Spring 2009 | NO 36

Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

Thomas L. Petty, MD

The purpose of ***Lung Cancer Frontiers*** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

Access current and past issues of ***Lung Cancer Frontiers*** via the Internet at njhealth.org, search Lung Cancer Frontiers

Screening for Lung Cancer

By Thomas L. Petty, MD

Several months ago, I asked Claudia Henschke, MD to write a present-day perspective on the pros and cons of screening an individual patient for lung cancer. Until recently, no society or task force recommended such screening. Now, the official position of these bodies is to make screening for lung cancer an individual decision, to be made by a patient and their physician. I believe this reflects progress and moves us a step away from the nihilism that has surrounded screening and early detection for decades.

I was also interested in Dr. Henschke's continued data on the survival of Stage I lung cancer, reported to be as high as 90% in a widely-quoted article (I-ELCAP Investigators, NEJM 2006;355:1763-1771). I had cited this paper in an earlier issue of ***Lung Cancer Frontiers***, as well as criticisms of its study design and conclusions (Welch H, et al., *Arch Intern Med* 2007;167:2289-2295). I was aware that some investigators had received partial support for their work from industries related to tobacco production, but I did not believe this introduced significant bias, because the thrust of these studies was to find and treat lung cancer and reduce smoking.

In my opinion, Dr. Henschke's article in this issue of ***Lung Cancer Frontiers*** provides additional data and perspective, and it clarifies some of the issues of potential conflict of interest. I believe it is an important contribution and should be accompanied by opposing or supportive views in future issues of ***Lung Cancer Frontiers***.

Today, all of the answers about early identification are not in, and we continue to strive to find more accurate methods of detecting and curing lung cancer. Hopefully, the dialogue contained in these pages will foster that goal.

Thomas L. Petty, MD

Founder and Editor Emeritus, ***Lung Cancer Frontiers***

In this issue

President's Message

Michael Salem, MD, FACS

Dear Readers,

More people die from lung cancer than from any other type of cancer. This is true for both men and women. In 2005 alone, according to the Centers for Disease Control, 159,217 people in the United States succumbed to lung cancer. As a surgeon, I am all too familiar with the devastating effect of this disease upon individual patients and their families.

Until new, more effective therapies are developed, the best hope for a cure for lung cancer lies in detecting small, solitary lesions that can be surgically resected. Unfortunately, most lung cancers are not found at this early stage, and, although advances in targeted chemotherapy and radiation therapy continue, the overall prognosis for these patients remains unacceptably poor.

There is great interest in finding effective ways to detect lung cancer in its earliest stages, before symptoms develop. Lung cancer screening trials, including the I-ELCAP study, upon which Dr. Henschke's conclusions in this issue of ***Lung Cancer Frontiers*** are based, address the questions of who should be screened and how. Dr. Henschke and her colleagues deserve much credit for taking on this difficult and important problem.

The results of the National Lung Screening Trial, a randomized, controlled trial, should be available in the next 2 years and will provide more information about the use of spiral CT scans in lung cancer screening. In the future, biomarkers and genetic testing will likely further refine the screening process.

As clinicians, and as a society, we eagerly await further advances that will save and improve the lives of patients suffering from lung cancer.

Michael Salem, MD, FACS
President and CEO
National Jewish Health

Professor of Surgery
University of Colorado Denver

National Jewish Health main health campus in Denver, Colorado.

Informing the Decision about Being Screened for Lung Cancer

By Claudia I. Henschke, PhD, MD, James P. Smith, MD, David F. Yankelevitz, MD, Daniel M. Libby, MD, Mark W. Pasmantier, MD, for the International Early Lung Cancer Action Program Investigators

Introduction

Would it be good for me to be screened for lung cancer? This – or some variant of this – is a question many current and former smokers now ask of their doctors. They ask because they have fear: they know that lung cancer is a deadly disease, and that it is possible that they may eventually be diagnosed with it[1]. And they ask because they have hope: that screening for the disease might be a reasonable way to reduce the risk of ultimately dying from it.

