Prevention and Early Diagnosis of Lung Cancer

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Sensitivity and Specificity of Chest X-Ray Screening for Lung Cancer

Review Article

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BACKGROUND. The incidence and mortality rates of lung carcinoma have been increasing during the last years. Despite this, medical public policy holds that chest X-ray screening is ineffective in the early detection of lung carcinoma.

METHODS. The authors reviewed the most important studies published in the literature regarding the role of chest X-ray screening in the early diagnosis of lung carcinoma in a high risk population. None of the four randomized, controlled trials on lung carcinoma screening conducted in male cigarette smokers demonstrated a reduction in the mortality rate. Accordingly, no organization that formulates screening policy advocates any specific early detection strategies for lung carcinoma.

RESULTS. A careful analysis of randomized, controlled trials showed that there was no improvement in the mortality rate in the screened populations, but there is considerable evidence that chest X-ray screening is associated with earlier detection and improved survival.

CONCLUSIONS. In the authors' opinion, the considerable improvements in distribution by disease stage, tumor resectability, and patient survival in the screened groups demonstrate the effectiveness of chest X-ray screening in the early detection of lung carcinoma. The authors conclude that radiographic screening is the only valid method of secondary prevention in cigarette smokers. ***Cancer*** **2000;89: 2453–6.** *© 2000 American Cancer Society.*

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Chest X-ray (CXR) screening for lung carcinoma (radiography performed to detect presymptomatic disease) is the most important tool for secondary prevention. There is widespread acceptance that screening for the early detection of lung carcinoma is not indicated, because no randomized trials have demonstrated a reduction in mortality rate as a result of screening.[1–3] This consideration, however, is now coming under increased scrutiny. Recently Strauss et al.,[4] after reviewing the data of some of the most important randomized, controlled trials,[5–11] stated that the effectiveness of CXR screening was underestimated in its ability to reduce the risk of death from lung carcinoma.

The major roadblock in the use of X-ray screening has been that it has not demonstrated any significant reduction in the mortality rate. In fact, when Strauss et al.[4] reviewed the studies, he noted striking improvements in distribution by disease stage, tumor resectability, and patient survival, but the only outcome parameter that did not show improvement was disease specific mortality.

It has long been accepted that "the only truly valid outcome

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measure for assessment of the results of a screening program is mortality from the disease in the total population screened in comparison with the mortality that would be expected in the same population without screening."[12] Screening trials that use survival as an end point are subject to well known biases, which include lead-time bias, length bias, and overdiagnosis bias, whereas mortality is not subjected to these biases. In conclusion, mortality and survival are not synonymous.

As radiologists, we are certainly not in a position to resolve the problem of mortality and survival or to discuss lead-time bias, length bias, or overdiagnosis bias. However, many trials (e.g., the Mayo Lung Project[3] and the Czechoslovakian Project[10]) have demonstrated a survival advantage in periodic CXR screening of male smokers age $>$ 45 years.

Four trials[9–11,13–15] that included a group of 79,045 men who were screened and a control group of 135,426 men demonstrated the following remarkable findings: an increased incidence of lung carcinoma in the screened population, an increased resection rate, and an improvement of survival in the screened population. There was a 35% increase in the incidence of lung carcinoma found in the screened group. The survival rate in the control group was 15.6% at 5 years compared with a survival rate of 29.6% in the screened group. However, all four trials failed to demonstrate a reduction in mortality.

Conversely, existing data unequivocally demonstrate that periodic CXR screening favorably influences distribution by disease stage, tumor resectability, patient survival, and fatality. Unfortunately, because early detection efforts are not practiced widely, most patients with lung carcinoma have advanced stage disease at the time of diagnosis. Such advanced disease almost invariably is fatal.

It has been demonstrated consistently that screening increases the proportion of patients who are diagnosed with Stage I diseaserelative to higher stages.[16] Within the context of early detection trials, the incidence of Stage I nonsmall cell lung carcinoma is reported to be 42–50%.[17,18] In contrast, data from the National Cancer Data Base suggest that 16–18% of the general population of patients with lung carcinoma have Stage I disease.[19]

Consequently, early detection through screening is the only method that is likely to decrease the survival rate in patients with lung carcinoma, because, until there is primary prevention in the form of smoking cessation, the control of lung carcinoma will depend on treatment, which, currently, is effective only in patients with early stage (localized) disease.

Flehinger et al.,[20] in their review of the Hopkins-Mayo-Memorial data, found a 5-year survival rate of 70% in surgically treated patients with Stage I disease compared with a 5-year survival rate of 10% in patients with Stage I disease who refused surgery ($P < 0.001$). The same authors, in a subsequent article,[21] described a simulation study that was designed to estimate (using the Mayo data) the parameters in a mathematical model of the natural history of lung carcinoma and to estimate the potential benefit associated with periodic screening of high risk individuals starting at age 45 years. They concluded that, "vastly improved methods of detection and treatment are required before mortality from lung carcinoma can be reduced by more than 50%."

