

## Screening for Lung Cancer\*

### ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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**Background:** Lung cancer typically exhibits symptoms only after the disease has spread, making cure unlikely. Because early-stage disease can be successfully treated, a screening technique that can detect lung cancer before it has spread might be useful in decreasing lung cancer mortality.

**Objectives:** In this article, we review the evidence for and against screening for lung cancer with low-dose CT and offer recommendations regarding its usefulness for asymptomatic patients with no history of cancer.

**Results:** Studies of lung cancer screening with chest radiograph and sputum cytology have failed to demonstrate that screening lowers lung cancer mortality rates. Published studies of newer screening technologies such as low-dose CT and “biomarker” screening report primarily on lung cancer detection rates and do not present sufficient data to determine whether the newer technologies will benefit or harm. Although researchers are conducting randomized trials of low-dose CT, results will not be available for several years. In the meantime, cost-effectiveness analyses and studies of nodule growth are considering practical questions but producing inconsistent findings.

**Conclusions:** For high-risk populations, no screening modality has been shown to alter mortality outcomes. We recommend that individuals undergo screening only when it is administered as a component of a well-designed clinical trial with appropriate human subjects’ protections.

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**Key words:** biomolecular markers; chest radiograph; low-dose CT; lung cancer screening; sputum cytology

**Abbreviations:** CXR = chest radiograph; ELCAP = Early Lung Cancer Action Project; LDCT = low-dose CT; QALY = quality-adjusted life year; SEER = Surveillance, Epidemiology, and End Results

Renowned for poor outcomes, lung cancer is expected to claim the lives of 160,390 Americans in 2007.<sup>1</sup> When diagnosed during early stages, lung cancer can be treated with surgical resection; how-

ever, symptomatic patients almost always present with advanced-stage disease. In principle, screening might intercept some fraction of eventually fatal cases of lung cancer earlier in the disease course. If intercepted early, when the cancer is localized and resectable, and then successfully removed, the outcomes of the patient might be altered. Randomized, controlled trials in the 1970s and 1980s did not validate this principle. These controlled studies showed that screening did detect more early-stage cancers, leading to increased rates of surgery, but there was no evidence that the cancers that were found through screening were actually cancers that would have progressed to cause advanced disease. Instead, the intervention and control arms in these studies had the same frequency of advanced cancer diagnoses and deaths from lung cancer, despite the

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intervention (screened) subjects' receiving a diagnosis more often of early lung cancer. Going forward, the hope is that a more sensitive screening modality, that can identify smaller lung cancers, will succeed where chest radiograph (CXR) has failed, preventing both advanced cases of lung cancer and deaths from lung cancer by intercepting the disease earlier.

Exhaustive reviews of lung cancer screening techniques have been published elsewhere, including one published by the American College of Chest Physicians in 2003.<sup>2</sup> All of these reports are in near complete consensus that screening for lung cancer with either CXR or sputum cytology is not appropriate.<sup>2</sup>

## MATERIALS AND METHODS

To update previous recommendations on lung cancer screening, we identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), the primary analysis of individuals who were screened for lung cancer between 2002 and May 2005, as well as studies that provided insights into the theoretical basis of screening or the clinical behavior of lung cancers found through screening. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (Medline) and review of the Thoracic Oncology NetWork reference lists of relevant articles. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians. This article is intended as an update of the existing lung cancer screening guidelines and focuses only on recent developments and recent new studies of screening technologies. The initial article contained a comprehensive literature review on the topic.

## RESULTS

Low-dose CT (LDCT) scanning remains the most promising of lung cancer screening techniques, but the results of ongoing randomized trials are not expected for at least another 2 to 3 years. In the meantime, researchers have pursued other approaches to evaluating the impact of CT screening on lung cancer outcomes and also focused on other issues that might affect how screening is used, such as investigating the hazard that smaller, early-stage, LDCT-detected nodules pose; the cost-effectiveness of LDCT as a screening modality; and the survival of subgroups of subjects who have been screened. Alternatives to imaging technologies such as biomolecular marker screening and proteomics are early in their development.