In 2004, the US Preventive Services Task Force changed its recommendation for screening for lung cancer from being against it (D recommendation) to neither being for nor against it (I recommendation) and suggested that individuals talk with their physicians about whether they should be screened[2]. The American Cancer Society had also made this recommendation earlier[3], and others are now recommending the same[4].

When an individual concerned about the risk of lung cancer consults his/her doctor about whether to undergo screening, the doctor is to inform the person, neither advocating for nor counseling against the screening, but merely objectively addressing the potential benefit and harm from the screening – and not in general terms, but with reference to the particular person who is seeking the information.

It is our purpose here to provide the doctor the information (s)he needs to inform – one by one – particular individuals. The information we present has an added aspect in that it derives from the International Early Lung Cancer Action Program (I-ELCAP) and is, thus, specific to screening according to its protocol/regimen. And here we focus on the first, baseline round of screening, which is the concern in the initial decision that must be made.

Potential benefit

It is important to understand that the potential benefit of the screening depends on the particular process of screening employed, what we call the regimen of screening. This regimen defines how the CT images are acquired, the criteria for a positive result, the workup of a positive result and ultimately the pathology. The regimen determines how early the diagnosis of lung cancer is made and how curable it is. Thus, this process must be well-defined and in this report the benefit is based on the use of the I-ELCAP protocol[5].

The probability of diagnosing lung cancer as a result of baseline screening

For a round of screening to convey benefit, a first requirement is that it lead to detection – rule in diagnosis – of a case of the cancer, present but still in the latent, asymptomatic phase of its development. The probability of this depends most notably on the person's age, pack-years of cigarette smoking and the time since quitting smoking. We studied this functional relationship by applying logistic regression analysis to the I-ELCAP data on person 60 years of age and older at baseline screening[6]. The estimated probabilities for particular ages and smoking histories are given in ***Table 1***. They range from 0.5% for a 60-year-old with 10-pack-years of smoking who quit 20 years ago to 6.8% for an 80-or 85-year-old with 100 pack-years of smoking who continues to smoke.

The probability of having a curable Stage I lung cancer

Attainment of an early – latent-phase – diagnosis of lung cancer is beneficial essentially only if the cancer still is in Stage I and, consequently, still commonly curable. In I-ELCAP, the estimated probability of achieving the diagnosis of lung cancer in clinical Stage I is 85% (95% CI: 82% – 88%)[7]. For the probability that the Stage I lung cancer is curable by prompt resection, the I-ELCAP estimate is 92% (CI: 88% – 95%)[7]. Thus, for the probability that a baseline-diagnosed case of lung cancer would be curable, the corresponding point estimate is 85% x 92% = 78%.

The probability of surviving 'competing' causes of death

This probability is the probability of not dying from some other cause before the possible lung-cancer death that could be averted by having undergone the screening process. We estimated this probability using the subcohort of men and women whose baseline screening took place in 1993 – 1999 on whom long-term follow-up for all causes of death was available until the end of 2006[6]. As screening during this time was limited to persons 60 years of age or older with a history of at least 10 pack-years of cigarette smoking, we estimated this probability only for this subcohort. These estimated probabilities are also given in ***Table 1***. They range from the high of 98%, for a 60-year-old with 10 pack-years of smoking

who quit smoking 20 years ago, to 37%, for a 85-year-old with 100 pack-years of smoking who continues to smoke.

The probability of survival benefit

The probability of survival benefit for an individual of a given age and smoking history as a result of baseline screening for lung cancer – from its associated early intervention – is estimated as the product of the probabilities given above. In calculating this, we assumed lung cancer to be uniformly fatal in the absence of screening.

Table 2 provides estimates of the probability of the survival benefit. For current and former smokers 60 – 85 years of age with at least 10 pack-years of smoking, the probability ranges from 0.4% for a 60-year-old with 10-pack-years who quit 20 years ago, to 3.1% for a 70-year-old with 100 pack-years who continues to smoke, to 2.0% for a 85-year-old with 150 pack-years who continues to smoke. While the probability of diagnosing a cancer increases with age, the probability of dying of other causes increases so that the overall benefit for a current smoker starts to decrease at age 81.

