INTRODUCTION
Lung cancer is occurring in epidemic proportions. In the U.S. alone, there were projected to be >160,000 deaths in 2007 [1]. Lung cancer is the number one cancer killer in both men and women. The majority of patients present with advanced-stage disease. Most patients are symptomatic at the time of diagnosis and symptomatic lung cancer is mostly advanced-stage disease. Though treatments for advanced-stage disease have improved, nearly all patients with advanced-stage disease will die of the disease. Prevention and early detection offer means to reduce the current devastation from lung cancer. Early detection is uncommon in usual clinical practice; only 16% of all new lung cancers are localized (stage I/II) at diagnosis [1]. These individuals are usually asymptomatic and the cancer is detected by an incidental radiograph performed for other reasons. Patients with stage I disease have the best chance for cure. There is a great need for a screening test that results in the detection of asymptomatic lung cancer, at a time when there is a substantially better chance for curative treatment. The question is whether or not computed tomography (CT) is that screening test.

SUCCESSFUL SCREENING
Screening has been defined as testing individuals at risk who are asymptomatic for lung cancer. The purpose of screening is to interrupt or delay the development of advanced disease in those individuals who have a preclinical form of lung cancer [2]. A successful screening test should diagnose more patients in an early stage of disease, reduce the number of patients with late-stage disease, and result in fewer deaths from lung cancer.

Disease-specific mortality is the most appropriate outcome measure in the evaluation of screening effectiveness. Mortality is a population-based measure, and the denominator includes the entire population in the study. Lung cancer mortality in the screened population is the ratio of the number of deaths from lung cancer to the number of person-years of observation. Effectiveness of screening is determined by the reduction in deaths from lung cancer in the screened group versus the control group in a randomized controlled trial (RCT) [2].

Some authors suggest that longer survival in a nonrandomized, observational study demonstrates the effectiveness of screening. Survival is the proportion of individuals with lung cancer (diagnosed in the screening trial) who are alive 5 years (or some given time point) after diagnosis. Survival is a case-based measurement and includes only those individuals diagnosed with lung cancer in the screening trial; it does not take into account the entire screened population. Survival and mortality are distinctly different measures. Welch and associates used population-based statistics from the Surveillance, Epidemiology, and End Results program to evaluate the relationship over time between survival and mortality for the 20 most common solid tumor types [3]. There was little correlation between change in 5-year survival rate and change in tumor-related mortality for a specific tumor. From 1950 to 1995, there was an increase in the 5-year survival rate for each of the 20 solid tumor types. Over that same time period, mortality rates de-
clined for 12 tumors and increased for the remaining eight. The lung cancer 5-year survival rate was 6% in 1950–1954 and increased to 14% in 1989–1995. However, lung cancer mortality increased by 259%, and the incidence increased 249% over that same period. Screening will improve survival whether or not it leads to fewer people dying of lung cancer and is an inadequate measure of effectiveness.

The Mayo Lung Project (MLP), which was a screening RCT with chest radiography and sputum cytology conducted in the late 1970s and early 1980s, demonstrated that the 5-year lung cancer survival rate in the screened group was more than double that observed in the control group (33% versus 15%) [4]. However, there was no difference in lung cancer mortality in the screened versus control group (3.2 per 1,000 person-years versus 3.0 per 1,000 person-years). Despite the fact that, in the MLP there were more early-stage resectable lung cancers in the screened group, there were no fewer advanced cancers than in the control group. Deaths in the screened group and control group were similar (122 versus 115). The final interpretation of the MLP was that screening with chest radiography and sputum cytology was not effective and was not recommended for screening of high-risk smokers [5].

