Autofluorescence Bronchoscopy Improves Staging of Radiographically Occult Lung Cancer and Has an Impact on Therapeutic Strategy*

Tom G. Sutedja, MD, PhD, FCCP; Henk Codrington, MD; Elle K. Risse, MD, PhD; Roderick H. Breuer, MD; Johan C. van Mourik, MD; Richard P. Golding, MD; and Pieter E. Postmus, MD, PhD, FCCP

Background: The ability of conventional CT scans and fiberoptic bronchoscopy to localize and properly stage radiographically occult lung cancer (ROLC) in the major airways is limited. High-resolution CT (HRCT) scanning and autofluorescence bronchoscopy (AFB) may improve the assessment of ROLC before the most appropriate therapy can be considered.

Patients and methods: We prospectively studied 23 patients with ROLC, who were referred for intraluminal bronchoscopic treatment (IBT) with curative intent. Additional staging with HRCT and AFB was performed prior to treatment. Twenty patients were men, 9 patients had first primary cancers, and 14 patients had second primary cancers or synchronous cancers.

Results: HRCT scanning showed that 19 patients (83%) had no visible tumor or enlarged lymph nodes. With AFB, only 6 of the 19 patients (32%) proved to have tumors ≤ 1 cm² with visible distal margins. They were treated with IBT. In the remaining 13 patients, abnormal fluorescence indicated more extensive tumor infiltration than could be seen with conventional bronchoscopy alone. Six patients underwent radical surgery for stage T1–2N0 (n = 5) and stage T2N1 (n = 1) tumors. Specimens showed that tumors were indeed more invasive than initially expected. The remaining seven patients technically did not have operable conditions, so they were treated with external irradiation (n = 4) and IBT (n = 3). The range for the time of follow-up for all patients has been 4 to 58 months (median, 40 months). The follow-up data underscore the correlation between accurate tumor staging and survival.

Conclusions: Our data showed that 70% of patients presenting with ROLC had a more advanced cancer than that initially diagnosed, which precludes IBT with curative intent. Additional staging with HRCT and AFB enabled better classification of true occult cancers. Our approach enabled the choice of the most appropriate therapy for each individual patient with ROLC.

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Key words: autofluorescence bronchoscopy; occult lung cancer; staging

Abbreviations: AFB = autofluorescence bronchoscopy; HRCT = high-resolution CT; IBT = intraluminal bronchoscopic treatment; PDT = photodynamic therapy; ROLC = radiographically occult lung cancer; RT = radiation therapy; WLB = white-light bronchoscopy

Of all prognostic factors for non-small cell lung cancer, the most important one by far is the size of the primary tumor. This implies that, despite an overall disappointing low cure rate of only 13%, efforts to detect and treat lung cancer at the earliest stage are rewarded and will result in a much better outcome. The early detection of radiographically

*From the Departments of Pulmonology (Drs. Sutedja, Codrington, Breuer, and Postmus), Pathology (Dr. Risse), Surgery (Dr. van Mourik), and Radiology (Dr. Golding), Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands.

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Correspondence to: Tom G. Sutedja, MD, PhD, FCCP, Department of Pulmonology, Academic Hospital Vrije Universiteit, PO Box 7057, 1007 MB Amsterdam, The Netherlands; e-mail: tg.sutedja@azvu.nl
occult lung cancer (ROLC) is difficult, but at that stage it has the best prognosis, even among patients with early-stage cancers. One of the advantages of ROLC is the current availability of several therapeutic modalities, even in patients with severe COPD or cardiac problems, or after undergoing pulmonary resections. Treatment with curative intent is possible. Reduced physical fitness may deem patients to have inoperable conditions, such that intraluminal bronchoscopic therapy (IBT) may be considered as an alternative for surgical resection. Intraluminal therapy such as photodynamic therapy (PDT) and electrocautery have been reported to be potentially curative for ROLC.2–4

The most difficult aspect of IBT with curative intent is to select patients who are really candidates for cure by this modality. IBT with curative intent is only possible in areas accessible by the fiberoptic bronchoscope in the visible part of the tracheobronchial tree. Furthermore, the penetration into tissue of any modality used for IBT is finite and limited to a few millimeters. In surgically treated patients, it has been demonstrated that for ROLC, the size of the involved area in the bronchial mucosa and the degree of invasion through the bronchial wall are important prognostic factors.5–7 Since ROLC may consist of several cell layers of malignant cells, it is possible that prevention of invasion through the bronchial wall is more than what IBT modalities can achieve. Only by high-resolution CT (HRCT) scanning is it possible to get an impression of the thickness of the bronchial wall.8

From the results of a number of studies, it has become clear that the size of the involved area is an important determinant for success. However, even for very experienced bronchoscopists, it remains difficult to delineate the margins of ROLC in the involved bronchial mucosa, especially when the tumor may extend beyond the visible part intraluminally. For preneoplastic lesions in the central airways, autofluorescence bronchoscopy (AFB) has been shown to increase the detection rate compared to the use of conventional white-light bronchoscopy (WLB) alone.9–11 Central and proximal airway branches can be inspected with the fiberoptic bronchoscope during WLB, and the additional use of AFB may help to delineate tumor margins more precisely.

