et al detected other sites of moderate dysplasia or worse in 44% subjects with a known site of CIS referred for endobronchial therapy. Pierard et al found that in 43 preoperative lung cancer patients, 9.3% had a synchronous occult CIS, and 19% had dysplasia or worse. Pierard et al also found that 23% of 26 patients referred for treatment with high-grade preinvasive lesions or CIS/microinvasive cancer had synchronous severe dysplasia/CIS/microinvasive cancer on AFB, van Rens et al reported the preoperative evaluation of 72 NSCLC patients and found three synchronous NSCLC in three patients (4.2%) and 13 high-grade dysplasia in 10 patients (14%). The discovery of the synchronous carcinoma altered the therapeutic plan in these patients.

After successful curative resection of NSCLC, a high rate (1 to 3%/yr) of second primary (metachronous) tumors has been reported. It is also estimated that 2 to 13% of patients surviving small cell carcinoma per patient per year will have NSCLC develop. In a subset of patients with previous early central SqCC, the reported rate of metachronous lesions appears even higher with up to nearly 30% having a second central carcinoma develop within 4 years. Weigel et al reported findings in 31 AFB examinations on 25 patients after complete resection of NSCLC, in which three lesions of moderate/severe dysplasia and one microinvasive cancer developed during an average of 20.5 months postoperative follow-up in 12% of patients. The relative sensitivity of AFB over WLB was 3.0. A follow-up report by the same authors with a total of 51 patients found one invasive cancer and three high-grade dysplastic lesions (6% yield) after a median of 13 months after surgery. Three of the four lesions were found in patients with previous SqCC. Pasic et al found that 28% of patients with a previous lung cancer had metachronous central SqCC develop during AFB surveillance within a median of 47 months of follow-up. Moro-Sibilot et al reported that in patients with a previous resected SqCC, 30% had high-grade dysplasia or worse compared to only 4% with a previously resected adenocarcinoma, or 20% overall of resected NSCLC on AFB examination.

Patients who have had either a previous curative resection for NSCLC or successful chemoradiotherapy for small cell lung cancer are at high risk for second lung cancers. Whether AFB may be useful in the long-term follow-up and surveillance in these patients has not been adequately studied (see chapter on “Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy”). Patients with previous SqCC may be particularly at high risk for subsequent intraepithelial neoplasia and multiple metachronous central carcinomas.

**Patients With Early Central Lung Cancer Eligible for Curative Endobronchial Therapy**

When considering an early central carcinoma for curative endobronchial therapy, AFB may play a role in correctly determining the size of the lesion and whether all margins can be visualized. These factors have an important impact on the success of endobronchial treatment, and may not be accurately assessed with WLB. Sutedja et al performed AFB on 23 patients referred for intraluminal therapy of
134 lesions were followed up: squamous metaplasia 
clinically determined margins. There was better correlation between margins
determined by AFB than WLB with histopathologically determined margins.

**Recommendation**

2. For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, AFB may be considered to guide therapy. Grade of recommendation, 2C

*Follow-up of High-Grade Bronchial Intraepithelial Neoplasia*

Longitudinal data using serial bronchoscopy and biopsy in patients with intraepithelial neoplasia detected by AFB have now been reported by a number of authors. In a study by Breuer et al.,52 subjects with either positive sputum cytology findings, previously resected upper respiratory tract cancer, or clinical suspicion for lung cancer had AFB. A total of 134 lesions were followed up: squamous metaplasia (n = 45), mild/moderate dysplasia (n = 64), and severe dysplasia (n = 25). The highest progression rates to CIS/invasive carcinoma were seen in severe dysplasia (32%) vs mild/moderate dysplasia (9%) and metaplasia (9%). The median time to progression was most rapid with severe dysplasia at 16.5 months compared to 21.5 months with all other lesions. Interestingly, many sites were found to show non-stepwise fluctuations between the histologic grades.

