Bimodality surveillance of high-risk patients for lung cancer

Gordon H Downie

Are new diagnostic strategies providing answers?

Thoracic oncology providers confronted with the task of diagnosing and following patients at risk for cancer of the lung face a number of major dilemmas, some of which directly affect the ability to diagnose. First, the majority of patients with lung cancer are diagnosed at a late stage and <15% survive 5 years, so a degree of nihilism is present in patients, providers and policy makers. Second, risk paradigms are changing, from smoking only to occupational, environmental or home carcinogens to the risk associated with premalignant airway changes. Third, advances in early diagnostic options have the potential to discover lung carcinoma while still in a pre-invasive, minimally invasive stage or as small peripheral nodules. These points, taken in conjunction with the initial clinical results of the ELCAP study suggesting that cure is possible, raise the need to examine early diagnostic strategies critically.

In this issue of Thorax (see page 335) Loewen et al report their initial clinical findings in bimodality surveillance of high risk for lung cancer populations using low dose spiral CT scanning (SCT) and autofluorescence bronchoscopy (AFB). They examined two null hypotheses: (1) AFB was equivalent to conventional sputum cytology (CSC) for the detection of pre-malignant lesions and (2) AFB and SCT would be equivalent to SCT alone for the detection of lung cancer in high-risk patients. The authors conclude that AFB is significantly superior to CSC for the detection of airway pre-malignancy in this cohort of high-risk patients and, in fact, argue that, as a surveillance tool, AFB exceeds the cancer detection rate of colonoscopy in patients with positive fecal occult blood. However, the authors were not able to demonstrate a significant superiority of bimodality surveillance with both AFB and SCT over SCT alone, but question whether a larger sample size would have found bimodality significantly better.

Beyond their null hypotheses, the article raises several points that are healthy components of any discussion of the future approach to patients at high risk of lung cancer. These include:

1. Premalignant changes are common (66% of the 169 patients receiving all components of surveillance) in this high-risk cohort.
2. AFB is reasonable in patients with atypia in CSC; however, CSC was inadequate for detection of pre-malignant cytology when frank carcinoma was not present.
3. Screening and surveillance are very different and surveillance of a select population may be a superior strategy in lung cancer management.
4. Regardless of the histology of the lung cancers detected in this study (>50% were adenocarcinoma), the majority of patients had central airway pre-malignant transformation.
5. Spiral CT scan protocols are not adequate at this time for detecting central airway disease by themselves.
6. Central airway pre-malignant lesions appear to be predictive of the presence of peripheral adenocarcinoma identified by SCT.

Several of these observations or conclusions have not been supported by other articles in the field. Haubinger et al performed a prospective, randomised, multicentre trial comparing white light bronchoscopy (WLB) with or without AFB. The high-risk group defined by chronic obstructive pulmonary disease plus occupational exposure failed to demonstrate severe dysplasia or carcinoma-in-situ (CIS), although it was unclear to what extent metaplasia or mild dysplasia were seen in this cohort. Swensen et al and Bechtel et al in two separate studies used bimodality testing using CSC as one portion of their testing and suggested a more significant contribution for CSC in lung cancer detection than was suggested by Loewen et al. However, because of different study designs including inclusion criteria, biopsy and statistical methods and patholoy review variations, it may be nearly impossible to compare findings from one study to another.

Although Loewen et al raise several compelling clinical questions in their paper, the most pivotal may well be management issues of airway cellular transformation including dysplasia and CIS. The diagnosis, progression and treatment of dysplasia and CIS, especially in high-risk populations, are demanding more clinical attention to determine surveillance strategies and may affect overall outcomes of lung cancer in the near future. Intense interest in this topic was indicated when most sessions at the 11th World Congress on Lung Cancer in
Barcelona (IASLC) included several abstracts directly or indirectly discussing research or clinical aspects of airway cellular transformation. These presentations ranged from the basic science of biomarkers for cellular transformation to endoscopic detection and surveillance. In clinical thoracic oncology, a discussion of airway transformation usually revolves around three basic questions:

1. What is the natural history of mucosal transformations in the airway?
2. How much cellular transformation needs to be present to warrant treatment: moderate or severe dysplasia, CIS?
3. What is the best approach for detection: routine screening, high risk surveillance or early diagnosis strategies?