Because very limited data regarding the impact of any of the new screening modalities on patient outcomes have become available since the publica-

tion of our last set of guidelines, our conclusions regarding the efficacy of various approaches to lung cancer screening have not changed meaningfully. They continue to be broadly consistent with those published by other organizations (Table 1),<sup>39,40</sup> and our conclusions are consistent with a recent health technology assessment of lung cancer screening with LDCT, conducted for the National Health Service R&D Health Technology Assessment Programme.<sup>3</sup> Many organizations are not yet offering recommendations regarding CT screening in advance of results from the National Lung Screening Trial, a randomized, controlled trial of LDCT. The guidelines that we offer are meant to help physicians and patients discuss the potential risks and benefits of lung cancer screening and to ensure that patients who agree to be screened appreciate that screening for lung cancer with any modality should be considered experimental, and that they are entitled to protections that are afforded all human subjects who agree to participate in research.

### *Screening With LDCT*

Using relatively low radiation exposure to create a low-resolution image of the entire thorax, LDCT screening is capable of detecting very small, early-stage cancers so that their shape and growth can be observed noninvasively. Previous research has demonstrated that compared with CXR, LDCT detects approximately three times as many small lung nodules; of those that are subsequently diagnosed as cancer, the overwhelming majority are stage I.<sup>4</sup> For the additional early detection to benefit patients substantially, these early lung cancers that are found through LDCT must be reasonably likely to progress to advanced lung cancer, such that they represent a reasonable proportion of cancers that would otherwise manifest as advanced disease and lead to death. Because only data from observational studies of LDCT screening are available and do not include a control group, it is hard to determine whether increased detection of early-stage lung cancers by LDCT screening will lead to a decreased frequency of either advanced lung disease or death as a result of lung cancer.

Previous screening studies that evaluated CXR raised some general concerns about screening with any type of imaging. These studies<sup>2,5,6</sup> showed that although screening does increase the rate of detection of early-stage lung cancers, it fails to reduce the number of late-stage lung cancers or the risk for dying from lung cancer. One possible explanation for this is that screening detects a large number of small, slowly growing, less aggressive lung cancers that are unlikely to progress to a point that they cause clinical

**Table 1—Guidelines on Screening for Lung Cancer**

Recommending Body	Topic	Recommendation
National Cancer Institute ( <a href="http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional">http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional</a> )	CXR and sputum cytology	On the basis of fair evidence, screening does not reduce mortality from lung cancer. On the basis of solid evidence, screening would lead to false-positive results and unnecessary invasive diagnostic procedures and treatments.
National Cancer Institute ( <a href="http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional">http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional</a> )	LDCT	The evidence is inadequate to determine whether screening reduces mortality from lung cancer. On the basis of solid evidence, screening would lead to false-positive results and unnecessary invasive diagnostic procedures and treatments.
American Cancer Society <sup>39</sup>	CXR and sputum cytology	Lung cancer screening is not a routine practice for the general public or even for people who are at increased risk, such as smokers
US Preventive Services Task Force ( <a href="http://www.ahrq.gov/clinic/uspstf/uspstlung.htm">http://www.ahrq.gov/clinic/uspstf/uspstlung.htm</a> )	CXR, sputum cytology, and LDCT	The evidence is insufficient to recommend for or against screening asymptomatic individuals for lung cancer with LDCT, CXR, sputum cytology, or a combination of these tests.
Canadian Coordination Office for Health Technology Assessment ( <a href="http://www.cadth.ca/media/pdf/213_ct_cetap_e.pdf">http://www.cadth.ca/media/pdf/213_ct_cetap_e.pdf</a> )	LDCT	Currently, the evidence does not exist to suggest that detecting early-stage lung cancer reduces mortality. At present, screening for lung cancer with multislice/helical CT would be premature.
Society of Thoracic Radiology <sup>40</sup>	LDCT	Mass screening for lung cancer is not currently advocated. Suitable subjects who wish to participate should be encouraged to do so in controlled trials so that the value of CT screening can be ascertained as soon as possible.

disease while missing cancers that advance rapidly and cause the majority of deaths from lung cancer. The phenomenon of detecting more slowly growing cancers through screening is well accepted and is referred to as *length-biased sampling*. However, the amount of overlap between screening-detected cancers and lung cancers that will ultimately cause death remains uncertain. That LDCT is a more sensitive technology than CXR does not necessarily equate to LDCT finding more aggressive cancers; it could equate to detecting more small, indolent cancers that would have never grown to a size detectable by conventional CXR. If true, then this might mean that rather than benefiting patients more than CXR, LDCT screening could instead lead to more unnecessary and nonbeneficial procedures than CXR.

