

Editorial

Lung Cancer Surveillance: New Technologies and Novel Strategies

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There is a renewed interest in the identification of cohorts of "high risk for lung cancer" individuals. The older trials that stated that screening for lung cancer was of no use are being questioned and are slowly being relegated to historical interest. Changes in technology, as well as an increased understanding of the evolutionary nature of airway carcinogenesis, have fostered this revolution. Present and former smokers with a tobacco consumption of 20 pack years or greater (especially with evidence, on routine spirometry, of chronic obstructive pulmonary disease) and patients with previous upper aerodigestive malignancies have received the greatest attention for entry into these new trials of secondary prevention. In this issue of *Annals of Surgical Oncology*, Weigel et al.¹ describe the use of autofluorescence bronchoscopy to detect preclinical pre/neoplasia in patients who have had a curative resection of their lung cancer. This cohort of high-risk individuals represents an ideal study population, because the per year risk of developing a second primary lung cancer is reported to be as high as 4% (in T1N0 and T2N0 patients).² The obvious goal of such a program would be to define lesions that would remain occult by the usual surveillance techniques (i.e., follow-up chest x-ray or computerized tomography), and institute therapy at an earlier time. As the authors point out in this preliminary study, neither the cost benefit nor the impact on survival can be commented upon. Moreover, for the reader who is introduced to the concept of screening for lung cancer for the first time, a little background information not only on autofluorescence tech-

nology, but also on how it fits into the big picture of lung cancer secondary prevention, should be provided.

The holy grail of lung cancer screening for the new millennium will be to define what *combination of screening components* will have the highest yield of discovery in a given population. It is well known that patients with radiographically occult preinvasive and microinvasive cancers that are found by cytologic examination of sputum have survival rates > 90% after surgical removal or local therapy, but they constitute less than 1% of newly diagnosed cases.³ Autofluorescence bronchoscopy is only one component of a surveillance program, and indeed is a controversial component. The cost of the unit, as well as its operator-dependent qualities, has led to limited dissemination of this technology, chiefly confined to academic centers. The study by Weigel et al.,¹ like the majority of other reports using Laser Induced Fluorescence Endoscopy (LIFE), has documented an increased sensitivity (400%) for detection of preneoplastic lesions compared with white light bronchoscopy.⁴ Unfortunately, however, we do not know the total number of lesions biopsied to get the yield of 4 in 26 patients, which would help define the specificity in the author's hands. This is crucial because there is indeed some controversy regarding the actual efficacy of the instrument. The results of those studies using LIFE with less than satisfactory results, however, can be explained by the use of the system in populations where the technology is not ideal, i.e., former smokers who ceased smoking many years before the LIFE examination and in populations with a high proportion of females (who have been found to have statistically less high-grade lesions than men). Moreover, the LIFE scope has less discriminatory power for metaplasia and mild dysplasia compared to more severe degrees of atypia.⁵ Close examination of the studies that do not endorse the use of LIFE reveals discordant reading of the pathological biopsies between pathologists, as well as a lesser number of

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biopsies per patient. Unfortunately, availability of the LIFE system in the future will depend on user demand as well as the resolution of international patent agreements.

On the whole, it is generally agreed by those who have the system that fluorescence technology is a major improvement in airway surveillance. What needs to be addressed however, is *exactly where does the actual visualization of the airway fit into the algorithm for patients at high risk for lung cancer*, which will include postresection patients as well as patients who eventually have less invasive screening measures that are at present under evaluation for efficacy? The approach by Wiegel et al.¹ for this initial effort was use of the scope. Probably more desirable, however, would be some sort of screening examination that points the thoracic surgeon or pulmonologist to perform LIFE exam selectively. Obviously, the most likely candidate for examination would be sputum from the candidate—not just any sputum, but probably sputum induced by hypertonic saline that would be satisfactory for examination and reflect the deeper recesses of the airway. The methods of sputum examination in the future will be complemented by staining techniques that may predict the development of malignancy despite normal morphologic criteria for the bronchial epithelial cells examined. The Lung Cancer Early Detection Working Group is evaluating whether an antibody to heterogeneous nuclear ribonucleoprotein (hnRNP) will improve the accuracy of preclinical lung cancer detection. HnRNP is overexpressed in exfoliated airway cells as a prelude to the development of lung cancer.² In a background of normal appearing airway cells, abnormal staining for hnRNP with the antibody can be performed by quantitative densitometry of immunostained slides. In separate, ongoing prospective studies, sputum has been collected annually from stage I resected non-small-cell lung cancer patients at high-risk of developing a second primary lung cancer and Yunnan tin miners at high-risk of primary lung cancer. These two prospective studies accurately predicted that 67% and 69% of those with hnRNP upregulation in their sputum would develop lung cancer in the first year of follow-up.² It can be hypothesized that the combination of overexpression of hnRNP with LIFE examination may allow one to discriminate that the individual is at high risk, and then, perhaps lead to earlier detection of the source of the hnRNP overexpression.

