Commentary (Ganti et al): Current Issues in Lung Cancer Screening

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The role of screening in order to detect lung cancer at an earlier stage has been widely debated for the past 4 decades. In this review, Dr. Mulshine focuses on the current issues in lung cancer screening in light of the findings of the International Early Lung Cancer Action Project (I-ELCAP). As the article mentions, the diagnosis of lung cancer is often made at a stage when the disease is no longer amenable to cure. This is probably the most important cause for the dismal outcomes of patients with lung cancer overall.

Lung cancer satisfies the criteria proposed by Wilson[1] for a disease amenable to screening. The major problem with screening, however, has been the lack of availability of an appropriate diagnostic technique that would detect lung cancer at an early stage. Large randomized controlled trials in the 1960s and the 1970s demonstrated that chest x-rays and sputum cytology were too insensitive to make any impact on lung cancer-related mortality. Rapid progress in the technology for computerized tomographic (CT) scanning makes this modality very attractive for lung cancer screening.

Low-Dose CT Scanning

Multiple nonrandomized studies performed in different countries have demonstrated the utility of detecting lung cancer at an early stage using low-dose CT scanning.[2-4] This approach has detected lung cancer at a preinvasive stage that was not previously apparent clinically, eg, atypical adenomatous hyperplasia, which may be a precursor of invasive adenocarcinoma.[5] However, as mentioned by Dr. Mulshine, these studies have generated a major controversy since they did not follow the traditional concept of a screening study, ie, a randomized clinical trial with reduction in lung cancer-related mortality as an end point. In this age of rapidly advancing technology, it is unlikely that a randomized study sufficiently powered to answer this question can be completed before advances in the speed and quality of CT imaging render it obsolete.

Although an argument can be made that the data from the Cornell study and other similar studies conducted in Japan, the Mayo Clinic, and Italy are so impressive that screening for lung cancer with low-dose CT scans will lead to an improvement in lung cancer-related mortality, they were all observational studies using volunteer cohorts; the findings may represent the impact of bias rather than a true effect.

Another argument put forth by the critics of this approach is the possibility of overdiagnosis of lung cancer, because although over 80% of the screen-detected tumors were stage I disease, there was no stage shift. A true stage shift is defined as an increase in early-stage disease associated with a corresponding decrease in late-stage disease. Comparison of incidence of advanced-stage disease in the low-dose CT studies with the results of chest radiographic trials shows no differences in the two approaches (~3/1,000 patients). Also, there are no mature mortality data using low-dose CT scans for lung cancer screening.[6-8] However, autopsy studies suggest that overdiagnosis may not be a significant problem in lung cancer, as in one autopsy series, undiagnosed lung cancer was found only in 0.8% of all autopsies.[9]

In addition, Bianchi et al compared the gene expression profile of spiral CT-detected lung carcinomas with a matched case-control population of patients presenting with symptomatic lung cancer and found that all of the tumors detected by screening were histologically malignant according to the...
World Health Organization classification and had a gene expression pattern similar to that of symptomatic lung carcinomas.[10]

**Screening Costs**

An issue with any screening study is the cost of screening a large group of asymptomatic individuals in order to detect a few patients with early malignancy. As discussed by Dr. Mulshine in his article, there have been divergent findings on the cost-efficiency of screening. One of the studies quoted in the current manuscript, the study by Mahadevia et al, used a computer-simulated model of a large population that underwent screening and treatment for lung cancer based on the Mayo Clinic experience and estimated the cost of screening to be $116,300 per quality-adjusted lifeyear under favorable assumptions.[11]

However, other analyses based on the ELCAP and the Italian studies have come to much different conclusions. Wisnivesky and associates analyzed the ELCAP data and concluded that incremental cost-effectiveness ratio of a single baseline low-dose CT scan was $2,500 US per year of life saved under actual favorable conditions.[12] Similarly, based on the findings of the Milan study, Pastorino et al suggested that the findings of Mahadevia were too pessimistic.[3]

As aptly suggested by Dr. Mulshine, the decision whether or not to screen someone for lung cancer using CT scans should be based on a detailed discussion with the patient describing the current recommendations and discussing the available data on low-dose CT scanning, taking into consideration that the technology that was associated with the studies may be outdated at the time of the actual discussion.

**Genetic and Proteomic Techniques**

One aspect of lung cancer screening that Dr. Mulshine did not address in this article is that the emerging field of genetic and proteomic techniques will have an impact on the early detection of lung cancer. Although there are no concrete data from this field, these approaches have the potential to be used as screening tools for lung cancer. The transformation of normal bronchial epithelium to invasive cancer is associated with changes in the genetic makeup of cells that may be evident far before the patient becomes symptomatic from the actual tumor. Epigenetic changes, particularly hypermethylation of DNA, seem promising in the search for biomarkers for the early detection and therapy of lung cancer.[13]

**Conclusion**

Survival in patients with lung cancer will be improved when small, early-stage tumors are detected. The need of the hour is to find a cost-effective detection technique to target the entire population at risk so as to make screening feasible.

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**References:**

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