COUNTERPOINTS

Current Controversies in Hematology and Oncology

Should Lung Cancer Screening With Low-Dose Computed Tomography Be Routine for Smokers and Former Smokers?

The U.S. Preventive Services Task Force (USPSTF) gave a grade of B to low-dose computed tomography (CT) for lung cancer screening in smokers and former smokers. The American Academy of Family Physicians, however, said that the evidence is "insufficient" to recommend for or against such screening. What should physicians recommend? Here, Drs James Jett and Debra Dyer argue in favor of screening, whereas family physician Dr Steven Brown advises against lung cancer screening until more is known.

Should Low-Dose CT Be Routine in These Patients? Most Certainly!

James R. Jett, MD, is a professor of medicine at National Jewish Health in Denver, Colorado.

Debra S. Dyer, MD, is a professor and the chair of radiology at National Jewish Health in Denver, Colorado.

Lung cancer kills more than 1.5 million people per year worldwide, according to a GLOBOCAN 2012 estimate.[1] In Europe and the United States, lung cancer is the number one cause of cancer death, with 353,000 deaths in 2012 in Europe and a projected 158,000 deaths in 2014 in the United States.[2,3]

The 5-year survival rate for lung cancer in the United States is just 17%. A major reason for this low rate is the fact that lung cancer is usually diagnosed at an advanced stage. Currently, 15% of lung cancers are diagnosed at stage I, when the chance of cure with treatment is highest, and approximately 60% are diagnosed at stage IV, when the disease is incurable.[3] Stage I lung cancer is asymptomatic; there are no signs or symptoms of early-stage disease. Our current approach—without screening—is to wait for the patient to develop symptomatic lung cancer and then diagnose advanced-stage disease. If we hope to change these dismal lung cancer statistics, we must detect and treat the disease while it is asymptomatic and in an early stage.

(continued on page 702)

The Evidence Is Insufficient to Support Routine Low-Dose CT in These Patients

Steven R. Brown, MD, is the program director for Banner Good Samaritan Family Medicine Residency and a clinical associate professor in the Department of Family and Community Medicine at the University of Arizona College of Medicine in Phoenix, Arizona. He is also the chair of the Commission on the Health of the Public and Science for the American Academy of Family Physicians.

In December 2013, the USPSTF issued a B recommendation for lung cancer screening with low-dose CT in selected smokers and former smokers.[1] Prior to that, in March 2013, the American Cancer Society made a more modest recommendation: physicians should "initiate a discussion" with appropriately selected patients if there is access to "high-volume, high-quality lung cancer screening and treatment centers."[2] Subsequently, the American Academy of Family Physicians concluded that the "evidence is insufficient to recommend for or against" such screening.[3]

These conflicting recommendations highlight the "perilous potential"[4] of screening for lung cancer. Despite data from a large randomized trial, there is insufficient evidence to support a national program of routine lung cancer screening for 5 reasons: (1) uncertain generalizability

(continued on page 704)

(continued from page 701)

Should Low-Dose CT Be Routine in These Patients? Most Certainly! (cont)

Screening for Lung Cancer

Previous screening trials in the 1980s with chest radiography and sputum cytology failed to show a decrease in lung cancer mortality, so screening was abandoned for almost 25 years. Early trials with low-dose (radiation) CT yielded promising results that led to the large National Lung Screening Trial (NLST) in the United States, in addition to other, smaller randomized controlled trials. The NLST randomly assigned high-risk individuals to screening with low-dose CT or chest radiography for 3 yearly screenings, and then followed participants for a median of 6.5 years.[4]

In the NLST, a total of 1060 lung cancers were diagnosed in the low-dose CT arm and 941 were diagnosed in the chest radiography arm at the end of the study. During the first 3 years of active screening, 649 and 279 lung cancers were diagnosed in the low-dose CT and radiography arms, respectively. There was a 20% reduction in mortality from lung cancer in the low-dose CT arm in comparison with the chest radiography arm (356 vs 443 lung cancer deaths). Additionally, there was a 6.7% reduction in all-cause mortality in the low-dose CT arm.[4]

Stage Shift and Mortality Benefit

Stage I lung cancer was diagnosed in 63% of the participants with lung cancer in the low-dose CT arm and 48% of those in the chest radiography arm during the first 3 years of active screening. Lung cancer was stage IIIB/IV in 21% and 31% of the patients in the low-dose CT and radiography arms, respectively. At the end of the study (3 years of active screening plus a median 6.5 years of follow-up), 50% of the lung cancers on the low-dose CT arm were stage I, and 31% were stage IIIB or IV.[4] This decrease in stage I lung cancers from the time of active screening (63%) until the end of the study (50%) and the increase in stage IIIB/IV from 21% to 31% raises the possibility that the mortality benefit of low-dose CT screening would have been even greater than the 20% benefit observed if low-dose CT screening had been continued yearly rather than stopped after 3 scans.

