SPIRAL CT SCREENING FOR LUNG CANCER IS READY FOR PRIME TIME

James R JETT*

More Americans die of lung cancer than from any other cancer. In 2000, it was estimated that there would be 164,000 new cases and 157,000 deaths (1). There are more deaths from lung cancer in the United States than the next three most common cancer causes of death (colorectal, breast, prostate). The other repulsive statistic is the lack of improvement in 5 year survival since the mid 70s, for lung cancer. In contrast, there has been significant improvement in 5 year survival for the next 3 most common cancer killers (Table 1). Why the lack of improvement of survival for lung cancer? A partial answer is that we screen for colorectal, breast, and prostate cancer but not for lung cancer. The official position of the American Cancer Society is that there is no role for screening of lung cancer even in higher risk individuals such as smokers or those with significant occupational exposures. If we were to continue to follow this recommendation then we would wait for patients to present with symptomatic lung cancer. Symptomatic lung cancer is mostly advanced cancer (Stage III or IV). . Currently, only 15-20% of all lung cancers are Stage I at the time of diagnosis. Symptomatic lung cancer has a 10% 5 year survival while asymptomatic lung cancer has a 40-50% 5 year survival (2). If we wait for patients to present with symptomatic lung cancer then we will continue to bury them.

Table I:

Primary State of Cancer	Number of New Cases	Number of Deaths	5 Year Survival 1974-76	1989-95
Lung	164,100	156,900	13	14
Colorectal	130,200	56,300	50	62*
Breast	184,000	41,200	75	85*
Prostate	180,400	31.900	67	92*

* The difference in rates between 1974-1976 and 1989-1995 is significart ($p<0.05$).

Data from American Cancer Society (2000).

* Thoracic Diseases and Medical Oncology Mayo Clinic, Rochester, Minnesota, USA.

PAST SCREENING TRIALS

It is the goal of a screening program to detect cancer at an earlier stage when it is asymptomatic and when treatment results in a higher cure rate. As a result of early detection, there should be less cases presenting with more advanced diseases. In the 1970s the National Cancer Institute sponsored three lung cancer screening trials at Memorial Sloan Kettering Cancer Center, Johns Hopkins medical center, and Mayo Clinic (2-6). Each center enrolled approximately 10,000 men who were 45 years of age or older and were smokers. The Memorial and Hopkins trials randomized individuals at baseline to yearly chest radiographs versus yearly chest radiographs and sputum cytology every 4 months (4-5). Neither study observed a difference in the survival or mortality (deaths from lung cancer) in the dual screened versus the control group (7,8). Thus, they proved that adding four monthly sputum cytology to yearly chest radiographs does not decrease lung cancer mortality. The Mayo Clinic trial screened all individuals at baseline with chest roentgenogram and sputum cytology. If the initial screen was negative for cancer then they were randomized to chest roentgenograms and sputum cytology every 4 months or the control group. The control group was advised to have a yearly chest roentgenogram and sputum cytology (standard Mayo Clinic recommendations in 1970s) but then their individuals were never reminded again to have these tests. Both groups received subsequent questionnaires. In the Mayo trial, the screened group had 206 cases of lung cancer detected versus 160 lung cancers in the control group and the 5 year survival was 35% in the screened group versus 15% in the control. However, there was absolutely no difference in the lung cancer mortality in the two groups (3.2/1,000 person years versus 3.0/1,000) (9). Based on these three trials it was concluded that screening for lung cancer does not decrease mortality and, therefore, there was no role for any screening. In a recent report, Marcus et al, performed a follow-up of the Mayo Lung Project patients through 1996 (10). While all screening ceased in 1983, there continued to be a survival advantaged in the screened group versus the control, however mortality in the two groups was the same (4.4/1,000 versus 3.9/1,000 person years). They attributed the improved survival without mortality benefit to “over diagnosis.” An over diagnosed lung cancer was defined as a lesion that never would have progressed to clinical disease during a person’s lifetime. The concept of “over diagnosis” is difficult for a clinician to accept since we seldom see a case of lung cancer that does not progress. While an occasional case progresses slowly, they all

progress. Most do so rapidly. It is fair to assume that none of the 150,000 plus lung cancer deaths this year were "over diagnosed" cases.