Current attempts to address each of these questions are mostly in the form of expert opinion, as seen in a recent review of CIS treatments published by Mathur et al. Transformation within the central airway remains a pathological diagnosis with obvious grey areas overlapping dysplasia, CIS and frank early carcinoma and, as mentioned earlier, interobserver variability between pathologists on the same specimens is not uncommon. Clinically, there are two important pre-neoplastic non-small cell presentations within the lung: central airway CIS as a pre-neoplasm of squamous cell carcinoma and peripheral lung atypical adenomatous hyperplasia (AAH) as a pre-neoplasm of bronchoalveolar cell carcinoma and adenocarcinoma. By definition, CIS is radiographically occult, has a surface area of less than 2 cm with visible margins, and has no invasion beyond the bronchial cartilage. The prevalence of CIS might be as high as 20–30% based on the epidemiology of non-small cell lung cancer, but clinical screening or surveillance studies have not been done on the general population and the declining use of autopsies has further limited data collection to support this claim.

The issue of whether dysplasia or CIS is a pre-malignant state or an extreme cellular reaction to injury was explored by George et al. who assessed the microvessel count and suggested that, based on this count, a pre-malignant state is not reached until CIS develops. If it is a pre-malignant state, then the inability to accurately and completely describe the natural history of CIS undermines the ability to truly assess protocols for CIS screening, surveillance and treatment. However, several groups have recently reported data suggesting that pre-malignant cellular transformation does progress to invasive carcinoma, although the relative numbers that progress to frank disease are small and variable. George et al. have recently reported their experience with a high-risk cohort followed prospectively for several years. They report a cumulative risk of developing lung cancer from high grade lesions in their cohort of 33% and 54% at 1 and 2 years.

Pasic et al. defined “early stage” lung cancer as stage I (T1N0, T2N0) and stage II (T1N1, T2N1) and, as such, dysplasia and CIS (T0N0M0 or stage 0) do not fall within this definition. Other major epithelial-based tumours such as gastrointestinal and breast cancers rely on screening or surveillance methodology to identify their stage 0 cases and to optimise patient outcomes. CT scanning, positron emission tomography (PET), sputum analysis and bronchoscopy are all used to diagnose and stage early lung cancer, although PET and CT scanning have no established role as a sole modality in the identification of stage 0. Since CIS is radiographically occult, diagnosis must come from screening populations at risk for neoplastic transformation, performing surveillance on high-risk populations or early diagnosis in patients with suspicious clinical presentations.

Detecting radiographically occult disease relies in part on direct visualisation of the abnormal bronchial mucosa, but the ability to use direct visualisation optimally also depends on why and where CIS develops. Insight into growth patterns and how CIS may progress are important parameters for visualisation strategies. However, despite the ability of EBUS to accurately assess the critical point of irreversible transformation and neoplastic penetration of the bronchial cartilage, the addition of endobronchial ultrasound (EBUS) might improve the specificity of AFB by distinguishing between inflammation and neoplastic penetration of the mucosa. Miyazaki et al. demonstrated the ability of EBUS to accurately assess tumour depth.

In addition to optical technologies, diagnosis of airway CIS will include the molecular genetic changes of the progression from metaplasia to invasive carcinoma and the protein products produced by those changes. Detection of that critical point of irreversible transformation to cancer will inevitably include biomarkers and necessitate multimodality strategies.

The paper by Loewen et al. suffers as a stand alone protocol, limiting cohort size and not allowing comparisons to the other clinical trials looking at surveillance in high-risk populations for lung cancer. It does energise this topic by supporting multimodality approaches and defining a population that may benefit more readily from surveillance strategies. It is obvious that thoracic oncology providers have a forest of more questions than answers for managing patients at risk for lung cancer and, although these issues are daunting, Loewen et al. have provided us with one potential path through the woods.
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