#### *Natural History of Clinically Apparent and CT-Detected Lung Cancers: Findings on Doubling Rates*

Some research has explored use of the volume-doubling rate to predict the threat posed by smaller, screening-detected lung nodules, based on the hypothesis that nodules that are rapidly growing (*ie*, rapidly “doubling in size”) are more likely to cause significant disease. In other words, doubling times are examined on the basis of the assumption that the rate of doubling over a brief time period is at least crudely reflective of

a tumor’s past behavior and can be used as a proxy for the future behavior of the tumor; therefore, rapidly doubling cancers are more likely to continue to double in size rapidly. Even though the simplifying assumption that cancers double at a constant rate undoubtedly is inaccurate, the general model of doubling times can help to delineate differences in behavior between CT-detected lung cancers and the lung cancer that is common in clinical practice. To that end, the model is theoretically useful for evaluating nodules that are detected by CT screening and also for assessing whether CT-detected nodules have a clinical behavior that is as aggressive as lung cancer that is sporadically detected, usually in advanced stages. This issue is also discussed in the chapter addressing solitary pulmonary nodules.

Because the total number of doublings that typically precede cardinal clinical events have been identified and previous estimates of doubling times have been published, it is possible to assess directly whether reported doubling times of CT-detected nodules fits the doubling times that would be most consistent with the natural history of lung cancer, something that can be accomplished by evaluating epidemiologic data.

For instance, previous studies<sup>7,8</sup> estimated that 20 doublings are interposed between the initial cell division and a tumor’s having a diameter of 1 mm; 22 doublings before a tumor theoretically is visible, and

28 doublings before a tumor clearly is visible by CT screening; 35 doublings before it reaches a size at which it is usually clinically apparent; and 40 to 41 doublings to reach a diameter of 100 mm, at which point it is usually lethal. These key time points are illustrated in Figure 1.

Given these time points, we evaluated various hypothetical rates of doubling and the extent to which they mimicked the timing of lung cancer events as documented in the epidemiologic literature on lung cancer. We then compared the most probable doubling rates that fit the epidemiologic literature with the reported doubling rates of CT-detected lung cancer to determine whether CT-detected lung cancers grew more slowly than sporadically detected lung cancers, which today account for nearly all of the deaths from lung cancer.

Figure 1 illustrates the results of the analysis. If the doubling time is 40 days, for instance, and it takes 22 doublings for a tumor to be visible on CT, then the time from first cell division to visibility is 880 days ( $40 \times 22$ ), or 2.4 years (Fig 1). At this rate, the same tumor will take 3.8 years to reach 35 doublings, which is the size at which it would typically be detected in a clinical setting, and 4.6 years (41 doublings) to reach the size at which it likely causes death. We can also see that the average “lead time” (the time between typical CT and clinical detection) would comprise 7 doublings (35 doublings minus 28 doublings) and so in this case would equate to 280 days (a little more than 9 months). The typical time from clinical detection to death (*ie*, the “mean survival”) would comprise 6 doublings (41 doublings minus 35 doublings), or 240 days (8 months). The same calculations for slower volume doubling rates,

which would be more consistent with longer times between key events, are also shown in Figure 1.

We evaluated three pieces of epidemiologic information on the natural history of sporadically detected lung cancer and determined the range of doubling times that fit the data the best:

1. The Surveillance, Epidemiology, and End Results (SEER) data show that the “mean” survival time for patients with clinically detected lung cancer is < 1 year, even when treated with modern therapies. This survival time is consistent with shorter doubling rates of 40 to 65 days, which equates to a survival time of 0.8 to 1.3 years. By contrast, doubling times of 180 days would equate to a mean survival after diagnosis of 2.4 years, as seen in Figure 1.
2. The SEER data show that the median survival of patients who receive a diagnosis of stage I non-small cell lung cancer and are not treated with surgery is on the order of 14 months.<sup>9</sup> This result is most consistent with a doubling rate near 70 days. By contrast, a doubling time of 180 days would equate to a mean survival of 5.3 years.
3. Research regarding the impact of smoking cessation on lung cancer risk has been shown that risk begins to decline within just a few years of smoking reduction or cessation.<sup>10–12</sup> This finding is most consistent with a doubling time of 40 to 65 days. At a doubling rate in this range, the time from the first cell division to the time of usual clinical presentation would be approximately 3.8 to 6.2 years. By contrast, doubling rates of 180 or 400 days would equate to a 17.7-