MISS RATE FOR DETECTION OF LUNG CANCER BY CHEST ROENTGENOGRAMS

In a report from the Mayo clinic screening trial, 90% of peripheral carcinomas and 75% of perihilar carcinomas were visible in retrospect on older chest x-rays (11). Quekel and associates reviewed 259 non-small cell lung cancers presenting as nodular lesions and noted that in 49 (19%) cases the lesion was missed on a previous radiograph. The median diameter of the missed lesion was 1.6 cm (range 0.6-3.8). A recent report from New York City noted 31 cases of missed lung cancer by chest roentgenograms. The mean diameter was 2.0 cm 0.8 cm (range 0.6-3.6) (13). This included 6 cancers that were 3.0 cm. Sone et al compared chest radiographs to spiral CT scans in 44 cases of lung cancer detected in a spiral CT scan screening trial (14). The chest x-ray failed to detect 77% (34/44) of all cancers. The tumor diameters ranged from 6 mm to 45 mm but only 2 were greater than 20 mm. Accordingly, we can conclude that the chest roentgenogram is not a sensitive tool for screening purposes (11-14). Using chest radiographs we will miss the majority of lung cancer ≤ 2 cm in diameter. This should not surprise us since it is known that 25% of the lung parenchyma is hidden by normal structures such as the diaphragm, heart, and mediastinum on the standard PA chest radiograph.

SPIAL CT SCANS FOR SCREENING

The earliest report of the use of low dose spiral CT scan for screening was from Kaneko et al (15). They screened smokers who were at high risk and detected 15 cases of lung cancer. The chest radiograph in 11 of these individuals was negative. Most remarkable was the observation that 14 of the 15 tumors were Stage I. A second study was reported by Sone and colleagues (16). They diagnosed 19 cases of lung cancer. The mean size was 17 mm (a size usually missed by chest radiographs). Sixteen of 19 patients were pathological Stage I. This is most remarkable because of the fact that currently in the United States only 20% of newly diagnosed lung cancers are Stage I.

In 1999, a New York City group reported on their baseline screening results with low dose spiral CT scans. They screened 1,000 symptom free volunteers who were 60 years of age or older with at least 10-pack years of smoking (17). A lung cancer was detected in 27 individuals by CT for a detection rate of 2.7% but the cancer was visible by chest radiograph in only 7 (detection rate of 0.7%). Twenty-two of the 27 lung cancers were stage I A. Twenty-four of 25 patients who underwent operation were resectable for potential cure. In 15 of the 27 lung cancer cases, the tumor diameter was 10 mm or less and in another 8 patients the maximum tumor diameter was between 11 and 20 mm.

A Mayo Clinic screening trial enrolled 1,520 individuals 50 years of age or older, who had a smoking history of at least 20-pack years (18,19). All had a life expectancy of at least 5 years. As of October, 2,000 we detected 19 prevalence cancers (18). Two were small cell histology, a cell type for which screening is not likely to be beneficial due to the rapid tumor doubling time. Of the 17 non-small cell lung cancers, 6 were ≤1 cm and 8 were 1.1-2.0 cm in diameter. Fifteen of the 17 NSCLC cases were stage I or II (88%) and underwent curative resections. Thus it is clear from the studies from Japan, New York, and Mayo Clinic that spiral CT scans detect lung cancers at an average size of 1.5 cm or less and approximately 80% of patients will have stage I A disease (15-20). This size is a size that is usually missed on chest roentgenogram. Low dose spiral CT scan can be performed with a single breath hold and patients scanned in 12-15 seconds. The dose of radiation is approximately one-ninth that of a standard CT scan and roughly equivalent to that of mammography (19).

LIMITATIONS OF SPIRAL CT SCAN STUDIES

One major concern of the nihilistic pundents is the high rate of detection of indeterminate nodules with spiral CT screen. In the New York series they detected nodules in 23% of those screened (17) and in the Mayo series we detected at least one nodule in 51% (18). In the Mayo series, 89% of all the nodules detected were 7 mm or less and a size that we judged was safe to observe. Obviously, these nodules necessitate follow up scans at periodic intervals. The optimal frequency of follow-up is being evaluated. However, to date we have not detected a lung cancer in a nodule 7 mm or smaller. That is almost certain to occur as we follow the tiny nodules for a longer period. It should be remembered that mammograph screening has some of these same limitations. The estimated cumulative risk of a false positive mammogram is 49% after 10 mammograms and 19% of women without breast cancer will undergo a biopsy (21). Nevertheless, this has not deterred women

from subsequent screening mammography after an initial false positive scan (22). Most importantly, it should be noted that screening mammograph results in the detection of breast cancer at an average size of 1 cm and the 5-year survival for all breast cancer patients is 85% (23, 1). From 1990-1996, breast cancer deaths are decreasing at 1.8% per year and screening mammography is responsible in large part for the decreasing mortality. We now have a test for detecting lung cancer at a size similar to that of breast cancers detected by mammography. How can we not enthusiastically endorse such a new screening modality?

