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Lung cancer screening

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Abstract Lung cancer screening with CT remains controversial. Lung cancer is the leading cause of cancer death. To date, no screening test has been demonstrated to reduce mortality. Given the large population of adult cigarette smokers and former smokers worldwide, there is a large population at risk for lung cancer. While a lot has been learned from prospective single-arm cohort studies about the feasibility of performing annual CT to screen for lung cancer, many questions have also been raised. While we know that screening for lung cancer with CT detects many small nodules, with up to half the subjects having a positive baseline screen, and up to 75% of subjects having a positive screen at least once if screened annually for 5 years, the great majority of these nodules exhibit benign biologic behavior. The innumerable small nodules detected with screening CT, and diagnostic chest CT in general, present a daily clinical challenge, and result in extensive medical resource utilization and additional radiation exposure. Algorithms for how and when to follow small nodules detected on CT are in evolution. Ongoing studies are designed to determine if lung cancer screening with CT reduces lung cancer mortality.

Keywords Cancer screening · Lung, CT · Lung, nodule · Lung neoplasms, CT · Lung neoplasms, diagnosis

Introduction

There is a need for a test to screen for lung cancer. Cigarette smoking is the leading cause of lung cancer, and there is a large population of current and former smokers worldwide. In the United States alone there are over 90 million adults who are current or former smokers, representing over 40% of the US adult population [1]. Lung cancer is the leading cause of cancer death in the United States for both men and women, having surpassed breast cancer in women. Lung cancer kills more men and women in the US each year than cancers of the breast, colon, and prostate gland combined. Whereas screening tests are available and demonstrated to be effective in reducing mortality from these latter cancers, no screening test has yet been proven to reduce lung cancer mortality.

Attempts to screen for lung cancer with sputum testing and/or chest radiography have not been shown to reduce lung cancer mortality [2]. Advances in CT scanner technology over the past decade, with single-detector CT scanners followed by multidetector CT scanners clinically in use with up to 64 detectors, make consistent high-resolution imaging of the lungs possible in only a few seconds.

Lung cancer screening with CT is a widely controversial subject. While there are many things we know about the detection of small nodules or nodule-like abnormalities on CT, and how CT performs relative to other radiologic tests such as the chest radiograph, many questions remain unanswered at this time.

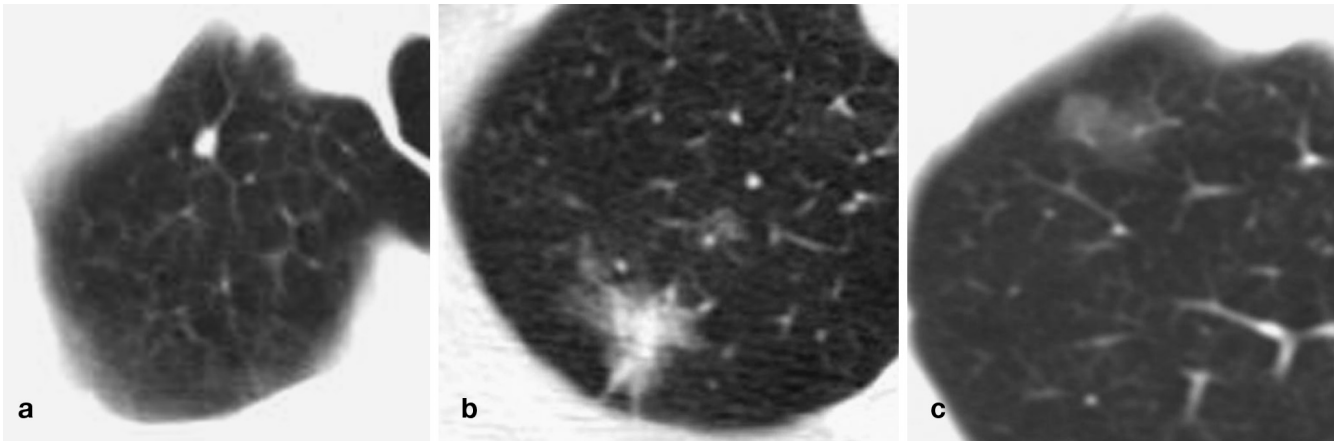

Fig. 1a-c Classification of pulmonary nodules on CT. **a** Solid nodule. **b** Part-solid nodule. **c** Nonsolid nodule, also referred to as a focal ground-glass opacity

Lung cancer screening with CT: the data

Many single-arm prospective cohort studies using CT for lung screening have been published, from Asia, Europe, and North America, cumulatively reporting more than 20 000 subjects to date. At baseline, referred to as prevalence data, these studies have found noncalcified nodules in 12–51% of patients, with cancer detection rates in screening trials ranging from 0.4 to 3.0% [3–7]. The percentage of cancers detected that are stage I is generally high, but ranges from highs of 84–93% in Japan, to lows of 44% in Florida, and 58% in Germany. Cancers detected on screening CT at baseline have a mean size of 15–25 mm, with 0-56% of cancers being 1 cm or smaller in size [3-6, 8].

Incidence data refers to annual screenings performed annually after the baseline screen, in which changes from the baseline examination are used to determine if the new CT examination is positive. Centers that have published incidence data report that 2.5–12% of subjects have new or growing lung nodules, a cancer detection rate of 0.26–1%, with 71–89% of cancers being stage I [6, 9, 10]. Of note, in one study 20% of the nodules found on screening examinations performed 1 year after baseline were not originally detected by the CT readers on the baseline screen, demonstrating how difficult the detection of small nodules can be on large CT datasets generated by today's multidetector CT scanners, often with 1–2-mm slice thickness throughout the entire lungs [6]. Computer-assisted diagnostic (CAD) tools that can assist the reader by identifying candidate lung nodules, similar to mammography, are becoming available. Additional CAD tools that may be of use to readers include estimation of nodule volume, and change in volume over time, so that doubling time can be calculated, thereby assessing biologic behavior [11]. While many tools exist, head-to-head comparison of these tools in workstation face-off settings has demonstrated inconsistency among them, and further refinement of these tools is still necessary.

