In Search of the Holy Grail
Lung Cancer Biomarkers

A central paradigm in the care of patients with lung cancer is to offer surgery with curative intent (and hopefully outcome) to as many patients as possible while performing as few unnecessary surgeries as possible. “Unnecessary” surgery must be defined first as surgery in patients with advanced stage disease, in whom (at this time) surgery offers no benefit over chemoradiation therapy. Exactly who meets this definition may be in flux, as trials that employ neoadjuvant chemotherapy may change the answer to the question of “who does (or does not) benefit from lung cancer surgery?” In the current setting, patients whose lung cancer is clinical stage IIIa or worse do not gain a significant benefit from surgical resection. The initial evaluation of patients with suspected lung cancer has therefore focused on determining, with the least invasive approach possible, those whose disease is N2 or worse.

Biomarkers, easily detectable serum markers, are one of the highly prized targets of cancer research. Several facts about lung cancer make it unique among the common solid malignancies. Relative to other common malignancies, there is an especially high risk of morbidity from lung cancer surgery because of the population at risk for lung cancer, and the fact that it involves removal of a vital organ. Also, surgery for more advanced stage disease (most patients with IIIa and worse) offers no benefit over nonsurgical therapy. Because of these and other facts, a biomarker in lung cancer is needed not only for screening, but also as an aid in diagnosis, staging, and as a means of determining response to therapy.

Features of an attractive biomarker for lung cancer would include one or more of the following: (1) in screening, either as a primary tool, or to discriminate CT screened patients with cancer from those who do not have cancer, thus eliminating the need for invasive procedures in patients with benign disease; (2) to determine those patients with known or suspected lung cancer who are unlikely to benefit from surgery (those with bulky mediastinal lymph node enlargement due to N2 nodal involvement with cancer); (3) to signify response to therapy or lack thereof; and (4) to increase the accuracy of existing tests for diagnosis, staging, and treatment response, much like the use of the d-dimer assay in suspected venous thromboembolic disease.

The report by Tamura and colleagues in this issue (see page 342) examines the accuracy of serum levels of vascular endothelial cell growth factor C (VEGF-C) in patients with lung cancer for predicting the presence or absence of lymph node metastases preoperatively. VEGF-C is a specific promoter of the growth of lymphatic vessels. Investigators have shown that expression of VEGF-C (detected by immunohistochemistry) is associated with a worse prognosis in patients with lung cancer.

The paradigm of lymphatic metastases in cancer has included the notion that the lymphatic vascular system was a passive participant in the metastatic process. However, findings suggest that this is not the case. Data in support of this include findings that tumors elaborate substances that activate growth of lymphatic vessels, and the discovery by several groups that tumor cells preferentially home to metastatic sites (including lymph nodes) as a result of constitutive chemokine expression at those sites and expression of their receptors on tumor cells. Tamura and associates reasoned they would be able to determine those patients with locally advanced disease by measuring serum levels of a factor involved in promoting lymphatic metastases, namely VEGF-C. They detected elevated levels of VEGF-C in the serum of patients with lymphatic metastases (pathologic N1 and N2 disease), as compared to patients with pathologic N0 disease. Using a retrospectively determined cutoff value (as measured with a commercially available enzyme-linked immunosorbent assay), serum VEGF-C levels performed slightly better than standard CT criteria in detecting the presence of locally advanced disease.

This provocative study by this group falls short of the goals stated above for several reasons. First, there was a very large range of serum levels of VEGF-C in patients with lung cancer, and the ranges of those with and without nodal metastases overlapped to a great extent. More importantly, serum
levels of VEGF-C were not significantly different between the group of patients with N1 nodal metastases (in whom surgery is still beneficial), and those with N2 nodal metastases (in whom surgery has not demonstrated significant benefit). The most valuable finding of Tamura and coworkers was that classifying patients into quartiles based on serum levels of VEGF-C increased the accuracy of CT criteria alone in determining the presence or absence of lymph node metastases. However, the authors did not examine the ability of this approach to distinguish N1 and N2 lymph node involvement. Additionally, since these results are based on a retrospectively determined cutoff of VEGF-C levels, this must be viewed as a hypothesis-generating study. Prospective validation of these findings is necessary in a broader range of patients. Finally, given the increasing use of fluorodeoxyglucose (FDG) positron emission tomography (PET) in the preoperative evaluation of patients with suspected lung cancer, it is disappointing that this study did not address whether serum measurements of VEGF-C could add to the accuracy of PET scanning. It is doubtful that VEGF-C levels could significantly improve on the sensitivity of PET scanning (97%). However, it would be intriguing to determine the ability of serum VEGF-C levels, or other biomarkers, to improve on the specificity of FDG-PET (approximately 78%).

In pointing out these shortcomings, it is important to consider that any successful approach to this problem may eventually involve multiple markers that, like VEGF-C, reflect a known feature of the tumor biology (angiogenesis, apoptotic resistance, unrestricted growth, stroma formation). In addition to markers of activated lymphatic endothelium, other rational biomarkers may reflect “tumor-specific” antigens, angiogenic factors, growth factors, or markers of stromal activation. Such a multivariate approach may provide important information in the management of patients that is not possible with a single variable. Tamura and colleagues are to be congratulated for bringing some focus to the search for novel lung cancer biomarkers, but much work remains to be done.

References


Is Lung Cancer in the Nonsmoker a Different Disease?

Cigarette smoking is without any doubt the leading cause of preventable death in the United States. The health-related economic loss associated with cigarette smoking is approximately $157 billion, and 440,000 premature deaths occur annually only in this country. Worldwide, 10 million people will die annually from tobacco-attributable diseases by 2030. Eighty percent of the particle products of Nicotiana tabacum liberated through a lit cigarette deposit in the tracheobronchial tree. At least 55 of the > 2,000 chemical compounds identified in the tobacco leaf are proven carcinogens. The epidemiologic evidence accumulated over almost 6 decades since the reports of Doll and Hill prove an association between smoking and lung cancer. Tobacco smoke has a causal role as well in the tragic worldwide epidemic of lung cancer. Tobacco products not only cause harm to the users, but nonusers are affected as well (environmental tobacco exposure).

Tobacco smoking exposure is associated with all of the histologic subtypes of lung cancer. Patients who