Prevented Deaths From Lung Cancer

The NLST demonstrated that 1 in 5 deaths from lung cancer can be avoided with low-dose CT screening.

Approximately 8.6 million Americans were eligible for screening by the NLST criteria for high risk in 2010. If all eligible individuals had been screened with low-dose CT, then approximately 12,000 lung cancer deaths would have been avoided.[5] A lung cancer screening model based on the PLCO (Prostate, Lung, Colon, and Ovarian) Cancer Screening Trial has been shown to be a better risk prediction model than the criteria for eligibility used in the NLST.[6] With this model, the sensitivity increased from 71% to 83%, and there was no substantial change in specificity at 63%. When this high-risk prediction model was used, 41% fewer lung cancers were missed. A comparative modeling study for the USPSTF used 5 independent models of screening with low-dose CT and estimated that if all eligible individuals were screened, more than 18,000 lung cancer deaths might be avoided per year.[7]

> How can we justify not offering this potentially lifesaving test to high-risk individuals?

Smoking Cessation

In the NLST, 48% of participants were current smokers[8]; however, the NLST did not have a mandated smoking cessation program associated with screening.[9] In the NELSON trial (Dutch-Belgian randomised controlled lung cancer screening trial), 47% of participants were current smokers. Smoking behavior was evaluated in 2 random samples of male smokers in the low-dose CT screening arm and the no-screening control arm.[10] At 2 years, the smoking abstinence rates were 13.7% in the screening arm and 15.5% in the control arm. Although the difference in smoking cessation between the 2 arms of the trial was not significant, both arms of the study had higher rates of smoking cessation than that of the general adult smoking population, which is 3% to 7%.[10] Approximately 22% of smokers in the NLST with normal screening results quit smoking after 3 years.[11] Screening provides a teachable moment and can motivate behavioral change, especially when low-dose CT is used, which allows the patient to clearly see parenchymal abnormalities. Smoking cessation had a statistically significant association with screen-

detected abnormalities, and the rate was highest in those individuals whose screening result was suspicious for lung cancer and was new or changed from the previous screen (odds ratio, 0.66).[11] With modeling data, it has been estimated that offering smoking cessation with annual screening exams would improve the cost-effectiveness of screening by 20% to 45%.[12]

USPSTF Recommendation

The USPSTF reviewed the evidence on the efficacy of low-dose CT, chest radiography, and sputum cytology for screening and commissioned modeling studies to provide information about the optimal age to begin and end screening, optimal screening intervals, and relative benefits and harms.[13] The USPSTF recommended annual screening for lung cancer with low-dose CT in adults aged 55 to 80 years who have smoked 30 pack-years and are current or former smokers who have quit within the past 15 years.[13]

In conclusion, the evidence is overwhelming that annual screening with low-dose CT in high-risk individuals will prevent a substantial number of deaths from lung cancer. The addition of a smoking cessation program to CT screening will further enhance the smoking quit rate and the cost-effectiveness of the CT screening. The only way to improve on the bleak statistics of 160,000 deaths yearly in the United States and 5-year survival of 17% for all newly diagnosed lung cancers is to move the time of diagnosis to the asymptomatic phase of the disease. Currently, low-dose CT screening is the only tool that we have to accomplish this feat. How can we justify not offering this potentially lifesaving test to high-risk individuals?

References

1. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed August 20, 2014.

2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.

3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.

4. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.

5. Ma J, Ward EM, Smith R, Jemal A. Annual number of lung cancer deaths potentially avertable by screening in the United States. *Cancer*. 2013;119(7):1381-1385.

6. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013;368(8):728-736.

7. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;160(5):311-320.

8. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst*. 2010;102(23):1771-1779.

9. Aberle DR, Berg CD, Black WC, et al; National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. *Radiology*. 2011;258(1):243-253.

10. van der Aalst CM, van den Bergh KA, Willemsen MC, de Koning HJ, van Klaveren RJ. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. *Thorax*. 2010;65(7):600-605.

11. Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst*. 2014;106(6):dju084.

12. Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. *PLoS One*. 2013;8(8):e71379.

13. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.

(continued from page 701)

The Evidence Is Insufficient to Support Routine Low-Dose CT in These Patients (cont)

of randomized controlled trials to the community, (2) unknown harms from repeat screening and follow-up studies, (3) uncertain cost benefit, (4) need for further emphasis on smoking cessation in screening programs, and (5) need for improved targeting of patients at highest risk. Each of these reasons is detailed below.

