Review Article

Advancing and sharing the knowledge base of CT screening for lung cancer

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Abstract: CT screening for lung cancer is gaining in acceptance and is now moving from the research domain into standard clinical practice. Coincident with this, there is also increasing awareness of the usefulness of collecting large datasets obtained in the clinical domain and how this can be used to advance practice. Toward this end, in the United States, the Centers for Medicare and Medicaid Services (CMS) are requiring data from screening to be entered into certified registries. While this is still in its early stage and only limited datasets are required, this would be particularly relevant if images as well as clinical information were collected as it will allow for additional evaluation of all imaging findings including ancillary ones and understanding how they integrate into the screening process. All of this needs to be considered in the context of how this information can be shared with a person interested in being screened. In particular, the potential benefit of screening needs to be presented in terms of what is meaningful to the individual including their chances of having lung cancer and also their chance of being cured. This is very different then presenting it in terms of mortality reduction which was never meant to be used for that purpose. Also, how findings made on the CT scans, in addition to those related to lung cancer will be meaningful to them.

Keywords: Shared decision making; registries; protocols; ancillary findings

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The knowledge base for CT screening for lung cancer will continue to expand, not only in regard to early detection of lung cancer but also into many additional diseases impacted by tobacco use. The use of registries to collect the vast amounts of data that will become available as screening becomes more widespread will allow for development of further efficiencies in the lung cancer screening process and also for the advancement of a wide range of computer analytical tools that will provide information beyond just the early detection of lung cancer. How we provide this information to a person interested in screening will become of increasing importance as they weigh their decision about entering into a screening program.

Shared decision making

The process of shared decision making is defined as, "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences" (1). This approach has been encouraged by thought leaders in the United States as can be seen in the 2001 report by the Institute of Medicine suggesting that the health care system be redesigned according to ten rules which included shared decision making. Portions of these recommendations were incorporated into the Affordable Care Act (section 3506) to

emphasize and facilitate implementation of shared decision making, notably for federally funded programs (2).

In 2014, the US Preventive Services Task Force (USPSTF) concluded that low-dose CT (LDCT) screening for lung cancer should have a "B" rating. A "B" rating means that "The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial" and their suggestion for practice is "Offer or provide this service" (3). As a result of this rating, private insurers were required to cover this service for the high-risk population defined in the USPSTF recommendations. This recommendation was followed by a decision by the Centers for Medicare and Medicaid Services (CMS) in 2015 to also provide coverage for essentially the same high-risk population, although the upper age range was lowered from 80 to 77 (4,5). CMS also added several additional requirements including the need for shared decision making. In particular they state as one of the criteria for beneficiary eligibility:

(I) A beneficiary must receive a written order for LDCT lung cancer screening during a lung cancer screening counseling and shared decision making visit, furnished by a physician [as defined in section 1861(r) (1) of the Social Security Act] or qualified non-physician practitioner [meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in §1861(aa) (5) of the Social Security Act].

(II) A lung cancer screening counseling and shared decision making visit includes the following elements (and is appropriately documented in the beneficiary's medical records):

(i) Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;

(ii) Shared decision making, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;

(iii) Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;

(iv) Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions;

(v) And if appropriate, the furnishing of a written order for lung cancer screening with LDCT.

In response to public comments on their shared decision making requirement, CMS responded as follows:

We believe that a counseling and shared decision making visit that addresses the benefits and harms of screening is supported by the evidence and is essential for ensuring that appropriate eligible beneficiaries receive these initial services with full knowledge of the risks, benefits, and commitment necessary to receive the most benefit from a lung cancer screening program. Among other things, there is the potential for significant harms in starting a lung cancer screening program, including the risk for false-positive results leading to additional tests and treatments that may be more harmful. The goal of shared decision making is not merely to furnish a written order for such services, but that both the practitioner and the beneficiary are armed with a better understanding of the relevant risk factors, and are engaged with shared responsibility regarding the decision to proceed or not proceed with a lung cancer screening program. We believe that the initial counseling and shared decision making visit supports identification of individuals that would most benefit from a lung cancer screening program (4).

The potential benefit

In a discussion with a person interested in being screened, the critical element to initiate the discussion must focus on the potential benefit, for without a potential benefit, even minimal harm would be unacceptable. To determine this benefit, major organizations that provide guidelines have relied primarily on results from RCT's, in particular, in the United States, the National Lung Screening Trial (NLST) was the primary source for this determination. The core result of the NLST was as follows (6):

There were 247 deaths from lung cancer per 100,000 person-years in the LDCT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with LDCT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004).

However, this 20% mortality reduction has been widely misinterpreted. One of the early examples can be found in a systematic review jointly sponsored by the American

College of Chest Physicians (ACCP) and the American Society of Clinical Oncology (ASCO) on screening. The authors of that report took this core result to mean the following (7).

Four out of 5 people who are going to die of lung cancer will die of it even if they are screened. Screening prevents one in five deaths from lung cancer.

