Current status of lung cancer screening

An estimated 226,000 Americans will be diagnosed with lung cancer this year alone. It is the leading cause of cancer death for U.S men and women with an estimated 160,000 lung cancer deaths to occur this year [1]. Researchers have noted that historically patients with cancers detected earlier generally had better outcomes, leading to studies to evaluate the efficacy of screening. This article summarizes the current state of lung cancer screening.

Before discussing current thinking, historical prospective is important. For many years CXR was used to identify and characterize lung cancers. Regular chest x-rays certainly detected lung cancer and, by inference, CXR was thought to be useful to screen for lung cancer. However, in multiple studies, CXR was not been shown to save lives. One of the largest trials to examine effect on mortality was the PLCO (prostate, lung, colorectal and ovarian) Cancer screening trial, recently reported in JAMA [2]. This large long term study enrolled 155000 men and women, ages 55-74 between 1993 and 2001. Participants were assigned to either CXR screening or "standard usual care" and were followed for up to 13 years. Despite the large sample size and long term follow-up, annual screening with chest radiograph did not reduce lung cancer mortality compared with usual care.

With the advent of CT, its potential utility in patients with lung cancer was quickly realized. Not only was it invaluable in staging lung cancer, but it could discover smaller nodules than was possible with CXR. It was well known that death rate was less in Stage 1 disease compared to more advanced disease which lead several investigators to evaluate the utility of CT to screen for early disease. One of the largest studies was also probably the most controversial. The International Early Lung Cancer Action Program (I-ELCAP) study of CT screening for lung cancer was reported by Henschke et al in the NEJM in 2006.[3] That study concluded that annual spiral CT screening could detect lung cancer that was curable. They went on to claim screening could prevent some 80% of deaths from lung cancer. Many opponents suggested the study was significantly biased, over-diagnosis and only estimated survival benefit based upon too short of observation. Further, there was no control group included in the study. Despite the limitations, significant interest in CT lung screening was generated, although subsequent studies could not reproduce the reported survival benefit.

With the increase in CT utilization for screening and diagnosis, at about the same time investigators realized that small lung nodules were extremely common [4]. 50% of smokers over the age of 50 had at least one nodule. Existing guidelines were that every indeterminate nodule needed to be followed for a minimum of 2 years. The Fleischner Society proposed changes to this thinking. Based upon statistical data , they determined that nodules between 4 and 8 mm had less than 1% chance of malignancy and an incidental nodule less than 4mm in an otherwise low risk patient, had such a low probability of malignancy, it did not even need follow-up. Subsequent studies focused on risk stratification of the

"incidental pulmonary nodule". With the increasing database of morphologic features of benign and malignant nodules, the relative statistical risk of malignancy could be calculated based upon nodule size, borders, presence of calcification, PET activity, location in the lung and other factors. Interval growth was particularly important and thin section CT was excellent at determining very small changes in nodule volume. But even with the preponderance of CT data, until the NLST study, definite survival benefit using CT screening could not be established.

The National Lung Screening Trial (NLST)[5] study published last year in NEJM was designed to show benefit of low dose CT screening in a certain subset of the population. It studied a large number of patients over 5 years with strict standards of follow-up. It randomized patients to CXR or CT lung screening. To improve statistical significance, it only looked for modest survival benefit and utilized high risk heavy smokers. It concluded that in active smokers aged 55 to 74, with at least 30 pack year history, there was a 20% reduction in risk of dying from lung cancer with just 3 annual CT screenings. Further, the study found that CT detected lung cancer at an earlier stage and lower grade histology, but required many follow-up scans.

Proponents of screening suggest that, even with the modest survival benefit found, nearly 5000 lives could be saved if all of the approximately 7 million Americans who fall into the inclusion criteria were screened. Further, the study only looked at benefit of three consecutive annual screens. There could be further benefit with longer term screening. Perhaps people in other age groups, lesser smoking history or even those with exposure to second hand smoke might benefit. There are potential cost savings generated as well. Surgery for stage I lung cancer is less than half the cost of late-stage treatment.[6] Some thought that participation in screening programs might even help in smoking cessation.

But to what cost are these benefits worth? Opponents fear huge economic implications to national CT screening. Molecular markers in blood, sputum, and bronchial brushings had been studied but were currently unsuitable for clinical application.[7] And while these markers in themselves may not screen for cancer, they might help guide which patients would most benefit from CT lung screening. Funding of further research might be fruitful. Why not spend money on this type of research instead of mass CT screening? The incidence of heavy smoking is significantly declining in this country [8]. IN 1965, approximately 23% of adults were "high-intensity" smokers (>20 cigarettes/day), but by 2007, that number had decreased to 7.2%, attributed to both reduced smoking initiation and increase in smoking cessation. Coincidentally, lung cancer mortality also declined in this country since 1965. Many proposed funding of smoking cessation programs rather than nationwide screening. Wouldn't that decrease mortality too?

Is CT lung screening safe? While a relatively rare occurrence, in the NLST study 16 patients died within 60 days of a diagnostic procedure recommended from screening. 6 of them had benign nodules. There is little doubt that the radiation from CT scanning will cause cancers in a small fraction of patients. However, low dose techniques offered at many institutions limit this risk and screening CT can expose patients to as little radiation as a mammogram. Available data suggests the risk of cancer from each CT is probably less than 0.01%. [9] If the survival benefit from 3 screenings and interval follow-up scans is 20%, the benefit far outweighs the risk. However, this may not be the case in lower risk populations.

Despite all the potential limitations, the NLST did show benefit in a subset of population. The NLST is considered a landmark study by some, but at the very least cannot just be disregarded. The American Colleges of Radiology and Chest Physicians, American Cancer Society, the American Society of Clinical Oncology and the National Comprehensive Cancer Network have all issued updated statements on low dose CT lung screening. Whether they recommend "screening be routinely offered or merely suggest "patients may consider screening", CT lung screening probably has a role in certain patients. As with many studies, often more questions are posed rather than solutions. More studies like the NLST are already in the works. Stay tuned.

References

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