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REVIEW ARTICLE

SCREENING FOR LUNG CANCER: TO DO OR NOT TO DO?

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Screening for cervical cancer, breast cancer and colon cancer have all been shown to decrease deaths due to these cancers.[1] For these cancers, it has been accepted that early detection is beneficial. Is lung cancer different? Internationally, lung cancer is thought to be the number one cancer killer.[2] It is the number one cause of cancer deaths (160,000) in the United States[3] and most of the western nations. One estimate is that there are 500,000 deaths per year in China due to lung cancer (3). That number is likely to increase in East Asian countries as the current smoking rate is very high. Accordingly, there is a tremendous need for an early method of detection when the cancer is potentially treatable for cure. Presently in Western Europe and North America only 10-20% of patients with lung cancer are diagnosed with stage I disease, which is usually asymptomatic. Symptomatic lung cancer is usually advanced stage disease so if we are going to make progress then we need to diagnose patients before they are symptomatic. In the past 10 years, trials have been conducted with spiral CT scans in an effort to diagnose and treat early lung cancer. Those trials have demonstrated some promising results and associated risks.

BENEFITS OF CT SCREENING

The potential benefits of screening have been well demonstrated Table 1. First, CT screening detects much smaller lesions than those detected by chest radiographs.[4] Clinical trials have shown that when simultaneous chest CT and chest radiographs are performed, the radiographs will miss 70-80% of the cancers detected by CT.[5,6] The average size of the CT detected lesion is 1.2-1.5 cm versus 3.0 cm for chest roentgenogram detection.[4] These smaller size cancers are more frequently stage I.

Table 1. Positive results of ct Screening for lung cancer.

Detects more lung cancers
Detects smaller size cancers
Detects earlier stage cancers
Results in better survival
Improves rate of smoking cessation
Detects ancillary cancers and life threatening diseases

A number of non-randomized CT screening trials have reported the rate of lung cancers detected in stage I to vary from 60-90%.[4,7,8] The well known I-ELCAP trial reported 85% clinical stage I lung cancers. The Mayo Clinic Trial detected 70% of

prevalence cancers in stage I and 61% of incidence cancers in stage I.[8] Along with the early stage, investigators are reporting remarkable survival results.[7] The I-ELCAP study reported survival rate of 88% in their screen detected lung cancer. Bach and colleagues also noted a 94% 4-year survival in data pooled from 3 institutions conducting non-randomized CT screening trials.[9] An additional benefit of CT screening includes a high rate of smoking cessation of approximately 20% among participants. Screening serves as a teachable moment for the benefits of quitting smoking. Another potential benefit of screening is that it sometimes detects additional cancers or serious other medical problems.

Risks and Limitations of CT Screening

The risks and limitation of screening have also been delineated Table 2.[10] In the Mayo Clinic Trial, we detected non-calcified nodules (NCN) in 51% of participants on the baseline CT scan.[8] After 5 yearly scans, NCN were identified in over 70% of participants. Others have reported similar findings.[5,11] With 3 years of follow-up of the baseline NCN in the Mayo trial, less than 2% of NCN were proven to be malignant. Most did not change in size or resolved. The identification of a NCN in a high risk individual (current or former smoker and 50 years or older) requires follow-up CT scans at some interval. Recently, the Fleischner Society has published recommended guidelines for the frequency of their follow-up.[12]

Table 2. Drawbacks or limitations to Ct 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 over-diagnosis cases

Along with the discovery of a NCN is the risk of operation for benign disease. In the Mayo Clinic CT Screening Trial 10 or 55 (18%) thoracic operations were for benign disease.[13] A similar rate of operations for benign disease was observed by Pastorino and associates.[14]

A limitation of any screening tool is the development of interval cancer. These rapidly growing cancers cause the development of symptoms and are diagnosed between the annual CT screening examination. Many of these are small cell lung cancer. CT screening does not prevent all deaths due to lung cancer. In the Mayo Clinic Study, 9 NSCLC were diagnosed with stage III or IV disease, and a total of 12 deaths due to all cell types have occurred.[8] In a study out of Germany, Diederich observed 6 deaths out of 26 detected cancers (23%).[15]

Finally, there is the issue of over-diagnosis. This is not a misdiagnosis, because pathologically all of these lesions are cancer based on careful pathological review. Over-diagnosis is defined as a cancer that will not lead to the death of the patient. This is similar, ideologically, to the autopsy finding of prostate cancer in an elderly man who died of other causes, such as heart disease, trauma, etc. Over-diagnosis is generally accepted as the explanation for the results of the old screening trials with chest radiograph and sputum cytology versus observation alone. The screening arm diagnosed 206 lung cancers while only 160 cancers were observed on the control arm.[16] The screened arm had a significantly better 5 year survival, but there was no difference in lung cancer deaths on the screened versus no screening arm of the trial. The extra 46 cases of lung cancer on the control arm were thought to represent, "over-diagnosed" cases.[17] The two publications that strongly suggest over-diagnosis with CT screening are the reports from Japan and the United States.[18,19] Hasegawa and colleagues were able to calculate volume doubling time (VDT) in 61 cases of 82 CT detected lung cancers.[18] Twenty-seven or 33% of the 82 cancers had a VDT over 400 days. The lung cancers that

were of ground glass opacity on CT had an average VDT of 813±375 days. Lindell et all reported the VDT in the Mayo CT screening trial.[19] The VDT of bronchoalveolar carcinoma was 780±1545 days and adenocarcinomas had a VDT of 746±1238 days. In their report, 13 of 48 (27%) lung cancers had VDT greater than 400 days. With a VDT of 400 days, it would take over 7 years for a 3 mm cancer to grow to 15 mm based strictly on the mathematical model. A VDT of over 400 days may represent over-diagnosis, especially in older patients. Many would be likely to die of competing causes before the slow growing lung cancer resulted in their death.