In another series published by Bota et al.,49 AFB was performed in 104 patients who were either smokers, had previous asbestos exposure, had a previous curative lung cancer resection, or had a current operable aerodigestive cancer. A total of 380 lesions including hyperplasia/metaplasia (n = 152), mild/moderate dysplasia (n = 169), severe dysplasia (n = 27), and CIS (n = 32) were found and observed for 24 months, although persistent severe dysplasia/CIS lesions were treated at 3 months of follow-up. Severe dysplasia had high rates of progression, with 11% showing progression to CIS/invasive cancer, whereas 3.5% of mild/moderate dysplasia progressed to severe dysplasia, and 2% of hyperplasia/metaplasia showed progression to carcinoma. Many lesions showed regression, including 37% hyperplasia/metaplasia, 60% mild/moderate dysplasia, and 63% of severe dysplasia. In contrast, 75% of CIS persisted and were treated with endobronchial therapy.

The outcome of CIS was also evaluated by Venmans et al.,53 when he reported the short-term follow-up of nine subjects with CIS. Some lesions (67%) had initial endobronchial therapy to attempt cure. Overall, 67% of lesions progressed to invasive carcinoma. It is likely that the progression rate would have been higher if some of the lesions had not been treated at initial diagnosis. The same group subsequently reported that a higher prevalence of abnormal AFB sites in a patient predicted a higher probability for development of invasive carcinoma.

Lam et al.,50 reported the follow-up of 2,346 lesions detected in 566 subjects who had at least a 20–pack-year smoking history but no previous or current aerodigestive cancer. Lesions ranged from hyperplasia (n = 582), metaplasia (n = 459), mild dysplasia (n = 757), moderate dysplasia (n = 157), and severe dysplasia (n = 51), and there was a mean follow-up of 4.7 years. Eight subjects were found to have eight CIS and two invasive cancers (n = 3) from sites that showed hyperplasia, metaplasia (n = 3), moderate dysplasia (n = 2), or severe dysplasia (n = 3) in their first bronchoscopy. These tumors developed over a median interval of 21 months. Therefore, the progression rate of severe dysplasia to CIS/invasive carcinoma was 6%, and moderate dysplasia was only 1.3%.

Hoshino et al.,51 reported follow-up of 99 lesions in 50 subjects who had AFB performed because of either suspicious sputum cytology or previous lung cancer. The lesions included 11 severe, 56 moderate, and 32 mild cases of dysplasia. Overall, only three lesions progressed to carcinoma: two severe (18%), and one moderate (1.7%). However, the mean duration of follow-up was only 6.9 months. Lesions with increased telomerase activity, Ki-67 labeling, and p53 immunoreactivity tended to persist as dysplasia.

George et al.,52 reported the results of observation of 51 lesions in 22 subjects with a median follow-up of 23 months (range, 12 to 85 months). The majority of the patients had previous asbestos exposure, known COPD, or previous lung cancer (82%), and they were referred for AFB. High-grade lesions included 7 severe dysplasias and 29 CIS, and low-grade lesions included 17 mild/moderate dysplasias. Progression to invasive cancer was seen in 17% (6 of 36 high-grade lesions), and all of these were previous sites of CIS. Therefore, the progression of CIS to invasive cancer was 21% (6 of 29 lesions) in this series. Only half of these progressive CIS were successfully treated, raising concerns that delay in treatment resulted in a poorer outcome for these patients. Indolence was observed in 64% of
high-grade lesions. However, observation was discontinued early in a significant proportion of these persistent lesions because the subjects underwent other therapy that could have influenced outcomes (eg, lobectomy and radiotherapy). No progression was seen in low-grade lesions. Interestingly, five subjects (14%) with high-grade bronchial lesions had remote lung cancers that were detected by CT during the period of observation, suggesting that the presence of bronchial dysplasia may be a marker for overall lung cancer risk as previously noted by Pasic et al.20