Another example of a mistaken conclusion of this form is seen here (8).

As screening and earlier treatment delays death for only 20% of patients destined to die from lung cancer, 80% of screened people with fatal cancer will die at the same time they would have without screening.

These statements transform that core result of 20% mortality reduction to mean that among those cancers identified under screening that only 20% of those destined to die would be saved as a result of early treatment. However, this statement is knowable incorrect. The NLST by its very design of limited rounds of screening with limited follow-up was never meant to measure the magnitude of the benefit. Instead, because of constraints associated with cost of performing these types of studies, the investigators instead focus on hypothesis testing and not on quantifying a magnitude of benefit. As is appropriate for this type of study design the NLST was powered specifically to test the hypothesis the investigators chose and its core results was reported accordingly. Participants in the NLST underwent three rounds of screening in the LDCT arm with an average of 5 years follow-up post screening and when compared to the other arm using chest radiography, showed a statistically significant 20% mortality reduction. The mortality reduction found in the NLST comes about because some of the cancers are diagnosed and cured in the screening arm while their equivalent counterparts in the control arm, who are diagnosed later when the cancer is more advanced, die of it. However, that mortality reduction seen in the NLST is diluted by those cancers diagnosed in the screening arm after screening was completed who also died before the trial was completed. This occurs due to the very nature of stop-screen trial designs such as the NLST with limited rounds of screening and longer follow-up (9). In the NLST, 1/3 of the cancers fell into this category, the majority of which were late stage. Deaths from these cancers could not have been prevented by screening since screening had already stopped prior to their being detected, yet they are still counted as deaths in the screening arm. A second source of dilution comes from those cancers that are diagnosed under screening that were destined to have died had it not been for the early intervention, but their deaths would have come only after the trial's follow-up had ended. These cases are counted as diagnosed cancers in the screen arm but since their counterparts in the control arm would not have died until after the trial has ended, they are seen only as excess cases and considered to be examples of overdiagnosis even though they would have been fatal, and were cured as a result of the screening. Since follow-up for some participants in the NLST was as short as 3.5 years following their last screen, slow growing cancers and even small cancers with rapid growth rates could fall into this category.

Thus, for the reasons above, the mortality reduction in the NLST is an underestimate of the potential magnitude of the screening benefit and an underestimation of the reduction in the fatality rate of screen detected lung cancers (9). The question that naturally arises is how high might that actual mortality reduction be? Surely it is higher than 20%, and the I-ELCAP groups, based on estimating cure rates for the various subtypes of cancers, have estimated that it approaches 80%. In essence, this would mean that instead of saying 4 out of 5 will die, that 4 out of 5 will be cured under screening. Regardless of whether it is actually that high, it is surely substantially higher than that often quoted 20%. This point is enormously important when discussing the potential benefits with a person interested in being screened.

Role of registries

The CMS decision to reimburse for lung cancer screening also included the need to develop certified screening registries with a limited data set of elements. Specifically, when defining "Radiology imaging facility eligibility criteria" they include the following (5):

Collects and submits data to a CMS-approved registry for each LDCT lung cancer screening performed. The data collected and submitted to a CMS-approved registry must include, at minimum, all of the following elements…

In 2010 as part of a workshop conducted by the Institute of Medicine titled, "A Foundation for Evidence-Driven Practice: A Rapid Learning System for Cancer Care - Workshop Summary", they concluded the following (10):

It may seem as though new research emerges each day, promising advances in cancer treatment, and some forms of cancer already are curable. Yet despite modern advances in health IT, the way that evidence on cancer screening, early detection and treatment is gathered and applied has not moved forward rapidly enough. Individuals and

institutions working both in cancer research and treatment could take better advantage of existing resources and create new mechanisms for assessing and sharing information on the effectiveness and value of each individual treatment. Researchers already gather data on effectiveness through clinical interaction with patients, as well as from cancer registries, clinical trials, and networks of academic and community cancer centers. They could be sharing that information and aggregating it more effectively in order to accelerate advances. Health care payers, policymakers, and the public all could reap the benefits. Most importantly, patient care could be improved.

The requirement by CMS begins this process for lung cancer screening on a national scale. However, this is just a first step in the process as it only requires a minimal amount of clinically relevant data. Currently this is limited to smoking history and information derived from the interpretation of the scan according to a particular categorical classification system (ref). Far more data is potentially available in the CT images themselves which could have many uses. An example of this type of registry is seen in the I-ELCAP program where all of the image data was captured along with detailed clinical information.

Evaluation of coronary artery calcification is an example of how this additional data can be useful. The decision by CMS to cover lung cancer screening make screening available for approximately 7 million eligible high risk people (6). High risk was defined as having an extensive smoking history of 30 or more pack-years (quit less than 15 years ago) and age of 55–77. These two criteria are also two of the important risk factors for cardiovascular disease. This convergence of risk for both lung cancer and heart disease is evident in previous lung cancer screening studies performed in the US including those using chest radiographs for screening where death from ischemic heart disease was the major cause of death and this persisted in the NLST despite major advances in preventive cardiology (6,11).