While the CT screening trials have resulted in a great deal of new information, they have also raised a number of questions. It is anticipated that the National Lung Cancer Screening Trial in the United States[20] and the NELSON trial in Europe[21] will ultimately answer the question of whether or not CT screening can reduce the number of deaths due to lung cancer. These two trials have randomized 70,000 participants to either CT screening or chest radiograph (NLST) or CT versus observation alone (NELSON). Results of these two trials are anticipated within the next 1-2 years.

REFERENCES

1. Smith RA, Cokkinites V, Eyre AJ: Cancer screening in the United States, 2007, CA Cancer J Clin. 2007;57:90-104.

2. Parkin DM, Bray F, Ferlay J, Pisani P: Global Cancer Statistics, 2002. CA Cancer J Clin. 2005;55:74-108.

3. Jemal A, Siegel R, Ward E et al: Cancer Statistics 2007. CA Cancer J Clin. 2007;57:43-66.

4. Sobue T, Moriyama N, Kaneko M et al: Screening for lung cancer with low-Dose helical computed tomography: anti-aging cancer association project. J Clin Oncol. 2002;20:911-20.

5. Henschke CI, McCauley DE, Yankelevitz DF et al: Early lung cancer action Project: Overall design and findings from baseline screening. Lancet. 1999;354-99-105.

6. Sone S, Li F, Yang ZG et al: Characteristics of small lung concerns invisible on conventional chest radiography and detected by population based screening using spiral CT. Br J. Radiol. 2000;73:137-45.

7. Survival of patients with stage I lung cancer detected on CT screening. The International Early Lung Cancer Action Program Investigators N Engl J Med. 2006;355:1763-71.

8. Swensen SJ, Jett JR, Hartman TE, Midthun DE, Mandrekar SJ, Hillman SL, Sykes AM, Aughenbaugh GL, Bimgi, AO, Allen KL: CT screening for lung Cancer: Five-year prospective experience. Radiology. 2005;235:259-65.

9. Bach PB, Jett JR, Pastorino U, Rockman MS, Swensen SJ, Begg CB: Computed tomography screening and lung cancer outcomes. JAMA. 2007;297:953-61.

10. Jett JR: Limitations of screening for lung cancer with low-dose spiral computed tomography. Clin Cancer Res. 2005;11(13 Suppl) 4988s.

11. McWilliam A, Mayo J, MacDonald S et al: Lung cancer screening: A different paradigm. Am J Respir Crit Care Med. 2003;168:1167-73.

12. MacMahon H, Austin JHM, Gamsu G, Herold CJ, Jett JR, Naidich DP, Patz EF Jr, Swensen SJ: Guidelines for management of small pulmonary nodules detected on CT scans: A statement from the Fleischner Society. Radiol. 2005;237:395-400.

13. Crestanello JA, Allen MS, Jett JR et al: Thoracic surgical operations in patients enrolled in a computed tomographic screening trial. J Thorac Cardiovasc Surg. 2004;128:254-9.

14. Pastorino U, Bellomi M, Landoni C, De Fiori E, Arnaldi P, Picchio M, Pelosi G: Early lung cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet. 2003;362:593-7.

15. Diederich S, Thomas M, Semik M et al: Screening for early lung cancer with low-dose spiral CT: results of annual follow-up examinations in asymptomatic smokers Eur Radiol. 2004;14:691-702.

16. Fontana RS, Sanderson DR, Woolner LB et al: Lung cancer screening: the Mayo Program. J Occup Med. 1986;28:746-50.

17. Marcus PM, Bergstralh EJ, Zweig MH, Harris A, Offord KP, Fontana RS: Extended lung cancer incidence follow-up in the Mayo Lung Project and over-diagnosis. J Natl Cancer Inst. 2006;98:748-57.

18. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. Br J Radiol. 2000;73:1252-9.

19. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD, Mandrekar JN: Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology. 2007;242:555-62.

20. Aberle DR, Black WC, Goldin JG et al: Experimental design and outcomes of the National Lung Cancer Screening Trial: a multicenter randomized controlled trial of the helical CT vs. chest x-ray for lung cancer screening [abstract]. Am J Respir Crit Care Med. 2003;167:A736.

21. Xu DM, Gietema H, deKoning H et al: Nodule management protocol of the NELSON randomized lung cancer screening trial. Lung Cancer. 2006;54:177-84.