The variable rates in progression of these preneoplastic lesions may have been attributable to differences in the patient populations evaluated or histopathology reporting. In the report of Lam et al,50 with lower rates of progression of moderate/severe dysplasia to carcinoma, the subjects were current/former smokers who had no history of aerodigestive cancer or clinical suspicion of cancer. In the study by George et al,52 who also documented lower rates of progression of intraepithelial neoplasia, only 40% of study subjects had previous lung cancer, and the remainder had either COPD, significant smoking history, or asbestos exposure. Subjects were excluded if they had a clinical suspicion of lung cancer. In the series published,39,48–51,53 subjects with previous or current aerodigestive cancers or clinical suspicion of lung cancer were included and contributed a significant proportion or all of the population studied. It is well known that patients with a diagnosis of lung cancer or other aerodigestive cancers are at risk for second primary lung cancers, and this subset likely represents a very high-risk group, with subsequent higher observed rates of progression.48,49,52,53

Overall, the observed rates of progression to invasive carcinoma of moderate dysplasia range is 0 to 9%, and to severe dysplasia from 0 to 32%. CIS lesions are seen to either persist in > 60% cases with no regression or progress to invasive carcinoma in 20 to 60% cases, despite stopping smoking in some instances. When severe dysplasia and CIS are found, it is suggested that additional focused biopsies in the area of concern be performed to ensure microinvasive carcinoma is not an element of the lesion.

**Recommendation**

3. For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up. AFB should be used when available. Grade of recommendation, 2C

**Treatment of Early Stage NSCLC**

Roentgenographically occult lung cancers can be detected in patients at high risk with either sputum cytology or bronchoscopic inspection. Traditionally, the only treatment available for these cancers was surgical resection. Even though these cancers are small because of their central location, on average approximately 70% of cases require a lobectomy, and the remaining 30% require either a bilobectomy or pneumonectomy for curative intent resection.54 There are patients with reduced cardiopulmonary reserve who are not candidates for these surgical options. Additionally, 1 to 4% of these patients will have a synchronous lung cancer.55 Some studies56–58 report up to 17% of newly diagnosed early lung cancer cases have a synchronous lesion. The risk for second lung cancer ranges from 1 to 25%/yr.59

Endobronchial therapies that preserve lung function have been developed and include PDT,60 brachytherapy,61 electrocautery,62 cryotherapy,58 and Nd-YAG laser therapy.63 Most roentgenographically occult cancers (ie, lung cancers) not detected by either chest radiography or CT are histopathologically SqCC and are located in relatively large central bronchi.64 The majority of these occult cancers invade the bronchial wall but are not metastatic.65

In early stage SqCC, estimating the depth of intrabronchial invasion is a significant challenge, but bronchoscopic evaluation can provide valuable information regarding depth of invasion. Both the size of the lesion and its topographic appearance may determine the depth of penetration. Lesions < 10 mm in greatest dimension with only superficial thickening of the epithelium have been reported to invade beyond the bronchial cartilage in < 5% of cases examined. Those with a nodular or polyoid appearance showed invasion in 18% and 27%, respectively.66

Fujimura et al59 found that in surgically resected roentgenographically occult lesions with endoscopically visible margins, 10% of lesions were < 10 mm in length, 23% of lesions were 10 to 29 mm in length, and 67% lesions were > 30 mm in length and had lymph node involvement. Lesions with margins beyond endoscopic visibility had an increased risk of lymph node involvement. Nakamura et al41,67 also reported that increasing tumor dimension was associated with increased depth of mural invasion, decreased cure rates, and increased lymph node involvement. Endobronchial ultrasound is available to determine depth of invasion. The accuracy of this approach has been reported to be quite good in determining appropriate candidates for endobronchial therapy.68,69
PDT

PDT is based on the interaction of a photosensitizer with light of narrow bandwidth. In the presence of oxygen, tumor death occurs by several mechanisms including vascular shutdown, cell cycle apoptosis, and direct singlet oxygen membrane injury. The majority of clinical data using PDT in early lung cancer have been for treatment of patients who were deemed nonsurgical candidates. The greatest experience has emerged from Japan in the past 2 decades.\textsuperscript{55,60,70–78} One hundred forty-five patients with 191 early NSCLCs have been treated with PDT since 1980. This includes 99 patients with stage 0 and 56 patients with stage IA disease. There were 141 men and 4 women. The majority of cases (98\%) were SqCC. Complete response was achieved in 86\% of lesions, with a recurrence rate of 13\%, thereby resulting in a long-term response of 75\%. When success of treatment was evaluated according to lesion size, lesions < 1.0 cm had a complete response of 95\%, and lesions ≥ 2 cm had a complete response of only 46\%. Treatment success was also related to whether the distal margin of the tumor could be clearly seen bronchoscopically. If the margin were visible, a complete response rate of 92\% was achieved, compared to 67\% if the margins were not visible. If the lesion was < 1.0 cm and the margins were visible, complete response was achieved in 98\% of cases.\textsuperscript{72,76,77}