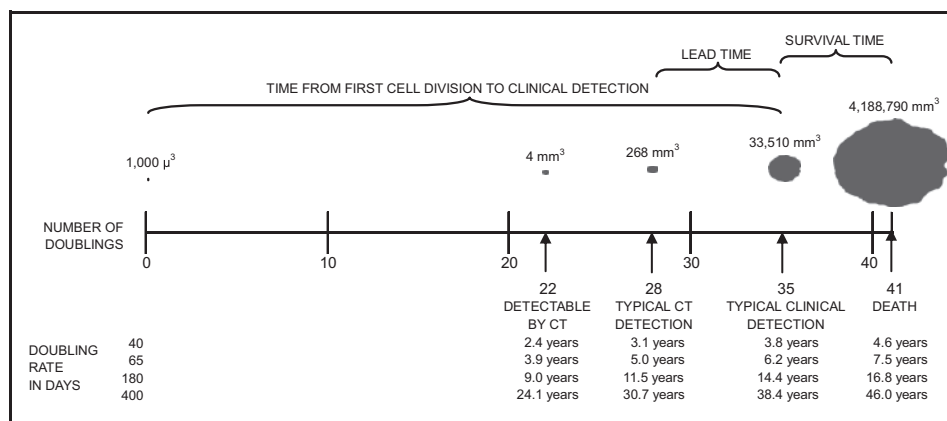


FIGURE 1. Timeline of lung cancer progression by number of tumor doublings and volume doubling rate. The volume doubling rate (measured in days) was calculated using the formula  $DR = (t \cdot \ln 2) / \ln (d_2/d_1)$ ,<sup>37</sup> where  $t$  equals time in days,  $d_1$  is the diameter at first scan, and  $d_2$  the diameter at second scan. The size of initial lung cancer cell for all calculations was 1,000  $\mu\text{m}$ .<sup>7</sup> Although the size of a lung cancer cell may vary significantly,<sup>38</sup> this will affect only the time from first cell division to first possible detection, not the time between detection and other clinical events.

or 38.4-year gap between smoking cessation and a fall in risk for lung cancer.

On the basis of epidemiologic benchmarks and the assumption that the model of doubling time is somewhat robust across the natural history of lung cancer, the evidence suggests that doubling times of approximately 40 to 70 days are most consistent with the natural history of lung cancers that are responsible for most lung cancer deaths. In this light, it is useful to examine reported doubling times in screening studies to help determine to what extent cancers that are detected by screening double at rates that are slower than the rates that are consistent with the natural history of the disease. For instance, Hasegawa et al<sup>13</sup> reported that among 61 lung cancers identified by CT screening, the doubling times ranged from 149 to 813 days—all rates much slower than the 40- to 70-day doubling times that best fit the epidemiologic data. Yankelevitz et al<sup>14</sup> documented that even CXR screening detects more slowly doubling lung cancers: only a minority of stage I lung cancers that were detected by CXR screening in the landmark New York and Mayo lung screening studies had doubling times < 100 days. By contrast, 35 and 11% of these cancers, respectively, had doubling times > 300 days. In other words, if doubling times are indicative of clinical behavior, then most lung cancers that are detected through screening are quite a bit more indolent than lung cancers that account for most clinical disease.

### *Cost-effectiveness of LDCT*

Researchers have been eager to determine the cost-effectiveness of lung cancer screening, a task made difficult by the absence of efficacy data (Table 2).<sup>15,17,18,41</sup> Two studies have examined the cost of a single, “prevalence” screening compared with no screening on the basis of the apparent shift in stage distribution reported in the Early Lung Cancer Action Project (ELCAP) cohort (85% stage I in screening arm vs 21% stage I in the no-screening arm).<sup>15,16</sup> Both estimated the incremental cost-effectiveness for screening a population with high lung cancer prevalence rates (2.7%, also derived from the ELCAP study) and low lung cancer prevalence rates ( $\leq 1\%$ ) and used similar costs for CT scans. Wisnivesky et al<sup>16</sup> estimated that a one-time LDCT scan will cost roughly \$2,500 per life-year gained under the assumption of high prevalence and \$19,000 per life-year gained under the assumption of low prevalence, assuming a 1.5-year lead-time bias. One-way sensitivity analyses showed that increasing the rate of overdiagnosis to 30% increased cost-effectiveness estimates to roughly \$10,000 per life-year; with 50% of cases overdiagnosed, the incremental cost-effectiveness was closer to \$80,000.