**Early-Stage Cancers in CT Screening Studies**

The International Early Lung Cancer Action Program (I-ELCAP) investigators reported the results of a large collaborative observational nonrandomized CT screening program. They screened >31,000 asymptomatic individuals at baseline and had repeat scans at 7–18 months in 27,000 plus participants. They detected a total of 484 lung cancers, of which 412 (85%) were clinical stage I lung cancer [6]. The percentage of stage I cancers reported is higher than that observed by others in other nonrandomized CT screening studies. In the Mayo CT screening trial, 39 of 66 lung cancers (59%) were stage I [7]. Novello et al. [8], in Italy, observed 73% stage I cancers and Diederich and associates [9], in Germany, reported 54% stage I cancers. Similarly, three small randomized CT screening trials also reported lower rates of stage I disease detection than in I-ELCAP: in the CT screening arm of the Lung Screening Study (LSS) [10], Depiscan trial [11], and the DANTE trial [12] 48%, 37.5%, and 57% were stage I, respectively. The reasons for the difference in the frequencies of stage I lung cancer in these trials versus the I-ELCAP trial are not known.

The I-ELCAP report calculated an 80% 10-year survival rate based on a median follow-up duration of 40 months [6]. While survival has been excellent in this and other nonrandomized screening trials, they all suffer from the three potential biases of screening: lead-time bias, length-time bias, and overdiagnosis [2]. Without a control arm, it is impossible to determine the degree of contribution of these biases to the survival results.

An RCT avoids the potential bias of single-arm screening trials that might enroll a more favorable population. Some of the centers in the I-ELCAP trial enrolled participants who had never smoked. Additionally, they screened a large number of East Asians, and recent observations have shown that adenocarcinomas in East Asians have a higher rate of epidermal growth factor receptor mutations and have a different biological behavior. The major limitation of all the screening trials reported to date is that none of them answer the question of lung cancer mortality benefit associated with screening. The need for an RCT was highlighted by the results of pooled data from three nonrandomized CT screening trials. In that report, the screened cohort of >3,000 participants was compared with a validated prediction model [13] (Table 1). CT screening found three times the number of expected cancers and resulted in 10 times the expected number of resections. Despite having a 94% actual 4-year survival rate for participants with clinical stage I cancers who underwent surgery, there were no fewer advanced-stage lung cancers or lung cancer deaths observed [13]. These results emphasize the need to evaluate the effectiveness of screening by mortality rather than survival.

**Problems with CT Screening**

In an attempt to obviate the pursuit of randomization at the point of screening, investigators have suggested that randomization of treatment could occur after diagnosis and provide the same information. This is problematic. The application of CT screening is expensive, results in a large number of false positives, and results in interventions for benign disease, some of which may be fatal, and the radiation involved increases the risk for cancer. As if those were not enough, randomization for treatment would be a patient care nightmare—could we really expect to randomize some participants with 2-cm cancers to surgery and others to observation? There may be some validity in randomizing treatments for pure ground-glass bronchoalveolar cancers (many of which likely represent overdiagnosis), but this does not begin to answer the effectiveness of screening versus no screening.

**Noncalcified Nodules—False Positives**

Noncalcified nodules (NCNs) detected by CT screening have the potential to be early cancers. The difficulty is in determining which NCNs are malignant and which are benign. All NCNs require some type of follow-up or evaluation based on the size of the lesion. Initial reports from
Japan and New York suggested a modest detection rate of NCNs of 17\%-26\% [14–16] (Table 2). However, these screening trials were conducted with single-detector CT scanners and used 1-cm thick CT slices. More recent trials with newer CT scanners have detected a much higher rate of NCNs [8, 9, 17, 18]. The Mayo Clinic CT screening trial employed a four-detector scanner with 5-mm collimation and 3.75-mm slice reconstruction and detected NCNs in 51\% (782 of 1,520) of participants on the baseline scan [17]. Studies from Canada, Germany, and Italy [8, 9, 18] used thinner collimation and detected NCNs in 43\%-60\% of their screened population. Accordingly, the number of NCNs does not reflect the geographic region of the world as much as it is determined by the CT slice thickness.

