CT Screening for Lung Cancer: Are We Ready for Wide-Scale Application?

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Lung cancer remains one of the most deadly of all human cancers despite decades of research. Although the 5-year survival rate nearly tripled from ~5% to ~15% in the last 25 years, and although adjuvant chemotherapy may yet inch up these statistics slightly to those predicted in the 2007 estimated cancer statistics (1), the sheer number of cases and the growing lung cancer problem worldwide dictate an urgent need to develop better means of both primary and secondary prevention. In the U.S. alone, >210,000 new cases are estimated for 2007 (1), and the number is in excess of 1.2 million worldwide (2). Yet, despite these data, tobacco products in general, and cigarettes specifically, remain very cheap with respect to the health consequences they cause. These products are protected by governmental agencies or even subsidized without any cognizance of the real financial burden that this imposes on society or taxpayers. Yet another concern is a societal sense that smokers brought this problem on themselves, and until now, a strong advocacy has not been heard.

One of the many possible reasons why lung cancer remains so deadly is the advanced stage of presentation in the vast majority of cases. Early stage disease, i.e., stage IA accounts for only ~5% of all cases, whereas stages III and IV represent >75% of all cases at presentation. Given that the 5-year survival of lung cancer ranges from 50% to 80% for surgically resected stage IA, and decreases dramatically as the stage progresses, the dismal overall 5-year statistics seems quite understandable. The most simple and logical conclusion one might derive from these data is that earlier detection should improve survival, and this is likely if lung cancer were biologically a homogeneously behaving disease. After all, early detection of cervical cancer resulted in a major reduction (~90%) in cervical cancer death. In addition, albeit less dramatic, early detection of breast cancer resulted in an ~30% reduction in risk of breast cancer death. Can the same principle be applied to lung cancer, and if so, what are the data thus far? This question is particularly germane in light of the recent article by the International Early Lung Cancer Action Program Investigators (3).

The Early Lung Cancer Screening Trials

The first attempts at lung cancer screening involved chest X-rays. Scamman (4) reported on the follow-up of a large group of individuals living in Boston who were screened for lung cancer by X-ray, and despite >500,000 screens, only 43 primary lung cancers were identified and survival statistics were not well defined. Subsequently, The Philadelphia Pulmonary Neoplasm Research Study (5) prospectively screened >6,000 men for lung cancer. Although the study led to very useful information about presenting X-ray features and risk factors, there was no evidence for survival efficacy. In fact, this trial suggests that by the time lesions were visible on chest X-ray, most cases were already inoperable. The authors stated, "...despite immediate emergency referral of persons whose photofluorograms were read 'suspect neoplasms' at two official Philadelphia chest X-ray units, resection could be done in only 30%..."

The next screening trial, The Early Lung Cancer Detection Project, was a set of randomized trials conducted at Memorial Sloan Kettering, Johns Hopkins, and the Mayo Clinic (6, 7). These trials compared usual care with chest X-ray or chest X-ray plus or minus sputum induction plus selective bronchoscopy. Although the Mayo Lung Project found more cases of lung cancer in the screened group, none of these three trials found an overall survival advantage for the screened group, raising the possibility that the screening found indolent cases. In a follow-up of the Mayo Clinic data, Marcus et al. (8) concluded that: "the persistence of excess cases in the intervention arm after 16 additional years provides continued support for overdiagnosis in lung cancer screening." The sputa collected from that trial are still under investigation to determine if some predictive biomarkers might be found, but the approach of X-rays and sputum induction was abandoned as a screening approach. Although newer techniques are under development to allow a better recognition of nodules on plain chest X-rays, their utility must ultimately rest on the demonstration that finding earlier nodules improves overall survival.

On Finding an Effective Screening Test

Given the potential confusion of various tests and claims of screening efficacy, what criteria best define the effectiveness of a given screening technique? First, the proposed test should have an acceptable level of specificity and sensitivity. Both must be satisfied to avoid false negatives (false reassurance) as well as false positives, which can lead to excessive invasive procedures. Second, the test must be widely available to permit population-based screening. Third, the test must be affordable to individuals or populations. Finally, the test must improve overall survival in the screened group (compared with a control group). This latter criteria is often confused with

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© 2007 American Association for Cancer Research. doi:10.1158/1078-0432.CCR-07-0315

www.aacrjournals.org 4951 Clin Cancer Res 2007;13(17) September 1, 2007

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disease-specific mortality, which is not an adequate substitute because excessive deaths in the screened group from other (related) causes might not be coded as cancer-related deaths, and thus, the disease-specific mortality would be shifted. Similarly, the disease-specific mortality might drop with invasive procedures, but if the overall survival is not affected, one might wonder if the screening led to useless and often morbid and unnecessary procedures as may well be the case for prostate-specific antigen screening among elderly men (9, 10). Another important element in defining the utility of a screening test is the “case-find rate” after the initial (prevalence) screen. Although an initial screening may find some cases, these could be low-virulence cases that would have been found anyway. Thus, the true test derives from the subsequently found (incidence) cases. Furthermore, cases that are found between screenings are considered screening failures. With these criteria in mind, chest X-ray is not an adequate screening test. What then of chest CT scanning as a screening test?

### Chest CT Screening

Spiral CT scanning of the chest can unquestionably detect more and smaller lesions than conventional chest X-rays. This led to the premise that routine CT scanning will detect lung cancers at an earlier and more surgically curable stage. Single arm, observational studies then showed that the CT scans could indeed detect more and smaller lesions, most of which were benign (11), whereas the small cancers are as yet of unknown clinical significance. Algorithms were then derived to follow these lesions for changes in size or shape (12), and innovative modeling now allows the lesions to be followed in three-dimensional space to detect early evidence of growth (13). Among the small lung cancers detected by this approach, the early surgical data look very promising, but the concern over overdiagnosis cannot yet be dismissed (14). The basic premise of the single arm noncomparison screening trials, however, is that all detected lung cancers would eventually (and rapidly) progress to incurable disease. This assumption may or may not be correct, as incidental lung cancers are occasionally seen at autopsies conducted for non–cancer causes (15–18).