Also assessing a prevalence screen, the baseline model of Marshall et al<sup>15</sup> assumed 100% detection rate for true cancers and a 21% benign nodule (false-positive) detection rate. With a 5-year cost horizon, these assumptions yielded cost-effectiveness estimates of \$5940 per life-year gained for a high prevalence cohort and \$23,100 for a low prevalence cohort. In two-way sensitivity analyses, a 1-year lead-time bias increased estimates to \$15,274 and \$58,183 per life-year gained under assumptions of high and low prevalence, respectively. Maintaining the adjustment for lead time while varying the rate of benign nodule detection generated cost-effectiveness ratios between \$11,500 and \$20,400.

At least three additional studies have explored the cost-effectiveness of annual LDCT screening, two of which presented their results in quality-adjusted life years (QALYs). A separate study by Marshall et al,<sup>17</sup> using the same assumptions about effectiveness described previously, estimated that for an annual screening for 5 years, the incremental cost-effectiveness per QALY was \$19,533. Sensitivity analyses considered a 1-year decrease in survival to account for potential confounding by lead-time and overdiagnosis biases, yielding a cost-effectiveness ratio of \$50,473 per QALY. Taking a slightly different approach, Mahadevia et al<sup>18</sup> stratified individuals by smoking status: continuing, quitting, and former (those who had quit > 5 years earlier). Expected diagnoses and mortality rates were obtained from SEER, and the model was sensitive to the degree of stage shift, adherence to screening, degree of length or overdiagnosis bias, cost of CT, and anxiety about indeterminate nodules. For current smokers, effectiveness was modeled as a 50% stage shift with a resulting 13% decrease in lung cancer mortality during the first 20 years. The incremental cost-effectiveness per QALY gained was \$116,300 for current smokers. For quitting and former smokers, the corresponding projections were \$558,600 and \$2,322,700 per QALY, respectively. In sensitivity analyses, only improbably favorable conditions generated costs within the range of the estimates provided by other studies: \$42,500 for current, \$75,300 for quitting, and \$94,400 for former smokers. It should be noted, however, that this study examined costs over a longer time horizon and considered numerous variables in its baseline model that the other cost-effectiveness studies elected to omit.

Although these analyses are highly speculative, from a public health decision-making perspective, they provide a useful preliminary indication of the practicability of screening for lung cancer. Generally, the models that assume some impact from lead-time bias and the detection of indolent (*ie*, overdiagnosed) lung cancers generate cost-effectiveness ratios that

**Table 2—Estimates of Cost-effectiveness per Life-Year Gained of Lung Cancer Screening With LDCT**

Source	Cohort	Prevalence	Screening Regimen	Effectiveness	Time Horizon	Cost of Screening LDCT (Diagnostic CT), \$	Cost-effectiveness per LYG, \$†
Mahadevia et al,* 2003 <sup>15</sup>	100,000 current, quitting, and former smokers; 60 yr old; >20 pack-year smoking history; 55% male	Varied with smoking status: 0.43 incidence for current smokers	Annual screening for 20 yr	50% stage shift	1–40 yr of follow-up for occurrence of clinical events	300 (429)	Current, 116,300; quitting, 558,600; former, 2,322,700
Marshall et al,* 2001 <sup>15</sup>	100,000 smokers; 60–74 yr old; median 45 pack-year smoking history; 45% male	High risk, 2.7%	Annual screening for 5 yr	85% stage I (21% in control arm)	5 yr	150 (280)	50,473
Chirikos et al, 2002 <sup>41</sup>	Cohort characteristics modeled in treatment costs and life expectancy	High risk, 2.7%; low risk, < 2.7%	Annual screening for 5 yr	50% localized disease (20% in the control arm)	15 yr	291 (340–416)	46,513
Marshall et al, 2001 <sup>17</sup>	100,000 smokers; 60–74 yr old; median 45 pack-year smoking history; 45% male	High risk, 2.7%; low risk, 0.7%	One-time screening	85% stage I (21% in control arm)	5 yr	150 (not reported)	15,274
Wisnivesky et al, 2003 <sup>16</sup>	1,000 participants; ≥ 60 yr old; ≥ 10 pack-year smoking history	High risk, 2.7%; low risk, 1.0%	One-time screening	85% stage I (21% in control arm)	1 yr after diagnosis, including terminal care costs	165 (300)	\$2,500

\*Estimates of cost-effectiveness are quality adjusted.