Potential harms

Potential harms of screening include those that might result from the exposure to radiation from the CT scans or from biopsy or surgery for non-malignant disease. They also include the bother of having to undergo diagnostic procedures, possibly including biopsy, and anxiety prompted by the process of screening.

The radiation exposure of a single low-dose CT test is about 0.8 milli-Sieverts (the dose in mammography being about 0.7 milli-Sieverts). This is about one-third of the annual background radiation exposure at sea level. Should another low-dose CT be needed, the total radiation exposure would still be less than that of the background radiation.

The result of the initial low-dose CT test at baseline is considered positive in terms of the I-ELCAP regimen if at least one non-calcified solid or part-solid nodule 5 mm or more in diameter or at least one nonsolid nodule 8 mm or more in diameter is identified. Such a positive result is obtained in about 15% of the baseline screening in I-ELCAP. The result is 'semi-positive' if non-calcified nodules are identified, but they all are less than 5 mm in diameter; and it is negative if no non-calcified nodules are identified.

If the result of the initial test is positive, further workup is recommended by the regimen of screening[5]. When the recommendations of the regimen are followed, the additional workup typically is limited to one follow-up CT prior to the first annual repeat screening. When biopsy is recommended according to the regimen, it follows documented growth of the nodule and/or positive PET scan and is recommended to be performed by percutaneous CT-guided fine-needle aspiration biopsy. Under these conditions, some 90% of such biopsies lead to pathologic diagnosis of malignancy while in the remaining 10% of such biopsies the resulting diagnosis is that of focal pneumonia, inflammation, granuloma, fibrosis, or some other benign lesion. By following these recommendations including biopsy prior to surgery, surgery for benign disease is minimized.

The anxiety caused by undergoing the test and waiting for the results has been addressed in detail in the ongoing randomized trial in the Netherlands (NELSON) and found to be limited in duration and modest in intensity[8].

In Practice

A 60-year-old current smoker with a 60-pack-year history of smoking consults a doctor about the justifiability of initiating screening for lung cancer as a means to avert death from this dreaded disease. The person is in generally good health relative to what is typical for people of that age and smoking history. The doctor is aware of the I-ELCAP regimen and its results. (S)he knows that for this person, the probability of survival gain resulting from the contemplated baseline screening is the product of 3 probabilities, that of the round of screening resulting in the diagnosis of lung cancer, that of the diagnosed cancer being curable by early treatment, and that of the person escaping death from other causes long enough to benefit from the thus prevented death from lung cancer. For these probabilities, the estimate from the I-ELCAP experience are 2.0% (***Table 1***), 78%, and 91% (***Table 1***), respectively; and for the probability product, then, the corresponding estimate is 100 (0.020 x 0.78 x 0.91%) = 1.4% (***Table 2***). This 1.4% is, for this person, the onetime survival benefit derived from and unique to the baseline round of screening.

The doctor should be able to convey to the person with great assurance the qualitative point that the screening does have the potential of preventing death from lung cancer. For this not to be the case, at least one of the relevant probabilities would have to be zero. That this might be the case, we believe, would be very difficult plausibly to argue.

This survival benefit would be realized if, and only if, each of the following were to be the case: the particular round of

screening (is actually carried out and) results in the diagnosis of lung cancer; early treatment of that cancer (is carried out and) is curative while late intervention – in the absence of screening – would not be; and the person avoids death from other causes until that cancer would exhibit its fatal outcome in the absence of intervention.

