Whither Screening for Lung Cancer?

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Carcinoma of the lung remains a devastating clinical problem (1). Whether one considers SCLC or non-SCLC, the outlook for patients with locally advanced or metastatic disease remains grim. The survival of patients with truly localized disease, however, is reasonably good, with up to 80% of surgically staged, T1N0 non-SCLC patients cured by surgery alone (2-4). The problem, of course, is that the vast majority of patients present with locally extensive or widespread disease.

The attempts to reverse the pattern to one in which most patients present with localized, and potentially curable, lung cancer have been frustrating. One approach, through aggressive screening of high-risk patients, has been only marginally successful (5). A trend was seen toward identification of earlier cases, but there was no impact on the overall survival of the screened groups. Recognition of these results led to abandonment of the American Cancer Society's recommendation for annual chest x-rays in asymptomatic patients, even smokers.

A second approach, outlined in the article by Gail et al. (6) in this issue, is the identification of serum markers that, alone or combined, can distinguish cancer from benign illness and localized from advanced cancer. Expanding upon their previous report (7), Gail et al. use a panel of sera from patients with localized lung cancer and benign lung diseases and sera from normal volunteers to develop a marker or group of markers for discriminatory purposes. The preliminary panel is then tested in a second group of sera to confirm its validity. The approach is not new (nor are the results), but the techniques used are statistically state of the art. Despite this, the best we can hope for is that 24% of patients predicted to have cancer would indeed not have it and that 22% of "negative" patients would indeed have early cancer. Gail et al. suggest that because of the high false-negative rate, thorough workup would still be required for marker-negative patients.

One can agree or disagree with this approach based on these outcomes, but the underlined clinical assumption is more important. The setting proposed by Gail et al. is a clinic in which 30% of the patients have lung cancer, an extraordinary figure. When the percentage drops to 10%, the positive predictive value becomes 45% and the negative predictive value rises to 93%. If the true incidence of lung cancer in this clinic were 1% (now beginning to approximate what one might actually see in the real world), the positive predictive value would be only 7% and the negative predictive value, 99%. These predictors might be useful if we could truly exclude patients with negative results, but the number of patients who had workup for a positive result would be prohibitive.

These studies are a part of our analysis of the problem only because we do not sufficiently understand the basic biology of lung cancer, despite enormous strides in this area (8,9). The present analysis is like playing solitaire with a deck of 37 cards. While we might be able to predict the result of a given hand after careful pattern analysis, it would be helpful to know that the overall total was supposed to be 52 cards and that there were supposed to be face cards, none of which happened to be in the original 37 cards.

Although our understanding of the biology of lung cancer has allowed us to see that there are indeed face cards, we have no idea if we have identified all of them. Gail and his colleagues conclude that exhaustive analysis of many "fair" markers is not likely to perform as well as combinations of

\textbf{ABBREVIATION USED: SCLC = small cell anaplastic lung cancer.}
only two or three “excellent” markers. How right they are! When we finally leave the era of nonspecific markers, we may indeed be able to predict the presence or absence of lung cancer. Until then, a statistical tour de force such as presented here will continue to be of marginal impact.

References