†All estimates include lead time of 1 to 1.5 years with the exception of the results from the Chirikos study, which do not adjust for lead time. LYG = life-year gained.

are fairly unattractive. Analyses that assume that all screening-detected cancers behave like typical clinical lung cancer and that each early-detected cancer displaces a case of advanced lung cancer tend to make screening more appealing. Perhaps a more useful function of these studies is their illustration of the significant impact that defining risk has on the potential cost-effectiveness of screening. Clearly screening only the people who are at very high risk for developing lung cancer will improve the efficiency of the test and its incremental cost-effectiveness; however, identifying the population at greatest risk remains a difficult task. One study<sup>19</sup> found that individual risk among smokers varied greatly on the basis of a person's smoking exposure, packs smoked per day, age, gender, and asbestos exposure. However, a large reservoir of cancers may appear in individuals who are at relatively lower risk, of whom there are many, such as groups of former smokers.<sup>20</sup> That the incremental cost-effectiveness for LDCT screening can theoretically differ by as much as \$2,000,000 according to present smoking status alone shows how critical a rigorous definition of "high risk" would be going forward, assuming that some approach is demonstrated to be beneficial.

#### *LDCT Ongoing and Future Studies*

At least two randomized trials of LDCT are under way. The National Lung Screening Trial has randomly assigned 50,000 high-risk smokers, between 55 and 74 years of age, to annual screening with LDCT or CXR at 36 sites in the United States (<http://www.cancer.gov/nlst/screeningcenters>). The study is designed to have a 90% power to detect a mortality reduction of 20% by 2009. The NELSON trial,<sup>21</sup> a collaboration between the Netherlands and Belgium, has randomly assigned 16,000 smokers to LDCT screening intervention at years 1, 2, and 4 or usual care and advice on smoking cessation. Designed to measure cost-effectiveness and powered to detect a 25% mortality reduction > 10 years, the study is set to close in 2016.

#### *Available Estimates of the Impact of LDCT Screening on Lung Cancer Mortality and Survival*

Although there are not yet comparative data on the rate of lung cancer mortality among patients who are screened with LDCT compared with what might have happened had individuals not been screened, some preliminary analyses are pessimistic. In a study of 1,520 smokers and former smokers who received 5 years of annual LDCT scans at the Mayo Clinic, Swensen et al<sup>22</sup> found that lung cancer incidence and mortality rates were comparable to those in the Mayo Lung Project, after adjusting subsets by age

and sex. The Mayo Lung Project was a study of CXR screening that demonstrated no reduction in lung cancer mortality among screened subjects. Patz et al<sup>23</sup> modeled the mortality rates for these same patients enrolled in the study at the Mayo Clinic as well as subjects enrolled in one of the ELCAP trials, by estimating the stage-specific number of lung cancer deaths over the person-years at risk in each subset. The findings were then compared with those of the original Mayo Lung Project, in which the lung cancer mortality rates were 4.4 deaths per 1,000 person-years in the intervention arm and 3.9 deaths per 1,000 person-years in the usual care arm. This approach produced estimates of similar or higher mortality rates in the LDCT-screened groups: 4.1 deaths per 1,000 person-years in the Mayo Clinic CT trial and 5.5 deaths per 1,000 person-years in the ELCAP trial.

The international ELCAP reported on the lung cancer-specific survival of 412 subjects who had screening-detected clinical stage I lung cancer, who represented 1.3% of 31,567 subjects who had been screened by the group for lung cancer.<sup>24</sup> The investigators reported that this subgroup, which was followed up for a median of 3.3 years, experienced lung cancer-specific survival that was superior to the overall survival of similar patients seen in epidemiologic cohorts. Sobue et al<sup>25</sup> also reported that as part of the Anti-Lung Cancer Association Project, 5-year survival for individuals with screening-detected lung cancer was much higher (65 to 76%) than current 5-year survival rates for sporadically detected lung cancers.

These studies that exclusively examine survival of individuals with screening-detected lung cancer have two weaknesses that limit the inferences that can be drawn. For example, in the international ELCAP analysis, there is no information on the outcomes of the 98.7% of subjects who did not have screening-detected stage I lung cancer, so the reader cannot determine whether a large or small number of lung cancer deaths occurred among the subjects. Second, the comparators in these studies are intrinsically biased, because screening improves survival through lead-time and length-time biases, even in the absence of an impact on natural history; therefore, these studies provide limited information regarding the potential benefit or harm of LDCT screening.