If, the person does decide to undergo the baseline screening, (s)he later faces a similar decision about the first round of repeat screening. The survival benefit from this would need to be addressed in a similar way, based on experience with repeat screening. The probability of diagnosing a cancer in each round of repeat screening, after a negative baseline, is lower than in the baseline round. While the cancer is typically more aggressive when found in repeat rounds, it is found earlier in its latent course and the diagnosis is still made in clinical Stage I in 85% of the cases, as at baseline. Thus, the

Table 1. Estimates of the probability of diagnosis of cancer resulting from application of the I-ELCAP regimen of screening at baseline, and of not succumbing to illness, other than lung cancer within 10 years, for select ages and histories of smoking. (Reprinted with permission from Eur Respir J 2007; 30:843-847)

	Continues to smoke			Quit 20 years ago	
Age	**Pack-years**	**Prob. of dx of cancer (p_1)**	**Prob. of surviving other causes for 10 yrs (p_2)**	**Prob. of dx of cancer (p_1)**	**Prob. of surviving other causes for 10 yrs (p_2)**
60	10	0.7%	97%	0.5%	98%
	30	1.1%	95%	0.8%	97%
	60	2.0%	91%	1.4%	94%
	100	2.9%	87%	2.0%	90%
	150	2.7%	89%	1.8%	92%
70	10	1.3%	95%	0.9%	96%
	30	2.1%	91%	1.4%	93%
	60	3.6%	83%	2.5%	88%
	100	5.2%	77%	3.6%	82%
	150	4.8%	80%	3.3%	85%
80	10	1.6%	86%	1.1%	90%
	30	2.7%	77%	1.8%	83%
	60	4.7%	63%	3.2%	71%
	100	6.8%	53%	4.7%	61%
	150	6.2%	58%	4.2%	66%
85	10	1.7%	76%	1.1%	82%
	30	2.7%	64%	1.9%	71%
	60	4.7%	47%	3.2%	55%
	100	6.8%	37%	4.7%	45%
	150	6.3%	42%	4.3%	50%

Table 2. Estimates of the probability of survival gain* from baseline screening by the I-ELCAP regimen, for select ages and histories of smoking. (Reprinted with permission from *Eur Respir J* 2007; 30:843-847)

Age	Pack- years	Continues to smoke	Quit 20 years ago
60	10	0.5%	0.4%
	30	0.9%	0.6%
	60	1.4%	1.0%
	100	2.0%	1.4%
	150	1.9%	1.3%
70	10	0.9%	0.6%
	30	1.5%	1.0%
	60	2.4%	1.7%
	100	3.1%	2.3%
	150	3.0%	2.2%
80	10	1.1%	0.8%
	30	1.6%	1.2%
	60	2.3%	1.8%
	100	2.8%	2.2%
	150	2.8%	2.2%
85	10	1.0%	0.7%
	30	1.4%	1.0%
	60	1.7%	1.4%
	100	2.0%	1.6%
	150	2.0%	1.7%

*Probability estimate for survival benefit: product of p_1 and p_2 from ***Table 1*** multiplied by an estimate of the Stage I cancer's curability rate (78%).

probability of finding a lung cancer that is curable with early treatment remains essentially the same as baseline. Naturally, the third probability of escaping death from other causes decreases as the person ages. The needed estimates for each round of repeat screening awaits further accumulation of cancers diagnosed as a result of annual repeat screening since the number of these are still small, even in the I-ELCAP experience.

Limitations

The probability estimates presented here are based on the largest currently available experience, but will need supplementation as additional screenings and longer term follow-up become available. The probability of diagnosing a Stage I lung cancer was based on the full I-ELCAP cohort, while the probability of otherwise surviving was based on a more limited cohort on whom at least 8 years of follow-up for all causes of death was available. Thus, future updating of these estimates, particularly the latter one will be needed.

References

1. American Cancer Society. Cancer Facts and Figures 2008
2. Humphrey LL, Johnson M, Teutsch S. *Ann Intern Med* 2004; 140:740-753.
3. Smith RA, von Eschenbach AD, Wender R, et al. *CA Cancer J Clin* 2001; 51:38-75
4. Strauss GM, Dominioni L, Jett JR, et al. *Chest* 2005; 127:1146-1151
5. International Early Lung Cancer Action Program protocol: website: www.IELCAP.org
6. International Early Lung Cancer Action Program Investigators. *Eur Respir J* 2007; 30:843-847
7. International Early Lung Cancer Action Program Investigators. *NEJM* 2006; 355:1763-1771
8. van den Bergh KAM, Essink-Bot ML, Bunge EM, et al. *Cancer* 2008, 113:396-404