It is important to deal with the radiologic problems of detection and the interpretation of CXR findings. Observer error is the major issue in detecting lung carcinoma.[22] The CXR must be optimized, impeccable from the technical point of view, and read accurately. Unfortunately, the early detection and interpretation of lung carcinoma using CXR is achieved in ≈30% of cases. A very important fact is that, in 90% of peripheral neoplasms and in 65–70% of central neoplasms, there was radiographic evidence many months before the malignancies actually were diagnosed.[1]

In retrospect, Muhn et al.[1] were very self-critical in the assessment of their results. Although 90% of the malignancies were present on previous radiographs, many of the early tumors were extremely small and vague. It is doubtful that many of these early tumors could have been diagnosed as malignancies prospectively. Still, the study by Muhn et al. does point out the limitation of plain film radiology in detecting early lung carcinoma.

Lovisatti et al.[23] analyzed 100 cases of lung carcinoma in which the correct radiologic diagnosis was made at variable time intervals from the initial failure to make a diagnosis. In 63% of those cases, the lesions were peripheral, and the average diagnostic delay was 8.1 months; in the remaining 37% of cases, the lesions were central, and the diagnostic delay was notably shorter (4.3 months). The failure to recognize a tumor (false negative) was the most frequent cause of error in peripheral and central malignancies. Errors of underdiagnosis were present in 12% of peripheral lesions and 8% of central lesions.

The diagnostic failure to detection of lung carcinoma early brings up two important points: 1) Lung carcinomas often grow slowly enough to be identified using X-rays when they are still localized and asymptomatic; and 2) we presently do not know enough about the psychophysical perceptive mechanism that may help us to make fewer errors in identifying early

malignancies. Brogdon et al.[24] observed that a radiologist working under standard condition has a probability of ≈50% of not identifying a pulmonary nodule of measuring ≤5 mm. The average greatest dimension of the neoplasms in patients who undergo surgery is ≈25 mm: It is true that many patients have not had any X-rays at all, but it also is true that some patients had X-rays in which the neoplasm was not diagnosed. Moreover, 3–5% of lung lesions are identifiable only with lateral X-rays, and 5–17% can be observed better laterally than frontally.

The most frequent cause of detection failure is the impossibility of comparing the X-rays with previous films, if they exist, to evaluate unclear zones that are not very opaque and may have scarcely defined margins or may be hidden totally by superimposition of other structures, particularly bones. The failure to identify lesions occurs most frequently on frontal X-rays of the upper lobes, particularly the right lobe in the paramediastinal region; in lateral projections, particularly of the apical lobes; and also when the lesions are covered by the spine. There are numerous causes of radiologic errors: Error analysis has shown that false negative results are about three times as common as false positive results. The false negative rate for the early detection of lung carcinoma may be reduced without an increase in the false positive rate by double reading.[1,25]

Environmental factors, such as the quantity of light and distraction, have a negative effect on the radiologist's performance. The human decision-making process plays a role in the failure to detect subtle lung neoplasms. Studies of radiologist's eye movements have shown that "missed" nodules often are scanned adequately by the fovea: This suggests that there is an active, unconscious mental process not to perceive a nodule. This limitation of nodule perception may not be correctable.[26]

The level of performance that is expected by patients and judges exceeds our capacity and is unattainable. This is the root of the problem that exists in medical practice. The failure to detect early lung carcinoma on CXR is well within an accepted, normal standard of care and does not constitute negligence or malpractice.[1,27] Moreover, no significant differences were found between conventional radiography, Amber-system radiography, and computer radiography in the number of detected nodules.[28]

The most important study regarding the sensitivity, specificity, and predictive value of CXR in the early detection of lung carcinoma was conducted by the National Cancer Institute Cooperative Early Lung Cancer Group in 1984.[29] The National Cancer Institute trials demonstrated that the sensitivity of CXR is 54% when only "suspicious" CXRs are coded as positive, with a specificity of 99%. When "indeterminate" CXRs are considered positive, the sensitivity of CXR increases to 84" with a specificity of 90". However, false negative CXR results continue to be a significant problem.

We conclude with the hope that, through an increased understanding of the problems that are discussed herein, radiologists will avoid some of the pitfalls that may be encountered initially in detecting and diagnosing lung carcinoma. Plain film itself is limited, the image of the lung is complex, and the human visual system and decision-making process contain potential pitfalls. Despite all of this, periodic screening (annual or semiannual) in the high risk lung carcinoma population with CXR improves the distribution of these patients by disease stage, tumor resectability, and patient survival.

The ability of computer tomography (CT) to visualize small pulmonary nodules may make it a possible substitute for chest radiography as the primary mass screening method. In fact, whereas, in the early 1980s, 55–60% of suspicious CXRs reflected malignancy, in the early 1990s, after the advent of CT, >90% were found to be malignant. Low dose spiral CT is superior to chest radiography in the screening and detection of peripheral lung carcinoma in high risk patients. Additional large scale studies are warranted, however, to clarify the efficacy and cost effectiveness of low dose spiral CT in a randomized, controlled population.

Davis[30] concluded his editorial: "Is it worth screening individuals who smoke with chest roentgenograms? If seen in terms of survival, the answer is yes. If seen in terms of mortality, the answer is no. The number of individuals who may benefit is not insignificant, but the cost of screening such a large population is quite high."

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