Uncertain Generalizability of Randomized Controlled Trials to the Community

The USPSTF recommendation is based largely on the results of the NLST.[5] Another 3 published randomized controlled trials, which were considerably smaller, demonstrated no benefit from screening.[6] The results of the NLST showed a decrease in both lung cancer mortality and overall mortality in smokers and former smokers screened annually for 3 years. The NLST showed that the number needed to screen with low-dose CT over 6 years to prevent 1 lung cancer death was 320, and the number needed to screen to prevent 1 death from any cause was 208. However, 39% of patients undergoing 3 screenings would have at least 1 positive test result, and 96% of these positive tests would be false-positives. The positive predictive value of a positive finding, a nodule 4 mm or larger, was 3.8% in the NLST. Half of patients with positive test results received standard-dose follow-up CT, and some patients received more-invasive testing.

Most of the 33 institutions involved in the NLST were large academic medical centers, and all were "recognized for their expertise in radiology and in the diagnosis and treatment of cancer."[5] Imaging and follow-up recommendations used a standard protocol, and radiologists and technologists completed specific training.

Implementation of these same conditions may be challenging in a community setting. The USPSTF notes that the "moderate net benefit" of screening depends on "the accuracy of image interpretation" and the "resolution of most false-positive results without invasive procedures."[1] The NLST authors note that the mortality benefit shown in the study largely depended on low complication rates from cancer treatment.[5] As such, the NLST results may not be generalizable to other settings. Recognizing this difficulty, the USPSTF notes that settings with "high rates of diagnostic accuracy," "appropriate follow-up protocols," and "clear criteria for doing invasive procedures" are "more likely to duplicate" the results found in the NLST.[1] In fact, the NLST authors themselves said:

> Although some agencies and organizations are contemplating the establishment of lung-cancer screening recommendations on the basis of the findings of the NLST, the current NLST data alone are, in our opinion, insufficient to fully inform such important decisions.[5]

Clearly, further studies should be done to replicate the NLST results in community settings, and registries should be established[7] before screening becomes routine.

Unknown Harms From Repeat Screening and Follow-up Studies

The harms of annual CT lung cancer screening are not yet known. Potential harms include complications from invasive procedures, overdiagnosis, exposure to radiation, incidental findings, and psychological distress from false-positive findings. Harms from invasive procedures were not common in the NLST; however, as mentioned above, it is not known if these harms can be similarly minimized in non-expert centers. The rate of false-positive results is high, and additional tests are often required. Overdiagnosis—that is, diagnosis (and in most cases, treatment) of cancerous lesions that would not impact a patient's quality or quantity of life—has been estimated at more than 18%.[8] Radiation exposure from imaging is associated with an increased rate of cancer.[9] Although this effect was thought to be minimal in the NLST,[5] the USPSTF recommendation includes annual low-dose CT screening for more than 20 years—with many patients likely to require a standard-dose follow-up CT. Incidental findings on chest CT can lead to a cascade of further testing. Although there is insufficient evidence to evaluate the harms associated with incidental findings,[1] these findings are common.[10] The NLST did not report the psychological impact from false-positive screening tests. Concerns of psychological distress have been emphasized by others[11] and have been demonstrated in studies of false-positive mammography.[12] Will patients with suspicious lesions agree to watchful waiting protocols when

Based on current data, such screening programs should not be prioritized.

indicated? If so, does watchful waiting cause substantial psychological distress?

Uncertain Cost Benefit

Concerns of cost-effectiveness have not been adequately addressed to recommend routine screening. There are many competing priorities for health care dollars, and there is a profound need to improve the value of care provided in the United States. The implementation of low-dose CT screening per the USPSTF protocol would cost tens of billions of dollars,[13,14] or $9 per Medicare member per month.[15] Initial estimates of cost-effectiveness fall in a fairly encouraging range, from $28,240 to $48,000 per quality-adjusted life-year gained,[13,16] but these estimates do not incorporate the uncertain generalizability and unknown harms.

Need for Further Emphasis on Smoking Cessation in Screening Programs

The cost-effectiveness of lung cancer screening may be greatly improved if smoking cessation efforts are included with screening.[13] Screening alone does not seem to decrease smoking rates,[17] but abnormal screening results may have a modest effect.[18] Given that smoking cessation is the most important intervention for decreasing deaths from lung cancer,[19] and in light of the fact that there are many effective interventions to improve cessation, linking smoking cessation programs to lung cancer screening should be considered. Further study is needed.