A major concern about low dose spiral CT scan screening is cost. Of note is that a single scan from the sternal notch to iliac crest can be performed in 12-15 seconds. There is no contrast involved. Patients are in and out of the scanner quickly. At Mayo, we are able to scan 6 patients in 30 minutes without difficulty. With this efficiency it is estimated that the actual cost of low dose spiral CT screening may be in the range of $150. When nodules or other abnormalities are detected this necessitate follow-up tests. Even when these follow-up scans, biopsies, and surgery for lung cancer are considered, one group of investigators have estimated the cost effectiveness for lung cancer screening to be less than $10,000 per year of life saved (24).

The spiral screening trials to date has mainly reported on prevalence (baseline or first screening) data. The Japanese data contains both prevalence and incidence cases but they are not easily separated out in their reports. Recently, Ohmatsu and colleagues did report a 5 year survival of 78% (20). Most investigators believe that the incidence scans (after baseline) will detect earlier stage cancers than the prevalence scans (first baseline scan). To date there are no randomized trials comparing screening with spiral CT versus chest radiographs or observations only. These trials will need to be performed before we can determine if spiral CT screening results in a deceased mortality from lung cancer. However, based on the early data, it is not unreasonable to hypothesize that spiral CT scan screening may very well result in a 20% reduction in lung cancer mortality. If that would turn out to be correct then there would be 30,000 less deaths per year due to lung cancer. This reduction in cancer deaths would almost be equivalent to curing prostate cancer or breast cancer (Table I).

PROMISING NEW DEVELOPMENTS

Two new developments that are likely to be implemented in the next few years are the computer aided diagnosis (CAD) systems and the nodule volumetric measurement software packages (25,26). The CAD system will aid the radiologist in the detection of small nodules and help decrease the miss rate for detection of small nodules (25). The volumetric measurements will provide us with a 3 dimensional technique for volume determination that is superior at detecting asymmetric growth of a nodule that could be missed by 2 dimensional measurement (26). A recent report has demonstrated that tumor doubling times of cancers can be determined with scan intervals as short as 30-40 days (26). With this system these tiny nodules will be accurately measured with an automated system and the volume calculated. The subjectivity of the radiologists' measurements will be eliminated.

In conclusion, spiral CT scan screening for lung cancer is the single most exciting new development in lung cancer that I have witnessed in my 20-year career (19). It offers us the hope of significantly increasing lung cancer survival and decreasing mortality. Even though there are issues of cost and mortality reduction that need to be determined, I would recommend spiral CT scan screening for my brother or sister if he/she were a smoker. From an objective viewpoint, I personally would like to see a definitive randomized trial conducted to evaluate lung cancer mortality in spiral CT scan screened versus chest radiograph screened individuals. However, until that evidence is available, I believe that spiral CT scan screening for lung cancer should be utilized for high-risk individuals.

REFERENCES

1. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer Statistics 2000. CA: A Journal for Clinicians 2000; 50:7-33.
2. Fontana RS, Sanderson DR, Taylor WF et al. Early lung cancer detection: Results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic Study. Am Rev Resp Dis 1984; 130:561-565.
3. Berlin NI, Buncher CR, Fontana RS, et al. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Am Rev Resp Dis 1984;130:545-549.
4. Frost JK, Ball WC, Levin M, et al. Early lung cancer detection: results of the initial prevalence radiologic and cytologic screening in the Johns Hopkins Study. Am Rev Resp Dis 1984; 130:549-554.
5. Flehinger BJ, Melamed MR, Zaman MB, et al. Early lung cancer detection: results of the initial

(prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering Study. Am Rev Resp Dis 1984;130:555-560.
6. Early Lung Cancer Detection: Summary and Conclusions. Am Rev Resp Dis 1984; 130:565-570.
7. Melamed MR, Flehinger BJ, Zaman MB et al. Screening for early lung cancer. Chest 1984;86:44-53.
8. Tockman MS. Survival and mortality from lung cancer in a screened population. Chest (suppl) 89:324S-325S.
9. Fontana RS, Sanderson DR, Woolner LB et al. Lung Cancer Screening: The Mayo Program. J Occup Med 1986;28:746-750.
10. Marcus PM, Berstralh EJ, Fagerstrom RM, Williams DE, Fontana R, Taylor WF, Provok PC. Lung Cancer Mortality in the Mayo Lung Project: Impact of Extended Follow-up: J National Cancer Institute 2000;92:1308-1316.
11. Muhm JR, Miller WE, Fontana RS et al. Lung cancer detected during a screening program using four-month chest radiographs. Radiology 1983; 148:609-615.
12. Quekel GBA, Kessels AGH, Goei R, van Engelshoven JMA. Miss rate of lung cancer on the chest radiograph in clinical practice. Chest 1999;115:720-724
13. Kumar-Shah P, White CS, Haramati LB, Pearson GD, Shiau MC, Austin JH: Missed Non-Small Cell Lung Cancer: Radiographic Findings of Potentially Resectable Lesions Evident Only in Retrospect [abstract] Radiology (suppl) 2000; 217:244.
14. Sone S, Li F, Yang ZG, Takashima S, Maruyama Y, Hasegawa M, Wang JC, Kawakami S, Honda T. Characteristics of small lung concerns invisible on conventional chest radiography and detected by population based screening using spiral CT : Br J Radiology 2000;73:137-145.
15. Kaneko M, Eguchi K, Ohmatsu H et al. Peripheral Lung Cancer: Screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:698-802.
16. Sone S, Takashima S, Li F et al. Mass Screening for Lung Cancer with Mobile Spiral Computed Tomography Scanner. Lancet 1998;351:1242-1245.
17. Henschke CI, McCauley DI, Yankelevitz DF et al. Early lung cancer action project: Overall design and findings from baseline screening. Lancet 1999; 354:99-105
18. Jett JR, Swensen SJ, Midthun DE, Hartman TE, Aughenbaugh GL, Sloan JA, Sykes AM, Scanlon PD, Halling AC, Tazelaar HD: Screening for Lung Cancer with Low Dose Spiral Computed Tomography: The Mayo Clinic Trial [abstract] Am J Respir Crit Care Med 2001 (In press).
19. Jett JR: Screening for Lung Cancer in High-Risk Groups: Current Status of Low Dose Spiral CT Scanning and Sputum Markers. Sem Resp Crit Care Med 2000;21:385-392.
20. Ohmatsu H, Kakinuma R, Kaneko M, Moriyama N, Kusumoto M, Eguchi K: Successful Lung Cancer Screening with Low-Dose Helical CT in Addition to Chest x-ray and Sputum Cytology: The Comparison of Two Screening Periods with or without Helical CT [abstract] Radiology 2000; 217(suppl):242.
21. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW: Ten-year Risk of False Positive Screening Mammograms and Clinical Breast Examinations. New Engl J Med 1998; 338:1089-1096.
22. Burman ML, Taplin SH, Herta DF, Elmore JG. Effects of False Positive Mammograms on Interval Breast Cancer Screening in a Health Maintenance Organization. Ann Int Med 1999; 131:1-6.
23. Curpen BN, Sickles EA, Sollitto RA, Ominsky SH, Galvin HB, Frankel SD. The Comparative Valve of Mammographic Screening for Women 40-49 Years Old Versus Women 50-64 Years Old. AJR 1995;164:1099-1103.
24. Wisnivesky JP, Braz-Parente D, Smith JP, Yankelevitz DF, Henschke CI: Cost-Effectiveness Evaluation of Low-Dose Computed Tomography Screening for Non-Small Cell Lung Cancer. [abstract] Radiology 2000;217(suppl):244.
25. Armato SG III, Giger L, Moran CJ, Blackburn JT, Doi K, Mac Mahon H. Computerized detection of pulmonary nodules or CT scan. Radiographics 1999;19:1303-1311.
26. Yankelevitz DF, Reeves AP, Kastis WJ, Zhao B, Henschke CI: Small Pulmonary Nodules. Volumetrically Determined Growth Rates Based on CT Evaluation Radiology 2000;217:251-256.