We have reported previously8 on the value of HRCT in patients referred for intraluminal treatment for ROLC. Combining the findings during WLB and HRCT scanning made it possible to better select a subgroup of patients who might be suitable for IBT with curative intent. However, in a number of patients this approach failed, but, fortunately, subsequent surgery resulted in cures. Accurate tumor staging is therefore essential before a treatment decision is made, especially in patients with resectable ROLC.2,12,13 In order to improve the diagnosis of ROLC, we studied prospectively the value of adding AFB to WLB in patients with ROLC.

Materials and Methods

Twenty-three consecutive patients were referred with the initial diagnosis of ROLC. This was based on the findings of tumors detected intraluminally using conventional WLB that were not visible on standard chest radiographs and standard CT scans with slice thicknesses of 10 mm prior to referral.

HRCT was performed according to the protocol that has been published previously.8 WLB and AFB were carried out to inspect the accessible part of the tracheobronchial tree to localize, delineate, and measure the lesions. Biopsies were conducted strictly according to the protocol that has been published before.11 Biopsy specimens initially taken by the referring physicians were reviewed, and they confirmed the presence of squamous cell carcinoma in all patients.14

When HRCT showed bronchial wall thickening peribronchial tumor infiltration, or enlarged lymph nodes, patients were considered to have locally advanced cancers (group A), and these patients were treated accordingly by chemotherapy, surgery, radiotherapy, or a combination of these.

Occult tumors detected by HRCT but with distal margins invisible on AFB were classified as not true early-stage cancers (group B). Immediate surgery was performed when the results of mediastinoscopy were negative (stage N0). If a patient was considered to have an inoperable condition due to, for instance, severe COPD or previous resection(s), IBT was performed and an extra margin of at least 1 cm distal of the tumor border was included in the target area during intraluminal treatment. For tumors located on the bifurcations of the segmental bronchi, external irradiation was given because of the relatively inaccurate dosimetry of PDT and brachytherapy in this situation. External radiation therapy (RT) does not include the mediastinum. Intraluminal tumors ≤ 1 cm², with visible distal margins and without wall thickening, peribronchial extension, or lymph node enlargement on HRCT were classified as true early-stage cancers that were suitable for IBT with curative intent (group C).2,3,12 AFB was used to assist treatment by delineating the tumor margins more accurately. Four monthly follow-up visits included AFB with biopsies, cytology brush biopsies, and HRCT scans, especially in patients with cancers that were still technically operable. Patient demographics and the findings of HRCT scans and AFB procedures are shown in Table 1.

Results

Follow-up of all patients occurred over a range of 4 to 58 months after the initial diagnosis. In four patients with locally advanced cancers (group A, patients 1 to 4), AFB did confirm the presence of extensive intraluminal tumors, giving a much clearer view of how extensive tumor involvement was. The survival time of the four patients ranged from 4 to 28 months, and they all experienced tumor-related death.

In all six patients (patients 5 to 10) who underwent
surgery because occult tumors shown on HRCT scans were shown to be more extensive under AFB procedures, in contrast to the conventional WLB procedure, resection was radical. All but one patient had stage T1–2N0 tumors. In the resected lung of patient No. 5, two separate primary tumors were found. The patient developed a third primary lung tumor at 38 months and received RT. The remaining seven patients could not undergo surgical resection, and two developed metastases. One of them experienced tumor-related death due to brain metastasis.

Only 6 of the 23 patients (26%) who had received initial diagnoses of ROLC were considered to be suitable for IBT with curative intent. AFB confirmed the findings of both HRCT scans and WLB that tumors were indeed \( H11021 \) with clearly visible distal margins. Both electrocautery and extensive biopsy obtained long-term complete responses (Ta-
All patients except one have been shown to be free of disease after a follow-up period of 30 to 50 months. One patient died because of very severe emphysema, but no recurrence was found 6 months prior to her death. One patient showed carcinoma in situ as a recurrence after electrocautery treatment, and RT then was administered because AFB showed that the tumor gradually had extended beyond the 1-cm² limit.

