Computed Tomography Screening for the Early Detection of Lung Cancer

Rebecca P. Petersen, MD, and David H. Harpole, Jr., MD, *Durham, North Carolina*

Key Words
Lung cancer, screening, computed tomography

Abstract
Although lung cancer is the leading cause of cancer-related death in the world and has an increased chance of cure if detected at an earlier stage, routine lung cancer screening is currently not recommended in the United States. Unfortunately, most patients with lung cancer present only after the onset of symptoms and have advanced disease that cannot be surgically resected. The overall 5-year survival rate for all patients with lung cancer is only 15%. When the cancer is detected at its earliest stage (pathologic stage IA), however, the 5-year survival rate is more than 70%. Although past randomized screening trials evaluating the use of standard chest radiography or sputum cytology have not resulted in lower mortality, recent studies suggest that computed tomography (CT) may have promise as a screening tool. This article summarizes experience over the past decade of using low-dose spiral CT imaging as a screening tool to detect early lung cancers in asymptomatic, high-risk individuals. (*JNCCN* 2006;4:591–594)

Lung cancer is the leading cause of cancer-related death in the world, accounting for more deaths than breast, colon, prostate, and pancreas cancers combined. In 2000, it was responsible for 1.1 million deaths. In 2004, approximately 173,000 individuals in the United States were diagnosed with lung cancer, with only 45,000 (25%) presenting with surgically resectable disease.[1] The overall 5-year survival for all patients with lung cancer is only 15%; however, in patients with clinical stage I disease who have undergone resection with curative intent, the estimated 5-year cancer-free survival rate is as high as 50%.[1–5] Moreover, when detected at its earliest stage, pathologic stage IA, the expected 5-year survival rate is greater than 70% after resection.[2–4] Although lung cancer is a cancer killer and proven therapies exist that are much more efficacious in early stage disease, lung cancer screening is not routinely performed in the United States. This is primarily because several past randomized trials failed to show a survival advantage for high-risk patients undergoing screening through either standard chest radiography or evaluation of sputum cytology.[6,7]

From Duke University Medical Center, Durham, North Carolina.
Submitted February 22, 2006; accepted for publication May 2, 2006.
The authors have no financial interest, arrangement, or affiliation with the manufacturers of any products discussed in the article or their competitors.
Correspondence: David H. Harpole, Jr., MD, Chief of Cardiothoracic Surgery, Durham Veteran's Administration Medical Center; Professor of Surgery, Associate of Pathology, Duke University Medical Center, Box 3617, Duke University Medical Center, Durham, NC 27710. E-mail: harpo002@mc.duke.edu

Computed Tomography Screening for Lung Cancer: Past Studies

Since 1993, computed tomography (CT) screening for lung cancer has been performed in the United States and Japan. In the United States, CT screening is used in the ongoing Early Lung Cancer Action Project (ELCAP),[8] and in Japan it was integrated into an already existing active screening program previously based on chest radiography alone.[9,10] In 1996, a third prospective population-based Japanese lung cancer CT screening trial recruited more than 5000 participants.[11,12] Results of all 3 screening studies showed CT imaging to be significantly superior to chest radiography in detecting small, early lung cancers.

The ELCAP study conducted baseline and annual repeat screenings on 1000 high-risk persons aged 60 years or older with a smoking history of at least 10 pack-years. Using CT scanning, Henschke et al.[13] reported a 23% detection rate of solitary noncalcified nodules, of which 12% were later found to be malignant. This detection rate using CT scanning was much higher than the 4% obtained through chest radiography alone.[13] The Japanese study also showed a much higher detection rate with CT imaging than with chest radiography. The Japanese mass screening program study consisted of more than 5000 subjects aged 40 to 74 years, of which more than 50% were nonsmokers. Sone et al.[11,12] reported a 5.1% detection rate of suspicious nodules, of which 10% were malignant. An additional retrospective blinded analysis showed that chest radiographs only detected nodules in one third of the patients who had suspicious nodules detected through concurrent CT screening.[11,12] The detection rate of solitary noncalcified nodules was much lower in the Japanese studies compared with the ELCAP study, likely because the Japanese study populations consisted of a significant number of nonsmokers; however, the frequency of nodules identified through CT screening that were later found to be malignant was very similar (10%–12%). Regardless, the overall conclusion from these studies was that CT imaging is far superior in detecting early small cell lung cancers than is chest radiography.