After 5 years of annually screening 1520 subjects at the Mayo Clinic, 3356 total noncalcified lung nodules were found (mean 2.2 per subject), in 1118 or 74% of subjects [12]. Drawing on these data, three in four subjects enrolled in annual screening CT programs may have at least one noncalcified nodule over a 5-year period that warrants further evaluation. This evaluation may include at a minimum serial CT scans, and possibly PET scan, percutaneous biopsy, bronchoscopy, or even surgical resection, each with its attendant risks for morbidity, and in some cases, mortality. For example, screening CT with follow-up CT examinations for small nodules is associated with additional radiation exposure. According to one estimate, if we assume that the entire US population of 50–75-year-old current and former smokers undergoes annual lung screening CT until age 75, with a 50% compliance rate, and using the atomic bomb survivor cohort for predicting risk, there would be a 1.8% (95% CI 0.5–5.5%) increase in lung cancer attributed to screening CT, or 36 000 additional lung cancers [13]. In addition, these additional tests increase medical resource utilization and expense, at a time when per capita costs of medical care continue to rise.

So, what we do know is that lung screening CT detects many non calcified nodules, in up to half of screening individuals at baseline and up to three-quarters of individuals undergoing screening CT for 5 years. The majority of these nodules are benign. The fact that lung cancers found with screening CT are predominantly stage-I cancers is promising. There is no randomized controlled trial data of subjects undergoing and not undergoing CT, to know if lung cancer screening with CT reduces lung cancer mortality. The National Lung Screening Trial (NLST), funded by the National Cancer Institute in the

United States, is a randomized trial of CT versus chest radiography for lung cancer screening. With a study population of 50 000 subjects, the NLST is powered to detect a 20–25% reduction in lung cancer mortality as its primary outcome. Secondary outcomes include all cause mortality, stage distribution of lung cancer, and medical resource utilization, as well as the quality of life and psychological impact of a positive screen. Subjects in this trial are currently undergoing their third annual screening CT, and no data are available at this time.

An everyday clinical question is how to manage small lung nodules once they are detected. Nodules large enough for percutaneous biopsy or PET scan are generally 8-10 mm or larger in size. It is the smaller nodules, that are not amenable to percutaneous biopsy or PET, that present the greatest diagnostic dilemma. One way to approach this is by classifying nodules into solid, part-solid (solid and ground-glass) and nonsolid (ground-glass) nodules (Fig. 1) [14]. This is important, as nonsolid or ground-glass nodules have a higher likelihood of being malignant than solid nodules. For example, in the Early Lung Cancer Action Project (ELCAP) baseline CT screening cohort of 1,000 subjects, 233 had a positive result, with 31 cancers. Of the positive screens, in 44 (19%) subjects the largest nodule was either part-solid (n=16) or nonsolid (n=28). While 7% of solid nodules were malignant, the malignancy rate for nonsolid nodules was 18% (5/28) and for part-solid nodules was 63%. Given this information, nodules with a ground-glass or nonsolid component may warrant more intense follow up than solid nodules. Another way to classify the probability of malignancy based on CT alone is nodule size. The ELCAP group in a report of 2897 CT screened subjects found no cancers in the 374 noncalcified nodules that were less than 5 mm in size, while 5.9% of the 238 nodules 5–9 mm in size were malignant, suggesting that nodules 5 mm or smaller do not require follow up CT within less than 12 months [15]. The NLST recommendations are that nodules less than 4 mm go back to annual screening, and do not warrant shorter-term follow-up CT. So, for smaller nodules, less than 4–5 mm, follow-up CT examinations at 12 and 24 months is reasonable. Some would argue that such small nodules in patients not at risk for lung cancer (nonsmokers) do not require follow up at all. For nodules 5–10 mm in size, follow-up CT is usually performed at 6, 12, and 24 months. It is very difficult to visually estimate 1–2-mm changes in the diameter of small pulmonary nodules. Given the increased frequency of malignancy in nodules with a ground glass or non-solid component, an additional follow-up CT at 3 months is recommended. A short course of antibiotics in the interval may be useful for these latter patients as well, so that small infectious foci may more quickly resolve.

Lastly, CT allows us to detect lung cancer through the identification of changes in normal lung parenchyma. The advantage of CT over chest radiography is that CT can find more and smaller nodules. Basically, CT finds small nodules that may or may not be cancer. There is the inherent assumption that a small cancer is an “early” cancer; however, as some studies have reported as many as 42–56% of screen detected cancers are not “early” stage-I cancers. In clinical practice, it is not uncommon to come across a small adenocarcinoma when asked to perform chest CT in a patient who presents with brain metastases as a first manifestation of lung cancer. Furthermore, there is some evidence that size is not everything in lung cancer. Two studies have reported that there is no significant relationship in either the stage distribution of cancer or cancer survival in patients with smaller primary lung tumors [16,17]. So, the advantage of CT in being able to find small nodules may not be enough. Extensive work is ongoing to find biomarkers that could be screened for in blood or sputum samples in addition to or instead of screening CT.

Conclusion

In closing, prospective cohort studies confirm that lung cancer CT screening is feasible, and results are encouraging, showing a stage shift to earlier-stage cancers than in patients who present clinically. A mortality benefit has not yet been demonstrated. Active research in this area is extensive, and should provide answers to the many unanswered questions.

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