**Discussion**

Woolner et al\(^5\) showed that in only 29% of patients with early-stage lung cancers detected by sputum cytology could the primary tumor be located by the use of standard radiologic techniques. Two-thirds of these ROLCs are indeed only a few millimeters thick and can be classified as early-stage tumors. WLB relies on the visual judgment of the bronchoscopist. It is important to be diligent in the correct judgment of these minute lesions. Mucosal thickening, swelling, granularity, nodules, and polyps are quite obvious; however, redness, paleness, lack of luster, vascular engorgement, disruption of mucosal folds, loss of clarity, edematous change, small vesicles, tiny necrotic material, and the fact that the suspicious area easily bleeds are sometimes too subtle to be fully appreciated.\(^1\)\(^5\) The bronroscope has to be maneuvered carefully without touching normal mucosa. The accessibility of the tracheobronchial tree also is limited by the size of the fiberoptic bronchoscope. Tumor margins distal to the segmental bronchi are difficult to delineate. It is obvious that minute lesions are easily missed, as many patients also suffer from smoking-related chronic bronchitis. Patches of abnormal tissue also may form skipping lesions. Sampling errors for histology examinations also can lead to false-negative results. A previous study\(^1\)\(^6\) has shown the difficulty in detecting and localizing carcinoma in situ using WLB. False-negative findings led to an average delay of 29.2 months before the exact location of the early-stage cancer could be determined. Previously, we reported that HRCT scanning is useful in excluding patients selected by
WLB procedures for IBT with curative intent, because chest radiographs and conventional CT scans were relatively inadequate for accurately staging ROLC. The most important application of AFB (LIFE system [Laser Induced Fluorescence Endoscope]; Xillix; Vancouver, Canada) has been the early detection of preneoplastic lesions in the bronchial tree in high-risk patients. Data from previous studies showed that using AFB resulted in the detection of significantly more preneoplastic lesions. Another possible useful application is the more appropriate sampling of tissue for histologic investigation resulting in less sampling error. In this study, we describe a possible new application of AFB as part of the staging procedure for patients with ROLC, especially to delineate the tumor margins compared to what is seen during WLB procedures. Furthermore, it is possible to control the extent of the target area during IBT session by using, for example, electrocautery. Staging inaccuracy may lead to late tumor recurrences and delays in making the better choice of treatment. In carefully selected patients, the curative potential of PDT, brachytherapy, and electrocautery has been established. Electrocautery during AFB is possible, and the change of autofluorescence color from red-brown to white-green can be seen easily (Table 1). Treatment efficacy may be improved by using AFB to assure the exact spot of the tumor and to enable the radical treatment of tumor margins.

The best proof of the value of AFB is the microscopy findings of the resected tumor specimens. More extensive intraluminal tumors were found to have invisible distal tumor margins prior to surgery (Table 1, patients 5 to 10). Unfortunately, histological proof from resected specimens is not always possible. We had no definite proof from patients who could not undergo resection and in whom a complete response was achieved after IBT. Furthermore, it is not possible to perform an extensive radical biopsy of the target area, especially in the segmental bronchi. Therefore, long-term longitudinal studies combined with extensive biopsy specimens procured during AFB are the next best way to decide whether the AFB findings initially were correct.

Previous studies have reported the relationship of intraluminal tumor size and the depth of tumor infiltration. Tumor size is related to the presence of lymph node metastasis. Data from a previous PDT study also indicated the strong correlation between the long-term complete response and tumor dimension.

The classical study of Auerbach et al already has shown that early-stage lesions may contain malignant cells that are only several layers thick. Patient No. 20 had only a small intraluminal cancer on the segmental bifurcation and is currently without recurrence 38 months after extensive biopsy alone.

There are no nonsurgical procedures by which it is possible to detect accurately the extension of the ROLC into the bronchial wall; only HRCT scanning can indirectly give some information on this important issue. Whether endobronchial ultrasonography will improve our ability to assess tumor infiltration beneath the mucosa remains to be seen. Although endobronchial ultrasonography is clearly more sensitive than HRCT scanning for local staging of the bronchial wall, its impact on treatment strategy and outcome still has to be established. The accuracy of HRCT scanning and AFB cannot be compared with the ability of the pathologist to evaluate the resected specimen in retrospect after radical surgical resection. The fact that true early-stage squamous cancer does not have nodal disease, as has been shown in surgical series, encourages us to pursue the policy of commencing IBT with curative intent as an alternative to surgery. Figure 1 shows an example of radiographically occult, microinvasive squamous cell cancer. A small abnormality of the middle lobe carina is shown on the HRCT scan, and corresponding images of AFB and conventional bronchoscopy with the biopsy forces in situ also are shown. The patient was treated with curative intent using contact-mode electrocautery and is currently cured. However, the exact criteria of true early-stage cancer should be taken into account. Progression of the bronchoscopic finding is always an indication to proceed to surgical resection. We recently showed that most carcinomas in situ ultimately become microinvasive. Especially in this category of patients, one should exploit the curative potential of IBT at the earliest stage possible. If tumors are inoperable, a vigorous intraluminal treatment such as high-dose rate brachytherapy or small-volume external RT seems warranted.

In conclusion, both HRCT scanning and AFB provide better means to accurately stage ROLC patients, preventing both overtreatment and undertreatment. Follow-up data show that in dealing with the problem of ROLC, accurate staging is the real hurdle, not so much the treatment technique. With reappraisal of the screening and early detection of lung cancer, current techniques of AFB and HRCT seem to be valuable to improve the grim prospect of lung cancer in the population at risk.

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