Disclosures

Drs. Henschke and Yankelevitz are inventors among others on a patent and other pending patents owned by Cornell Research Foundation (CRF) and some are non-exclusively licensed to General Electric for technology involving detection and characterization of nodules in many medical situations. They receive royalties from CRF pursuant to Cornell policy, which in turn is consistent with the Bayh-Dole Act. They are also inventors on a pending patent application for lesion measurement. Dr. Yankelevitz is an inventor on a pending patent owned by PneumRx related to biopsy needles, serves as a medical advisor, and holds an equity interest in PneumRx.

No direct support was provided for this paper.

I-ELCAP collaboration has been supported in part by National Institutes of Health R01-CA-63393 and R01-CA-78905; Department of Energy DE-FG02-96SF21260; Department of Defense Grant; The City of New York, Department of Health and Mental Hygiene; New York State Office of Science, Technology and Academic Research (NYSTAR); American Cancer Society; Israel Cancer Association; Mills-Pensinsula Hospital Foundation, The Starr Foundation; The New York Community Trust; The Rogers Family Fund; Foundation for Lung Cancer: Early Detection, Prevention, and Treatment (primary source of funding was an unrestricted gift in 2000-2003 by the Vector group, the parent company of Liggett Tobacco); Foundation for Early Detection of Lung Cancer; Dorothy R. Cohen Foundation, Research Foundation of Clinic Hirslanden; Yad- Hanadiv Foundation; Jacob and Malka Goldfarb Charitable Foundation; Auen/Berger Foundation; Princess Margaret Foundation; Berger Foundation; Tenet Healthcare Foundation; Ernest E. Stempel Foundation, Academic Medical Development Corporation; Empire Blue Cross and Blue Shield; Eastman-Kodak Corporation; General Electric Corporation; Weill Medical College of Cornell University; Cornell University; New York Presbyterian Hospital; Clinic Hirslanden; Swedish Hospital; Christiana Care Helen F. Graham Cancer Center; Holy Cross Hospital; Eisenhower Hospital; Jackson Memorial Hospital Health System; Evanston Northwestern Healthcare.

Claudia Henschke, PhD, MD is Professor of Radiology and Professor of Radiology in Cardiothoracic Surgery at New York Presbyterian Hospital – Weill Cornell Medical Center, in New York, New York.

Lung Cancer Meetings and Symposia

International Conference
on Screening for Lung Cancer
April 27-28, 2009
Washington, DC
Contact: ielcap.org

European Multidisciplinary Conference
in Thoracic Oncology
May 1-3, 2009
Lugano, Switzerland
Contact: esmo.org/events/lung-2009

International Association for the Study of Lung Cancer
13th World Conference on Lung Cancer
July 31-August 4, 2009
San Francisco, CA
Contact: iaslc.org

Upcoming Continuing Medical Education Events at National Jewish Health

Regaining Control of Severe Asthma Dinner Series
Conference Co-Chairs:
Stan Szefler, MD and Harold Nelson, MD
Visit njhealth.org/regainingcontrol for locations
February – May, 2009

I Can't Breathe (Dyspnea Symposium)
Featuring:
Howard Weinberger, MD, Kern Buckner, MD
and Brett Fenster, MD
June 27, 2009

Second Annual Women's Health Conference
Conference Chair:
Esther Langmack, MD
October 3, 2009

First Annual International COPD Conference:
Phenotyping
Featuring:
Barry Make, MD and Russell Bowler, MD, PhD
November 10-12, 2009

Visit www.njhealth.org/proed or call 800.844.2305 for more information


Stan Szefler, MD


Harold Nelson, MD


Kern Buckner, MD, and Howard Weinberger, MD


Barry Make, MD

Lung Cancer Frontiers Editorial Board

Comments may be submitted to ***Lung Cancer Frontiers***
1400 Jackson Street J208
Denver, Colorado 80206
or by email to
langmacke@njhealth.org, or tlpdoc@aol.com