Recently, The International Early Lung Cancer Action Program Investigators published the results of their single arm screening study in >31,000 asymptomatic participants (3). This study identified 484 cases of lung cancer of which 412 had stage I disease. The projected 10-year survival for patients with stage I disease was 88%. The authors concluded that CT screening was cost-effective, and could reduce 80% of lung cancer deaths. This study raises several remaining questions. Although we all wish that this presumption will be correct, does this optimistic report now provide sufficient evidence to routinely screen all at-risk individuals? What should we do with the participants on the current randomized controlled trials? To answer these questions for now, let us examine the ELCAP-I trial a little more closely.

First, the screening was considered positive in 535 on either baseline or annual CT, and a malignant disease was established in 492. Lung cancer was diagnosed in 479 of the 535; other cancers in 13, and 43 (8%) had no malignant disease established. Second, among the 479 lung cancers identified, 405 were identified on the initial screen (prevalence cases), 74 were identified on annual scans (incidence cases), and 5 were identified between scans (screening failures). Seventy-nine (16%) of the 479 lung cancer cases were thus identified after an initial screening. 5 of the 79 (6%) were screening failures, and 43 of the 535 “positives” were false positives. Nevertheless, 412 of the 479 cases were identified in stage I, and this finding of early-stage disease looks very promising.

The preliminary survival figures also look very promising when compared with the established surgical series, which range from 50% to 80% 5-year survival in stage IA. When one considers the subset of small volume stage IA (<15 mm), however, the 5-year survival seems very similar to that seen in the ELCAP-I screening report (18). Wisnivesky et al. (19) observed an ~85% 5-year and a 69% 10-year survival among patients with 5 to 15 mm stage IA disease. Furthermore, this ELCAP-I report does not provide the median follow-up, but it seems to be far less than 4 years on the Kaplan-Meier survival curve. Given the very few individuals at risk beyond 5 years, a 10-year projection of 88% survival is far too premature, especially if the screening identified a lead-time bias, as was probably the case in the report by Wisnivesky et al. (19).

Specifically, if the historically identified more advanced stage disease were a product of more virulent disease with early dissemination, rather than just temporally later disease, then the identification of smaller nodules may not necessarily improve survival, or improve survival to the extent projected. Likewise, the cost-effectiveness can only be derived from the life-years gained. If earlier detection does not improve survival and posterior therapy is needed, then screening can increase the overall cost of therapy. The authors report that all eight cases with clinical stage I disease who received no treatment died within 5 years of diagnosis. This may suggest to some that the patient’s early disease was virulent, but there is no explanation of why the patients received no treatment, to what extent any staging work-up was explored, or the cause of death. Nonetheless, this very small group does not constitute a control group or serve as an adequate comparison group. Accordingly, and whereas suggestive, the ELCAP-I trial has not yet established a survival benefit for CT screening. How then, can these issues be resolved, and to what extent should we be prepared to institute wide-scale screening? What are the risks or benefits of presuming that this one arm study adequately defined the risk, benefit, or cost-effectiveness of CT screening?

### Are We Ready for Wide-Scale CT Screening?

Given the very promising findings and the preliminary projections of survival following CT screening, it is not surprising that many feel that we should begin to routinely screen all at-risk (current or prior smokers) individuals. This is an especially emotional issue for those at risk or those who have been touched by this devastating disease. Why should we not yet do so? First, because we do not have sufficient proof of the survival advantage, applying wide-scale screening opens the possibility that overdiagnosis could lead to excessive invasive procedures, increased morbidity among individuals with already compromised lung function, and a very large health care expenditure. Second, once such efforts are started, they become extremely difficult to stop, even when the efficacy of the procedure is called into question. It could be a terrible outcome if we were to immortalize a noneffective screening test. Third, reliance on an ineffective secondary prevention...
could lead to false reassurance, push-back from the individual’s efforts to implement primary prevention (smoking cessation), and an actual worsening of the population’s survival experience from a wide variety of smoking-related diseases. We thus need to await more rigorously proven conclusions.

The Randomized Trials

In response to the early promising preliminary data from CT screening, the National Cancer Institute sponsored two very large prospectively randomized trials comparing CT with X-ray screening (20, 21). These studies also collected specimens to define biological correlates. These studies are now fully accrued and awaiting their first interim analyses. Thus, the answers are within reach. These studies will provide the critical comparisons for incidence, stage shift, lead-time, and survival. In the final analysis, only these types of prospective comparison trials can provide the critical information to determine the efficacy of the screening test, the effect on survival, and the cost-effectiveness of the screening intervention. Only then should the wise physician routinely recommend CT screening for their patients at high-risk. Some individuals are now calling for the closure of these trials and for the screening of the control groups. Despite the very understandable impatience of these individuals, we must allow these trials to reach their planned conclusions. We should remember (among other possible examples) the circumstances surrounding the application of autologous bone marrow transplant) for high-dose chemotherapy in breast cancer. The preliminary single arm trials data suggested a beneficial effect, and there was a strong advocacy position for implementing the therapy without the benefit of the randomized controlled trials. As a result, the randomized trials took very much longer to complete, and thousands of women received these aggressive and often morbid therapies, which ultimately could not be shown as beneficial. The randomized Lung Cancer Screening Trials are the most likely to hopefully and critically prove the benefit of CT screening. The answer is nearly at hand, and we must protect the integrity of these trials for their answers.

References

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