The size of the majority of NCNs is ≤7 mm. In the Mayo trial, after one prevalence scan and four incidence scans, in total, 3,356 NCNs were detected in 74\% of participants [7]. Of these NCNs, 61\% were <4 mm, 31\% were 4–7 mm, and 8\% were ≥8 mm. In the LSS, 37\% of the NCNs detected were ≤3 mm and 86\% were ≤9 mm [14]. Data from CT screening trials have demonstrated that NCNs ≤4 mm can safely be followed with a repeat CT scan in 1 year [19, 20]. The rate of small nodules ≤4 mm being malignant is <0.5\%. The Fleischner Society has published guidelines for recommended follow-up and management of NCNs detected incidentally at the time of a CT [21] (Table 3). The frequency of recommended follow-up is based on a low-risk or high-risk category determined by the individual’s smoking history and presence or absence of a prior malignancy. These guidelines caution that nonsolid (ground-glass opacity) or partly solid nodules may require a longer follow-up to exclude indolent adenocarcinomas.

### Biopsy and/or Surgery for Benign Disease

The LSS was a multicenter feasibility trial that randomized 1,660 participants to low-dose CT screening and 1,558 participants to chest x-ray [10, 22]. Of the 522 participants with a positive baseline CT screen, 12\% (n = 63) underwent biopsies, of which 33 were resection or open surgical biopsies. In total, 89 biopsies were performed on 62 participants, of which 36 were diagnosed with lung cancer. Twenty-six of the participants undergoing biopsies did not have lung cancer.

Pastorino and colleagues enrolled 1,035 individuals in a CT screening trial in Milan, Italy [23]. After two yearly CT screening scans, they diagnosed 22 lung cancers, but six additional patients (21\%) underwent surgical biopsy for benign disease. In the first 3 years (1999–2002) of the Mayo CT screening trial, in total, 55 participants underwent a thoracic surgical operation [24]. Benign disease was present in 10 patients (18\%), and lung cancer was identified in 45 (82\%). Complications occurred in 27\% of patients and

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**Table 1. CT screening and outcomes**

<table>
<thead>
<tr>
<th>Country</th>
<th>Lung cancer</th>
<th>Lung resection</th>
<th>Advanced lung cancer</th>
<th>Lung cancer death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>144</td>
<td>109</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Predicted</td>
<td>44.5</td>
<td>10.9</td>
<td>33.4</td>
<td>38.8</td>
</tr>
</tbody>
</table>


**Table 2. Prevalence of CT-detected nodules by slice thickness**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Screened n</th>
<th>NCN %</th>
<th>CT collimation</th>
<th>n of detectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al. [14]</td>
<td>Japan</td>
<td>1,369</td>
<td>588</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Nawa et al. [15]</td>
<td>Japan</td>
<td>7,956</td>
<td>2,099</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Henschke et al. [16]</td>
<td>U.S.</td>
<td>1,000</td>
<td>233</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Swensen et al. [17]</td>
<td>U.S.</td>
<td>1,520</td>
<td>782</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td>McWilliams et al. [18]</td>
<td>Canada</td>
<td>561</td>
<td>259</td>
<td>36 (60%)</td>
<td>7 (1.25)</td>
</tr>
<tr>
<td>Diederich et al. [9]</td>
<td>Germany</td>
<td>817</td>
<td>350</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Novello et al. [8]</td>
<td>Italy</td>
<td>520</td>
<td>278</td>
<td>53</td>
<td>8.8b</td>
</tr>
</tbody>
</table>

bNumbers in parentheses were observed on a four-detector scanner.

Abbreviations: CT, computed tomography; NCN, noncalcified nodule.

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there was one operative death (1.7%) in a patient with a resected cancer. Diederich and Wormanns summarized the rate of invasive procedures for benign lesions detected by CT screening. Invasive procedures were performed in 22%–55% of benign lesions [25].

In the report by Bach et al. [13], results of three CT screening trials from Instituto Tumori, Moffitt Cancer Center, and Mayo Clinic were pooled, and the results were compared with a validated prediction model for high-risk individuals [13]. In total, 109 lung resections were performed, which was 10 times the number of resections that were predicted (Table 1). Biopsies and/or operations for benign disease are a risk and cost that are associated with CT screening.

