Commentary: Lung Cancer Screening—Progress or Peril

JAMES L. MULSHINE

Rush University Medical Center, Chicago, Illinois, USA

Disclosure: This article references unlabeled/unapproved use of CT scans (machines manufactured by General Electric, Siemens, Phillips, Toshiba) for lung cancer detection. No potential conflicts of interest were reported by the author, planners, reviewers, or staff managers of this article.

INTRODUCTION

Two reviews of lung cancer screening have been presented in this journal across the last two journal issues [1, 2]. These articles differ markedly in content and tone. Lung cancer screening is a topic that has commanded considerable recent attention. This is a result, in part, of the fact that this cancer is the leading cause of cancer death worldwide, with a 15%, 5-year survival rate in the U.S. [3]. Considerable attention may also be related to the numerous papers reporting the utility of spiral computed tomography (CT) to find early lung cancer. Most notable was the recent report of an international observational trial using spiral CT screening in a cohort of 31,000 generally high-risk individuals suggesting that the stage I disease detection rate and 10-year survival rate could both exceed 80% [4]. Adding to the media attention was a second article some months later that was a modeling report analyzing data from three previously published trials involving 3,246 individuals [5]. The central finding of that article was that the use of spiral CT screening may not reduce the risk for dying from lung cancer in a meaningful way. Both articles were extensively discussed in a variety of forums. The issue to the readership of The Oncologist, who may be called upon to provide patient recommendations in this context, is what to make of this confusing situation.

From a general perspective, it is evident that, even outside lung cancer, there is much controversy about the cost, complexity, and feasibility of providing cancer-screening services, such as with breast cancer and colon cancer, there is a major challenge in how to effectively deliver these services [8, 9]. For prostate cancer, where the level of evidence supporting a benefit from screening for prostate-specific antigen (PSA) is classified by the U.S. Preventive Services Task Force as comparable with lung cancer screening, the Center for Medicare and Medicaid Services provides reimbursement nationally for PSA screening [10]. The American Cancer Society [11] recommends that PSA testing and digital rectal examination be offered annually, starting at age 50, for men who have a life expectancy of at least 10 years, but expresses concerns about the strength of the data supporting that recommendation. This confusion is further reflected in the current situation, with more states mandating that insurers cover PSA screening compared with colon cancer screening, despite the strength of the recommendation from the U.S. Preventive Services Task Force [10] being much stronger for colon cancer screening.

The issue of lung cancer screening has recruited considerable attention from authors who have also previously published extensively on the issue of breast cancer screening [12–14]. In a recent paper, these authors have taken issue with a number of issues with lung cancer screening that include concerns previously discussed in the context of breast cancer [15, 16].

The very long-standing controversy about breast cancer screening took a major coordinated screening benefit modeling effort to resolve [17, 18]. In part, this controversy re-
lates to the complex issue of how to precisely establish an objective basis for determining the benefit of cancer screening [17, 18]. For the current breast cancer screening resolution, it took seven modeling groups, with abundant randomized trial data, 4 years to work through the profoundly complicated methodological issues.

For some, the challenge of cancer screening begins with the concern that the issues are not communicated fully or the public does not understand the issues of the potential risks and benefits of preventive services [19, 20], and the probability of some harm to many, does not justify the potential to benefit a few. There is also concern about the cost of screening services and whether the health care system can afford to provide expensive new services at a time of rapidly growing health care expenses.

Many cancers, including those of the pancreas, esophagus, and ovary, are routinely found at a late stage and have poor 5-year survival rates [3]. Finding better approaches to routinely detect early cancer is an important research opportunity. Independent of the situation with lung cancer, progress across the board in cancer research will benefit from increased attention and consensus on the methodology for responsibly developing, evaluating, and then delivering cancer-screening services [6, 7, 10]. This is a profoundly important underappreciated public health challenge.

**ISSUES WITH LUNG CANCER SCREENING**

In their review on lung cancer screening, Drs. Jett and Midthun were concerned about limitations to lung cancer screening [2]. One major concern involves the number of nodules that require follow-up. This concern resonates with dermatologists, who track a number of skin changes in heavily sun-exposed elders, as well as gastroenterologists, who track many changes in the bowels of older individuals. However, despite the large numbers of nodules found, even in the Mayo Clinic screening trial, strategies are emerging to selectively target invasive evaluations of these nodules [21–23]. As a result, the frequency of individuals undergoing follow-up invasive procedures for benign disease has decreased to the range of 10%–15%, with a low rate of interval-detected cancers [4, 24].

Jett and Midthun are also concerned about the potential psychological impact of discovering a nodule [2]. While of theoretical concern, this issue has not been well explored in heavily tobacco-exposed individuals, who already have chronic concerns about a range of significant health risks related to their decades of smoking. Other concerns include the potential for thoracotomies performed for benign disease. The International Early Lung Cancer Action Program and other emerging experiences are suggesting more effective noninvasive diagnostic options with this process [4, 24]. This raises the larger issue of determining the optimal invasive approach to lung cancer screening management. This issue has many dimensions, as we have previously outlined [25], and constitutes an area where important research on addressing surgical management issues could be done in the interval while awaiting definitive evidence for a lung cancer screening benefit.

Another issue raised by Jett and Midthun is the issue of interval cancers, or what is also called the failure of screening [2]. This was a major concern with chest x-ray screening [26]. To date, with the major reported spiral CT experience, the frequency of interval-detected cases has been remarkably low [4, 21, 27], especially compared with the rates reported for chest x-ray screening, but even when compared with validated screening for other organ sites.