These encouraging results have caused increasing research interest in, and a heightened public awareness of, the use of low-dose spiral CT imaging as a routine screening tool for the early detection of lung cancer.[13–15] This heightened interest will only continue to gain momentum as advances in lung cancer therapies result in improved overall survival. For example, the recent change in the standard of care from primarily observing patients with stage IB-IIIA non-small cell lung cancer (NSCLC) after resection to the addition of adjuvant platinum-based chemotherapy has resulted in a survival advantage as high as 15%.[17–20]

Since the initial results of ELCAP and the Japanese studies were reported, the advances in CT imaging technology have led to decreased slice thickness (<1 mm), higher resolution, and the ability to obtain these images within a single breath hold.[15] Unsurprisingly, these advances have led to a significantly higher detection rate of noncalcified nodules, with most being less than 5 mm.[15] Also, a new type of subsolid nodule was identified that, on further investigation, was found to have a threefold higher malignancy rate when compared with solid nodules.[21] These new findings changed the definition of a positive screening to "one or more noncalcified solid or part-solid nodules 5 mm or larger or a nonsolid nodule 10 mm or larger,"[15] resulting in a reduced detection rate of 10% without an increased false-negative rate.

To better understand the many issues surrounding lung cancer screening, the ELCAP organized the First International Conference on Screening for Lung Cancer because of the additional findings and concern that, when CT imaging is used as a screening tool in randomized settings, flaws in trial design may cause its fate to be similar to chest radiography and sputum cytology. After this initial consortium, the International ELCAP (I-ELCAP) was formed and 12 semiannual conferences were held, all having the overall mission to better assess the usefulness of CT screening in decreasing lung cancer mortality.[22]

CT Screening for Lung Cancer: Ongoing Studies

When the efforts of Henschke et al.[15] helped establish the First International Conference on Screening for Lung Cancer, leading to the formation of I-ELCAP, they also initiated a screening trial involving 10,000 high-risk persons, referred to as the New York ELCAP (NY-ELCAP).[15] Both efforts are currently collecting data under the same protocol and following a predefined treatment algorithm for individuals diagnosed with suspicious nodules on baseline and annual follow-up CT images. This will be central to the pooling of these data for future analysis of long-term outcome.

In 2002, ELCAP and other groups initiated the National Lung Cancer Screening Trial (NLST), which is financially supported by the National Cancer Institute. This trial was designed to include volunteers aged 55 to 74 years with a smoking history of 30 pack-years. The trial randomized participants for screening using either low-dose spiral CT imaging or digital chest radiography. The trial was designed to have a 90% ability to detect a 20% difference in lung cancer mortality. All participants underwent baseline and 2 subsequent annual studies and then were followed up for at least 6 to 12 months. Almost 50,000 individuals from more than 30 study sites across the United States are currently enrolled in the NLST, and enrollment is now closed. Additional analyses will include cost-effectiveness and quality-of-life issues.

Cost Effectiveness of CT Screening

Although multiple studies have evaluated the cost-effectiveness of lung cancer screening, the results have varied greatly. The cost per life saved has ranged from $2500 to more than $2 million.[23–26] The cost-effectiveness component integrated into the design of NLST will be most informative; unfortunately, these results will not be available for approximately 5 more years.

Future Directions

Future investigations taking advantage of recent technologic advances in the fields of genomics and proteomics offer some exciting prospects for alternative screening tools to CT imaging. Novel biomarkers easily identified in accessible screening specimens such as serum, sputa, and exhaled breath may help facilitate the identification of precursor lesions associated with subsequent progression to invasive carcinoma. Although multiple studies have investigated single molecular biomarkers for early detection of recurrence, most of which still require prospective validation, no studies have investigated the use of proteomics or genomics as a screening tool to detect primary lung cancer before it is evident on spiral CT imaging. Several studies in other cancer types have shown that proteomic cluster patterns identified in serum can accurately differentiate patients with specific cancer types from cancer-free control subjects.[27,28] Undoubtedly, with further technologic advancements, future studies will investigate the effectiveness of new candidate biomarkers or genomic/proteomic cluster patterns in detecting early lung cancers before these can be detected through low-dose spiral CT imaging.