Need for Improved Targeting of Patients at Highest Risk

The USPSTF model considered many screening recommendation options. Their "highlighted program" recommends annual screening to patients aged 55 to 79 years who have at least 30 pack-years of smoking. Screening should be stopped, or not initiated, after 15 years without smoking. This "highlighted program" expects that 19% of the US population will be screened. The number needed to screen to prevent 1 lung cancer death is 550. Another USPSTF model that requires at least 40 pack-years of smoking and starts at age 60 years would improve the number needed to screen to 419, and only 13% of the US population would need to be screened.

An alternative plan suggests sorting smokers into quintiles of lung cancer death risk.[20] In the NLST, smokers in the lowest quintile had a 0.15% to 0.55% risk of death from lung cancer over 5 years, whereas smokers in the highest quintile had a greater than 2% risk of death from lung cancer over 5 years. Patients in the lowest quintile were much less likely to benefit from screening, as only 1% of cancer deaths prevented in the NLST came from patients in the lowest quintile. Lower-risk patients also were more likely to have false-positive results. Screening should be based on a patient's absolute risk, such as with osteoporosis screening,[21] cholesterol treatment,[22] and breast cancer chemoprophylaxis.[23] Screening could be recommended for patients starting at a 5-year risk of 1%, which includes part of quintile 3 and quintiles 4 and 5.

Someday there may be strong, generalizable evidence that deaths can be prevented by targeted CT screening of smokers. However, based on current data and in light of myriad uncertainties, such screening programs should not be prioritized.

References

1. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.

2. Wender R, Fontham ET, Barrera E Jr, et al. American Cancer Society lung cancer screening guidelines. *CA Cancer J Clin*. 2013;63(2):107-117.

3. Evidence lacking to support or oppose low-dose CT screening for lung cancer, says AAFP. http://www.aafp.org/news/health-of-the-public/20140113aafplungcarec.html. American Academy of Family Physicians. January 13, 2014. Accessed July 20, 2014.

4. Bach PB. Perilous potential: the chance to save lives, or lose them, through low dose computed tomography screening for lung cancer. *J Surg Oncol*. 2013;108(5):287-288.

5. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.

6. Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive Services Task Force recommendation. *Ann Intern Med*. 2013;159(6):411-420.

7. Goulart BH, Ramsey SD. Moving beyond the national lung screening trial: discussing strategies for implementation of lung cancer screening programs. *Oncologist*. 2013;18(8):941-946.

8. Patz EF Jr, Pinsky P, Gatsonis C, et al; NLST Overdiagnosis Manuscript Writing Team. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014;174(2):269-274.

9. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med*. 2009;169(22):2078-2086.

10. Brown SR, Newman DH, Shreves AE. Potential harms of computed tomography: the role of informed consent. *Am Fam Physician*. 2013;88(5):294-296.

11. Rzyman W, Jelitto-Gorska M, Dziedzic R, et al. Diagnostic work-up and surgery in participants of the Gdansk lung cancer screening programme: the incidence of surgery for non-malignant conditions. *Interact Cardiovasc Thorac Surg*. 2013;17(6):969-973.

12. Bond M, Pavey T, Welch K, et al. Systematic review of the psychological consequences of false-positive screening mammograms. *Health Technol Assess*. 2013;17(13):1-170, v-vi.

13. Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. *PLoS One*. 2013;8(8):e71379.

14. Goulart BH, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with low-dose computed tomography: costs, national expenditures, and cost-effectiveness. *J Natl Compr Canc Netw*. 2012;10(2):267-275.

15. Roth JA, Sullivan SD, Ravelo A, et al. Low-dose computed tomography lung cancer screening in the Medicare program: projected clinical, resource, and budget impact [ASCO abstract 6501]. *J Clin Oncol.* 2014;32(5)(suppl).

16. Patel AR, Wedzicha JA, Hurst JR. Reduced lung-cancer mortality with CT screening. *N Engl J Med*. 2011;365(21):2035-2038.

17. Slatore CG, Baumann C, Pappas M, Humphrey LL. Smoking behaviors among patients receiving computed tomography for lung cancer screening. Systematic review in support of the U.S. Preventive Services Task Force. *Ann Am Thorac Soc*. 2014;11(4):619-627.

18. Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst*. 2014;106(6):dju084.

19. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013;368(4):341-350.

20. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013;369(3):245-254.

21. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2011;154(5):356-364.

22. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2889-2934.

23. Moyer VA; U.S. Preventive Services Task Force. Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;159(10):698-708.

"Counterpoints" is a section in *Clinical Advances in Hematology & Oncology* in which we address clinical controversies and other questions of importance to oncologists and hematologists. We feature between 2 and 8 panelists for each question.

What topics would you like to see addressed in future issues? Please send your ideas to editor@clinicaladvances.com.