## CONCLUSIONS

### *LDCT*

At present, the risks of LDCT are readily observable, but the impact on mortality remains unknown. Even if LDCT is ultimately shown to effect a mortality reduction, the legitimate concern about overdiagnosing cancers, the uncertainty about how to assess nodule growth

rates, the influence of patient risk level on effectiveness and cost-effectiveness, and the high rates of benign nodule detection and subsequent treatment prompted by such detection all suggest that the cumulative consequences of screening may not be favorable. However, the high rate of small nodule detection is a reason for optimism. Given the conflicting data and the potential benefit to the public health of an early detection modality that is capable of reducing the frequency of advanced lung cancer and death from lung cancer, it is appropriate to pursue research studies that are designed to clarify the issues that remain unanswered at this time. Several randomized trials are evaluating the risks and benefits of LDCT screening in the United States and Europe, particularly focused on patients who are at high risk for lung cancer. There may very well be further such studies begun; if so, then it would be appropriate for physicians to help interested patients identify and enroll in such studies. Any such trial should have a reasonable possibility of generating new knowledge about the harms and benefits of screening and should have appropriate human subjects protections in place, including informed consent procedures. By contrast, the evidence to date does not support offering LDCT screening for individuals, irrespective of their risk for lung cancer, in the absence of an experimental protocol that has been approved by and is being overseen by an institutional review board. This recommendation applies only to individuals with no history of lung cancer. Disease surveillance for individuals with a history of lung cancer is addressed in a separate chapter.

### *Screening With Biomolecular Markers*

Several promising biomolecular marker tests, including sputum analysis and screening the breath for volatile organic compounds and DNA alterations, have gained momentum as lung cancer screening techniques. Evaluated primarily in the context of a supplement to CXR in the randomized, controlled trials in the 1970s and 1980s, sputum cytology was not shown to confer any mortality benefit. Because the trials were often underpowered and seldom concentrated on sputum cytology, its discrete efficacy was unclear.<sup>26</sup> Newer research is focusing on similarly noninvasive technologies that test for biomarkers that are unique to lung cancer.<sup>27,28</sup> Although no single marker is likely to indicate malignant nodules, one strategy that tests for volatile organic compounds has shown that the presence of as few as nine compounds may suggest extant lung cancer.<sup>29,30</sup> More recently, Carpagnano et al<sup>31</sup> showed that micro satellite (DNA) alterations that are specific to lung cancer can also be detected in exhaled breath condensate, which may lead to a more sensitive screening tool. In addition, sensor array analysis using an electric nose has shown promising sensitivity

(71.4%) and specificity (91.9%) for lung cancer detection and may ultimately be less expensive than laboratory-based screening tests.<sup>32</sup>

Another evolving screening strategy uses proteomics, identifying patterns of genetic changes in blood and tissue that might signify lung cancer.<sup>33</sup> Researchers<sup>34</sup> have explored expanding this technique to analyze multiple tumor-associated antibodies at once, which may improve the accuracy of screening tests. A proteomic profile of tissue may also be used to screen for both invasive lung tumors and preinvasive lesions and may help to characterize the entire process of lung tumor development on a molecular level.<sup>35</sup> Potentially useful for both screening and monitoring, pattern diagnostic technologies might eventually lead to advancements in therapeutic targeting and customized treatments for patients.<sup>36</sup>

### *Biomolecular Markers*

Biomolecular marker screening techniques for the early detection of lung cancer are still under investigation. Biomarker screening limits patient exposure to potentially damaging constituents such as radiation and tends to be brief and easy for the patient. It remains unclear whether the tests under development will be associated with excesses of false-positive and false-negative results. Screening with biomarkers requires further clinical validation as well as subsequent cost-effectiveness evaluation before any formal recommendation may be made.

#### SUMMARY OF RECOMMENDATIONS

**1. We do not recommend that low-dose CT be used to screen for lung cancer except in the context of a well-designed clinical trial.**

Grade of recommendation, 2C

**2. We recommend against the use of serial chest X-rays to screen for the presence of lung cancer.** Grade of recommendation, 1A

**3. We recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer.**

Grade of recommendation, 1A

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