The real question, however, is whether there will be bias with this type of screening for the more central squamous cell carcinomas. In fact, in the postoperative situation where the original primary was an adenocarcinoma, should patients have LIFE bronchoscopy? Wiegel et al. do not really address this issue, nor do we really get

a feel for how often these high-risk patients should have surveillance. These issues are not only important for logistical as well as oncological reasons, but also need to be addressed to define the cost effectiveness of such a postoperative surveillance scheme. For the peripheral adenocarcinomas, computerized tomography still remains the best way to follow patients postoperatively, especially those cases of multicentric bronchoalveolar cancer. As recently reported by Henschke, low dose helical computerized tomography of the chest is being investigated as a screening tool for the high risk smoker, and in selected institutions, is able to detect early lung cancers (at a rate of 2% in 10 pack per year smokers older than 60 years).⁶ Moreover, specificity for defining which lesions to biopsy is very acceptable.

The article by Weigel et al. also highlights novel therapeutic options in this population of high-risk patients with documented preneoplasia or invasive cancer. Endobronchial photodynamic therapy (PDT) has been approved for use in the United States for cases of microinvasive lung cancer where standard options for therapy are not indicated. Japanese investigators, as well as those at Mayo Clinic, have documented an 84% histologic complete response rate for these early lesions using PDT.^{7,8} For patients with a more diffuse field effect with preneoplasia only, inhalational technologies with chemopreventive agents are on the horizon.

Our thinking about what to do about the lung cancer epidemic is greatly enhanced by forward thinking contributions that combine appropriate at-risk populations with technology as described in the Weigel et al. report. What we have to learn, however, is how all the parts of the lung cancer screening puzzle (including exactly whom to screen) can complement each other for the greatest yield and with the least cost to the patient, both physically and monetarily.

REFERENCES

1. Weigel TL, Yousem S, Dacic S, Kosco PJ, Siegfried J, Luketich JD. Fluorescence bronchoscopic surveillance after curative surgical resection for non-small-cell lung cancer. *Ann Surg Oncol* 2000;7:176–80.
2. Tockman MS, Mulshine JL, Piantadosi S, et al. Prospective detection of preclinical lung cancer: results from two studies of heterogeneous nuclear ribonucleoprotein A2/B1 overexpression. *Clin Cancer Res* 1997;3:2237–46.
3. Bechtel JJ, Kelley WR, Petty TL, Patz DS, Saccomanno G. Outcome of 51 patients with roentgenographically occult lung cancer detected by sputum cytologic testing: a community hospital program [see comments] [published erratum appears in *Arch Intern Med* 1994;154:1582]. *Arch Intern Med* 1994;154:975–80.
4. Lam S, Kennedy T, Unger M, et al. Localization of bronchial

- intraepithelial neoplastic lesions by fluorescence bronchoscopy. *Chest* 1998;113:696–702.
5. Kurie JM, Lee JS, Morice RC, et al. Autofluorescence bronchoscopy in the detection of squamous metaplasia and dysplasia in current and former smokers [see comments]. *J Natl Cancer Inst* 1998;90:991–5.
 6. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening [In Process Citation]. *Lancet* 1999;354:99–105.
 7. Kato H. Photodynamic therapy for lung cancer—a review of 19 years' experience. *J Photochem Photobiol B* 1998;42:96–9.
 8. Cortese DA, Edell ES, Kinsey JH. Photodynamic therapy for early stage squamous cell carcinoma of the lung [see comments]. *Mayo Clin Proc* 1997;72:595–602.