**OVERDIAGNOSIS**

Overdiagnosis is defined as the detection of a lung cancer that will not lead to an individual’s death because of slow growth and age-related competing risks for death. In the MLP, Fontana et al. [4] detected 206 lung cancers in the screened group and only 160 in the control group. They observed a higher 5-year survival rate, but no difference in lung cancer mortality, in the screened group [4]. Forty-six more cancers were diagnosed in the screened group, but they observed no difference in the number of lung cancer deaths. The most accepted explanation for these data is overdiagnosis.

Marcus and associates extended the follow-up period of the MLP for an additional 16 years (1999) and reported 585 participants with lung cancer in the screened arm and 500 in the control arm [26]. They concluded that the persistence of excessive cases in the intervention arm provided continued support for overdiagnosis in lung cancer screening.

In an analysis of data from the Mayo Clinic and Memorial Sloan-Kettering Cancer Center screening trials with chest radiography, Yankelevitz et al. [27] noted a mean volume doubling time of 101 days in the Mayo study and 144 days in the Memorial study. Only four of 87 cancers in those two trials had a volume doubling time < 400 days. The authors judged that a doubling time of > 400 days would be consistent with overdiagnosis. With a doubling time of 400 days, it would take a 3-mm lesion a total of 7.7 years to increase to the size of 15 mm (diameter) based on the exponential growth mathematical model doubling time.

In a Japanese CT screening trial by Hasegawa and colleagues, the authors detected 82 lung cancers and had serial CT scans on 61 of those cancers [28]. The cancers were classified into three different radiographic types: (a) ground-glass opacities (nonsolid), (b) part ground glass and part solid, and (c) solid lesions. The volume doubling times (VDTs) of these three groups were 813 ± 375 days, 457 ± 260 days, and 149 ± 125 days, respectively. At least 27 of these 82 CT-detected lung cancers had a VDT < 400 days and would be potential cases of overdiagnosis.

Lindell et al. [29] analyzed the Mayo CT screening trial and assessed the VDT of 48 lung cancers. The VDT for bronchoalveolar cell carcinomas (780 ± 1,545 days) and adenocarcinoma (746 ± 1,238 days) was substantially longer than the VDT for squamous cell cancer (103 ± 58), non-small cell lung cancer, not otherwise specified (81 ±

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**Table 3. Recommendations for follow-up and management of nodules <8 mm detected incidentally at nonscreening CT**

<table>
<thead>
<tr>
<th>Nodule size (mm)</th>
<th>Low-risk patient</th>
<th>High-risk patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>No follow-up needed</td>
<td>Follow-up CT at 12 mos; if unchanged, no further follow-up</td>
</tr>
<tr>
<td>&gt;4–6</td>
<td>Follow-up CT at 12 mos; if unchanged, no further follow-up</td>
<td>Initial follow-up CT at 6–12 mos then at 18–24 mos if no change</td>
</tr>
<tr>
<td>&gt;6–8</td>
<td>Initial follow-up CT at 6–12 mos then at 18–24 mos if no change</td>
<td>Initial follow-up CT at 3–6 mos then at 9–12 and 24 mos if no change</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT at around 3, 9, and 24 mos, dynamic contrast-enhanced CT, PET, and/or biopsy</td>
<td>Same as for low-risk patient</td>
</tr>
</tbody>
</table>

Newly detected indeterminate nodule in a person aged ≥35 years.

*Average of length and width.

*Minimal or absent history of smoking and of other known risk factors.

*History of smoking or of other known risk factors.

*The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.

*Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.

Abbreviation: CT, computed tomography; PET, position emission tomography.

31), and small cell cancer (49 ± 36). Thirteen lung cancers (27%) had VDTs >400 days. Eleven of the 13 lung cancers with VDTs >400 days were in women.

While the existence of “overdiagnosed” lung cancer is questioned by some, many physicians believe that it is a significant problem in the interpretation of current nonrandomized screening studies. The frequency of overdiagnosis is uncertain, but the reports summarized above suggest that perhaps 25% of CT-detected cancers may be “overdiagnosis.”