Imamura et al\textsuperscript{56} studied 29 patients (39 cancers) and achieved complete response in 64\% of lesions. Recurrence occurred in 36\%, giving a long-term response of 41\%. On evaluation of lesion size, 72\% of lesions that were < 3 cm\textsuperscript{2} achieved a complete response. Ono et al\textsuperscript{78} studied 36 patients (39 cancers) and achieved a complete response rate of only 31\%, with a recurrence in 33\%. Therefore, the long-term response was only 21\%. A number of smaller studies\textsuperscript{79–82} from Europe and Canada reported complete response rates of 62 to 91\%. A multicenter investigator-initiated experience\textsuperscript{83} was collated and presented to the Food and Drug Administration for approval of porfimer sodium in the treatment of early superficial SqCC. A total of 102 patients with radiologically occult (stages 0, IA, and IB) SqCC were treated. An overall immediate complete response rate of 78\% was achieved (95\% confidence interval, 7 to 87\%). Forty-four percent of the patients had recurrent tumor on follow-up, giving a long-term response rate of 43\%. The median time to tumor recurrence was 2.8 years (range, 0.1 to 10 years). Analysis of the subgroup of the 24 inoperable patients revealed a complete response of 92\% (95\% confidence interval, 81 to 100\%). A similar recurrence rate of 46\%, a long-term response rate of 50\%, and a median time to tumor recurrence of 2.7 years were observed.

The Mayo Clinic has reported treatment of 58 nonsurgical patients with early lung cancer.\textsuperscript{84–90} An 84\% complete response rate was achieved after one treatment. Nineteen patients (39\%) recurred and had a second PDT treatment. The median time to tumor recurrence after the first treatment was 4.1 years. After the second treatment, 11 patients (22\%) had recurrence. The long-term complete response rate was 66\%. PDT as an alternative to surgical resection was studied in 21 patients with small bronchial cancers.\textsuperscript{88} A 71\% complete response (15 of 21 patients) was achieved, with 11 patients (52\%) maintaining a complete response > 12 months. Patients who did not respond or recurred were offered surgery. Of the 10 patients who underwent surgery, 3 were found to have N1 disease. Two patients refused surgery. A total of nine patients (43\%) were spared surgery.

In summary, PDT is effective in managing small superficial SqCC. The worldwide data showed that patients with early lung cancer treated with PDT achieve a complete response in approximately 75\% cases, with a recurrence rate of approximately 30\%. Complete response rates > 90\% can be achieved when lesions are small (< 1 cm in diameter), superficial, and all margins can be visualized. Experience remains limited using PDT for patients who are surgical candidates.

Electrocautery

Bronchoscopic electrocautery is the use of high-frequency electrical current that generates heat caused by tissue resistance, resulting in destruction of tissue. A small study\textsuperscript{62} in early lung cancer of 13 patients (15 cancers) showed a complete response in 80\% of lesions with no recurrence at 22 months of follow-up. Endoscopic treatment has a curative potential for patients with intraluminal microinvasive radiographically occult lung cancer. This is discussed in the report\textsuperscript{91} of the long-term follow-up of in a group of 32 patients ineligible for surgery who were treated with endobronchoscopic therapy. Treated tumors were ≤ 1 cm in size, intraluminally located in the central airways, with no bronchial wall invasion or extraluminal tumor growth on high-resolution CT, and with visible distal margin under conventional and AFB. Endoscopic therapy was performed with curative intent, and consecutive patients were treated with PDT (5 patients), Nd-YAG laser (1 patient), electrocautery (24 patients), and argon plasma coagulation (2 patients). Follow-up evaluation at 3- to 4-month intervals included high-resolution CT and both WLB and AFB, which allowed biopsies and brush
cytology for histologic evaluation. The average follow-up period was 5 years (range, 2 to 10 years). In three patients, local recurrence was again successfully treated with electrocautery. Sixteen patients died during follow-up. Eight of the nine patients who died because of lung cancer had a previous resection of a more advanced stage lung cancer up to 5 years before endoscopic treatment of the radiographically occult lung cancer. The cause of death in the remaining seven patients was not related to lung cancer. Sixteen patients are still alive without tumor recurrence. These data showed that bronchoscopic therapy is an effective treatment modality for patients at high risk with early lung cancer, who are not eligible for surgical resection.91