Conclusions

Lung cancer is the leading cause of cancer-related death in the world, killing more people than the next 4 most commonly fatal cancers combined. When detected at its earliest stage, the 5-year survival rate approaches 80%, which is much higher than the dismal 5-year survival rate of 15% for most patients who present with symptomatic, advanced disease. Multiple studies have investigated the use of chest radiography, sputum cytology, and, more recently, CT imaging as screening tools to decrease lung cancer mortality. Although earlier randomized trials did not show any decrease in mortality using either chest radiography or sputum cytology, ample evidence from several studies has shown CT imaging to be far superior to standard chest radiography in detecting early lung cancers. These encouraging results have led to further ongoing large-scale investigations, including a national randomized trial, which will be very foretelling as to whether CT screening reduces lung cancer mortality in high-risk individuals in the near future. Until more data on long-term outcomes are available from both the I-ELCAP and the NLST, current recommendations by the American Cancer Society and the United States Preventive Services Task Force neither support nor discourage routine lung cancer screening in high-risk individuals. Lung cancer screening is currently performed on an individual basis after the patient and physician discuss the potential risks and benefits.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2006. CA Cancer J Clin 2006;56:106–130.
2. Naruke T, Goya T, Tsuchiya R, et al. Prognosis and survival in resected lung carcinoma based on the international staging system. J Thorac Cardiovasc Surg 1988;96:440–447.
3. Strauss GM, Kwiatkowski DJ, Harpole DH, et al. Molecular and pathologic analysis of stage I non small cell lung carcinoma of the lung. J Clin Oncol 1995;13:1265–1279.
4. Harpole DH Jr, Herndon JE, Wolfe WG, et al. A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression. Cancer Res 1995;55:51–56.
5. Parker SL, Tong T, Bolden S, et al. Cancer statistics, 1997. CA-Cancer J Clin 1997;47:5–27.
6. Fontana RS, Sanderson DR, Woolner LB, et al. Lung cancer screening: the Mayo program. J Occup Med 1986;28:746–750.
7. Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer. Chest 1984;86:44–53.
8. Henschke CI, Yankelevitz DF, Kostis WJ. CT screening for lung cancer. Semin Ultrasound CT MRI 2003;24:23–32.
9. Kaneko M, Eguchi K, Ohmatusu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798–802.
10. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911–920.
11. Sone S, Takahima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–1245.
12. Sone S, Li F, Yang Z-G, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001;84:25–32.
13. 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.
14. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screening. Cancer 2001;92:153–159.
15. Henschke CI. Computed tomography screening for lung cancer: principles and results. Clin Cancer Res 2005;11[suppl 13]:4984–4987.
16. Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med 2004;350:1713–1721.

17. Arriagada R, Bergman B, Dunant A, et al. International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. New Engl J Med 2004;350:351–360.
18. Strauss, GA, Herndon JE, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. [abstract]. Proc Am Soc Clin Oncol 2004; Abstract 7019.
19. Winton T, Livingston R, Johnson D, et al. A prospective randomized trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non small cell lung cancer (NSCLC) Intergroup JBR.10 [abstract]. Proc Am Soc Clin Oncol 2004; Abstract 7018.
20. Douillard J, Rosell R, Delena M, et al. ANITA: phase III adjuvant vinorelbine (N) and cisplatin (P) versus observation (OBS) in completely resected (stage I-III) non-small-cell lung cancer (NSCLC) patients (pts): final results after 70-month median follow-up [abstract]. J Clin Oncol 2005;23(suppl 16S):7013.
21. Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053–1057.
22. Henschke CI, I-ELCAP Investigators. CT screening for lung cancer: update 2005. Surg Oncol Clin N Am 2005;14:761–776.
23. Jett JR. Limitations of screening for lung cancer with low-dose spiral computed tomography. Clin Cancer Res 2005;11[suppl 13]:4988–4992.
24. Wisnivesky JP, Mushlin AL, Sicherman N, et al. The cost-effectiveness of low-dose CT screening for lung cancer. Chest 2003;124:614–621.
25. Marshall D, Simpson KN, Earle CC, et al. Economic decision analysis model of screening for lung cancer. Eur J Cancer 2001;37:1759–1767.
26. Mahaderia P, Fleisher LA, Frick KD, et al. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. JAMA 2003;289:313–322.
27. Petricoin III EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002;359:572–577.
28. Jett JR, Midthun DE. Screening for lung cancer: current status and future directions. Chest 2004;125:158–162.