**Radiation Risk**

An issue of heightened concern is the risk for cancer associated with diagnostic x-rays [30]. The risk estimates associated with low-dose radiation were recently more accurately quantified based on 50-year follow-up data from survivors of the atomic bombs dropped on Japan in 1945. Survivors who received low doses of radiation, in the range of 5–150 millisieverts (mSv) (mean dose, 40 mSv), had a significantly higher overall risk for cancer. Similarly, large studies involving radiation workers in the nuclear industry, with an average dose of 20 mSv (range, 5–150 mSv), have demonstrated a higher cancer risk [30]. A report from the United Kingdom estimated that the attributed risk percentage of cancer resulting from diagnostic x-rays is in the range of 0.6%–1.8% of all cancers in developed countries [31]. It is estimated that 62 million CT scans were performed in the U.S. in 2006. The radiation dose in adults, to the organ being studied, is approximately 15 mSv [30]. The low-dose CT chest screening trial at Mayo employed 0.65 mSv of radiation and the scan was performed annually for 5 years. Any worrisome abnormality required follow-up interval CT scans and those were usually at full dose (5.8 mSv) [7]. Based on the estimate of CT use in the U.S. and the estimates of diagnostic radiation risk from the United Kingdom study, current CT usage may account for as much as 1.5%–2.0% of all cancers in the U.S. [30]. Although it is difficult to quantify the exact cancer risk associated with CT screening, it is fair to assume that there is some risk, and it is more than hypothetical.

**Summary**

The American Cancer Society states that: “Efforts at early detection (lung cancer) have not yet been demonstrated to reduce mortality.” “Newer tests, such as low-dose spiral CT scans and molecular markers in sputum, have produced promising results in detecting lung cancers at earlier, more operable stages when survival is better. However, there are considerable risks associated with lung biopsy and surgery that must be considered when evaluating the risks and benefits of screening” [32]. The American College of Chest Physicians in their evidenced-based guidelines made the following recommendations: “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” [5]. At present, no physician-based medical organization recommends screening for lung cancer in asymptomatic individuals, even if they are at high risk. Table 4 outlines the drawbacks or limitations of CT screening. A number of these points have been addressed above.

Currently, there are two large randomized screening trials that are nearing completion. The National Lung Screening Trial (NLST) is a multicenter trial that randomized >53,000 high-risk participants (2002–2004) to low-dose CT screening or chest radiography [33, 2]. Participants received a prevalence and two annual incidence rounds of screening. All participants were followed yearly by questionnaires after the screening rounds. Death certificates will be obtained on all deaths and the National Death Index will be searched for any participants lost to follow-up. Cumulative lung cancer mortality through August 2008 will be determined. The NLST is designed to be able to detect as little as a 20% decrease in mortality. These results will be reported in 2010.

The NELSON trial (Netherlands, Belgium, and Denmark) was launched in 2003, 1 year after the NLST [34]. High-risk participants were randomized to low-dose CT screening or no screening of any type. CT scans are performed at baseline, year 1, and year 3. Almost 20,000 participants have been enrolled, and the study will have an 80% power to detect a mortality reduction of 25%. These results will likely be available soon after the NLST trial results are known.

Based on the significant limitations in the results reported to date from nonrandomized, observational screening trials, we do not recommend CT screening for lung cancer. Results of these two large randomized controlled trials may provide the needed proof of efficacy in mortality reduction from screening.

**Author Contributions**

Conception/design: James R. Jett, David E. Midthun

Financial support: James R. Jett

Administrative support: James R. Jett

Provision of study materials or patients: James R. Jett

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**Table 4. Drawbacks or limitations to computed tomography screening for lung cancer**

| · Many nodules that require follow-up |
| · Potential psychological impact of discovering a nodule |
| · Surgery for benign disease |
| · Lung cancer deaths in screened participants |
| · Interval cancers (failure of screening) |
| · Potential overdiagnosis cases |
REFERENCES