Cryotherapy

Cryotherapy is a technique in which tissue is destroyed by freezing and is the least expensive treatment option for early lung cancer. A report58 included 35 patients (41 cancers) with early stage lung cancer. A complete response after cryotherapy was obtained in 91% of the patients with a recurrence rate of 28% within 4 years. A long-term response of 63% was achieved, similar to that of PDT.58

Brachytherapy

Brachytherapy refers to the placement of a radioactive source within or near an endobronchial malignancy to deliver local irradiation. This requires the insertion of an afterloading polyurethane catheter into the airway adjacent to the tumor during fiberoptic bronchoscopy.192 Ir is generally used. In two small studies,61,92 the use of high-dose brachytherapy in three to six sessions resulted in response rates similar to PDT. Marsiglia et al92 reported 34 patients with early stage lung cancer with a complete response of 85% seen > 2 years after follow-up. Perol et al61 reported 19 patients with early stage lung cancer with a complete response rate of 83%, which decreased to 75% at 1-year follow-up.

Nd-YAG Laser Therapy

Nd-YAG laser therapy is used for direct thermal ablation of tissue in endobronchial malignancy. It has been used extensively as a palliative measure to relieve airway obstruction. The use of laser treatment for early lung cancer has not been widely studied. A study by Cavaliere et al83 showed a complete response rate of 100% in 22 patients with small bronchial cancers. The long-term outcome of these patients was not reported. Nd-YAG laser therapy is not indicated for tumors that are located in the bronchial wall parallel to the bronchoscope or for tumors involving smaller bronchial branches because of the risk of perforation.53 This would occur because of heat sink effect and absorption of heat by the tissue.

After endobronchial treatment for early lung cancer, patients should be closely monitored for recurrent disease and development of metachronous lesions. Reevaluation at 3 to 6 months with WLB and AFB, if available, is reasonable (see chapter of “Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy”).

Recommendation

4. For patients with superficial SqCC who are not surgical candidates, PDT, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options. Use of Nd-YAG laser is not recommended because of the risk of perforation. Grade of recommendation, 1C

Conclusions

The detection and assessment of intraepithelial and microinvasive neoplasia in the central airways is significantly improved by the use of autofluorescence imaging. The range of its clinical application is still being explored but includes investigation of patients with abnormal sputum cytology, longitudinal surveillance of bronchial dysplasia, and assessment of early central lung cancer being considered for curative endobronchial therapy. A number of techniques are now available for curative endobronchial therapy in select central lesions.

PDT is the most extensively studied endobronchial treatment for early lung cancer for patients who are not candidates for surgical resection. Suitable lesions require careful assessment bronchoscopically and radiographically. The data for use of PDT for patients who are surgical candidates currently are limited. Other endobronchial treatments such as electrocautery, cryotherapy, and brachytherapy are not as well studied but appear to have similar response rates to PDT. The best response is seen in highly selected patients with small lesions and visible margins.

Summary of Recommendations

1. For patients with severe dysplasia, CIS, or carcinoma in sputum cytology but with chest imaging studies showing no localizing...
abnormality, standard WLB is recommended. AFB should be used when available. Grade of recommendation, 1B

2. For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, AFB may be considered to guide therapy. Grade of recommendation, 2C

3. For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up. AFB should be used when available. Grade of recommendation, 2C

4. For patients with SqCC who are not surgical candidates, PDT, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options. Use of Nd-YAG laser therapy is not recommended because of the risk of perforation. Grade of recommendation, 1C

References


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