The issue of potential overdiagnosis is also of concern in the review by Jett and Midthun [2]. Overdiagnosis is always of concern in a screening setting. The case for significant overdiagnosis with lung cancer screening was not considered persuasive when the U.S. Preventive Services Task Force evaluated this issue [28]. Since then there has been a careful analysis of stage I lung cancer outcomes using data from 19,000 individuals from the California Cancer Center registry. That study reported a 13-month median survival time for stage IA individuals diagnosed with lung cancer who were not treated for their disease [29]. The conclusion of that study was that, despite ongoing controversy regarding overdiagnosis, untreated lung cancer is a fatal disease in the great majority of patients with stage I disease.

The paper from Henschke and Yankelevitz [1] extensively reviewed their multi-institutional effort and their developmental approach to lung cancer screening research. However, there is new information from other sources that bear on this issue. In a rigorous modeling report, McMahon and colleagues used the results of the Mayo Clinic spiral CT–based lung cancer screening trials to evaluate the potential long-term benefit of this approach [21, 30]. To calibrate their model, McMahon et al. [30] used data from the Surveillance, Epidemiology, and End Results database. The authors reported that their analysis found a 26% relative reduction in the cumulative lung cancer–specific mortality with five annual screens and 6 years of follow-up [30]. This estimated benefit per subject is modest, but as the authors outline, there are a number of limitations of their modeling approach.

Like all other lung cancer models used to estimate lung cancer screening benefit, the basis for the model is experi-
ence calibrated from chest x-ray–detected cancer cases. As the modeling field matures and models derived from carefully followed cohorts of individuals at risk for lung cancer assessed with spiral CT become available, perhaps more robust predictive models will be validated. In addition, with existing data the median follow-up time is modest. The full benefit of lung cancer screening may not be evident until the full impact of prevalence cancers is washed through the cohort [31]. Finally, spiral CT screening management (i.e., cohort selection, image reading, diagnostic workup, surgical intervention, and intensity of follow-up) has not yet been optimized, and that could impact the ultimate mortality benefit of lung cancer screening. The McMahon modeling result is influence by the screening management of the relatively early Mayo experience. The frequency of invasive procedures for nonmalignant diagnoses was high, as was the iatrogenic mortality rate relative to that of later studies [4, 24, 27].

An interesting discussion in that manuscript was the delineation of the differential handling of early deaths in comparing the modeling methodology used by McMahon et al. [30] with that of another recent modeling paper [32]. If the handling of early deaths was conducted by Bach as it was in his original description of his model, both McMahon et al. [30] and Bach [32] would predict a 28%–29% mortality reduction benefit at 6 years with the two models. McMahon et al. [30] conclude that the ultimate mortality benefit may not be 80%, as predicted by Henschke, but is not likely to be without benefit, as suggested by Bach [32].

In another recent modeling effort, data from six prospective CT screening studies were analyzed with a three-state Markov model with a Bayesian approach [33]. The model projects results over a 10-year time horizon of follow-up based on an approach used in the NELSON screening trial. From early published reports, spiral CT for lung cancer was found to have a median sensitivity of 97% and may advance the diagnosis of lung cancer to 1 year earlier than with chest x-ray. With annual CT screening, there would be an estimated 23% mortality risk reduction, with a relative risk of 0.77 (95%, confidence interval, 0.43–0.98).

From three independent approaches, there are three analyses that suggest a potential mortality reduction benefit of at least 20% [30, 33, 34]. This is a profoundly important finding. Not because it is a definitive finding, but rather because it supports the notion that, even with the current immature state of lung cancer screening, as provided across the numerous research trials analyzed in the different modeling experiences, this unproven lung cancer screening approach is not harmful.

**CONCLUSION**

With continued research development, including more precise delineation of the target population, enhanced efficiency of the diagnostic workup of suspected cases, and further refinement of curative interventions, the potential benefit of lung cancer screening could significantly improve. The rapid increase in the resolution of CT could improve the timely detection of small cell lung cancers. Further improved resolution may permit the development of effective image-processing tools to allow for more reliable change assessment as a noninvasive discriminant of malignancy. Integration of CT lung cancer screening with other comorbid tobacco-related conditions of the thorax has an unprecedented opportunity to advance early disease management. However, screening for early disease is an extremely challenging process and weakness in any one aspect can readily undermine the overall benefit [34].

Even with an optimistic perspective on lung cancer screening, there are many critical unresolved research and health care policy questions that could significantly improve potential success with lung cancer screening. All of these research efforts would complement the prudent investment the National Cancer Institute has already made in conducting a major randomized trial of spiral CT versus chest x-ray screening for early lung cancer detection [36]. Just as the American Cancer Society did for breast cancer, it would be prudent to mount demonstration projects to help guide the refinement of lung cancer screening management [37, 38]. In that fashion, if the National Lung Screening Trial (NLST) is positive, then the knowledge would exist as to how to responsibly deliver early lung cancer detection services. During the time it takes to conduct the NLST, somewhere between 1.5 and 2 million Americans may die of lung cancer. Because lung cancer kills more women than breast cancer, ovarian cancer, and cervical cancer combined, and lung cancer kills as many men as colon cancer, prostate cancer, bladder cancer, lymphoma, and leukemia combined, a sense of urgency around these issues is respectful of the vast number of this lethal cancer’s victims. Controversies about screening in general and about lung cancer screening in particular are going to persist. The pace of innovation with imaging is not going to abate, and these capabilities will allow us to have an ever more robust window into early, curable lung cancer. Critics provide an important sense of caution in engaging the complex
screening process, given its myriad of opportunities for potential subject harm. Developing systems that minimize harm and maximize screening benefit is vital to the ultimate success of lung cancer screening.

REFERENCES