In 2006 and again in 2010, Shemesh *et al*. published two reports demonstrating that coronary artery calcium (CAC) scoring performed on scans obtained in the context of lung cancer screening using an ordinal scoring system were useful in predicting death from cardiovascular disease (12,13). It was the first time these non-gated low-dose scans were shown to provide useful information about cardiovascular disease. Also in that same 2010 journal issue, two other papers presented approaches to evaluate for illnesses that were part of the initial indication for the CT examination. In one article, bone mineral density was evaluated on cardiac CT studies and in the other, evaluation of the aorta was performed on routine CT scans (14,15). Together, these three articles led to an editorial by Lee and Forman titled, "What we can and cannot see coming" (16). In that editorial the authors note the following important consideration:

We would like to frame these reports and their implications in the context of the recently passed health care reform legislation and the future direction of radiology. Under the Patient Protection and Affordable Care Act, incentives are offered for developing patient-centered accountable care organizations, or ACOs, and similar multidisciplinary integrated health care models [5]. In the future, reimbursement for radiologic procedures will bear a stronger connection to our consultative abilities than to our aggregate number of studies and the billable items that we can document. With the increasing focus on patient-centered medical practice, radiologists will have to account for their influence on the entire well-being of patients. Providing risk assessments that could lead to future disease prevention on the basis of already available imaging data expands the radiologist's role in patient care. To the extent that we can demonstrate such increasing value from our efforts, we will be appropriately rewarded and appreciated.

The editorial ultimately leads to the following conclusion:

This paradigm shift allows for a rich avenue of further research and development. Rather than shying away from this new responsibility, the radiology leadership should embrace the possibility of adding a new dimension to our profession. By extracting potentially important information from existing images beyond our usual interpretation, we as radiologists can cement the three tenets that define our specialty: our mastery of technology, our clinical acumen, and our dedication to patient safety and quality [6]. In doing so, we can also expand our role and value in the overall well-being of patients in the current climate of health care reform.

The usefulness of the non-gated quantitative methods has been confirmed by several studies showing that these measures correspond to the major Agatston risk groupings (17,18). The American College of Radiology which has the only CMS approved lung cancer screening registry recommends use of their Lung-RADS reporting system which requires reporting of moderate to severe calcification as a separate data element (19,20). The Lung-RADS system describes the findings on the scan in a succinct manner including a description of the lung nodules and their management on a 0–4 scale (20). An additional category in that system is the "S" modifier which is used to describe any

"Clinically significant or potentially significant findings" (non-lung cancer) and moderate to severe calcification is considered significant.

As previously described, CMS requires a shared decision making discussion with a required element being a discussion about benefits and risks which includes ancillary findings. While no specific guidance is given regarding a discussion about CAC this clearly would be one of the potential findings that might bear on a persons' decision to be screened. Within that discussion, a consideration that might arise would be whether to perform the more advanced CAC evaluation, especially if it can be performed without additional harms (21). Under this assumption the only downside would be the additional time (and minimal direct expense) in performing the test and even this will all but disappear with anticipated technologic advances as it will become so easy to perform that it will not require any additional effort at all. Improvement in temporal resolution of the CT scanners will make gating unnecessary, and continued improvement in computer aided diagnosis (CAD) will allow for CAC scoring to be done automatically thus eliminating additional time and cost. Once this occurs, the argument against providing this on a routine basis will become moot as the test will provide better information than what is currently required in a limited form for the CMS population, at least in terms of recognizing moderate to severe calcification.

Beyond the consideration of evaluation of coronary artery disease, there are a wide range of additional findings that could also be evaluated in the context of an ongoing registry. These include various measures of lung health such as emphysema and airway analysis, evaluations for osteoporosis, breast density evaluation, and body fat distributions. The main point being that additional information could be gathered in the context of lung cancer screening that bear on multiple health concerns.

A more immediate benefit to having the images available and one that is the primary focus of the CMS requirement is to develop more efficient screening protocols. With the CMS registry the value will be limited to data extracted from the images and reported in the limited dataset. However, more detailed information about nodules is available from the images in terms of each aspect of their appearance. The ability to further characterize their appearance will continue to improve as computer assisted techniques improve. Currently there are several large datasets with images available to develop and update management protocols. In the US this includes the publically accessible NLST dataset as well as the I-ELCAP database. Several other databases from ongoing trials in Europe are also available. The power of these databases can be seen in several examples. The threshold for positive result was raised from 4 mm in a single dimension on baseline screening to a dimensional average of 6 mm. This was defined first on the I-ELCAP database and subsequently confirmed on the NLST (22,23). This was quickly accepted by the imaging community and incorporated into the current version of Lung-RADS as well as other authoritative guidelines (20,24) Another example relates to the management of nonsolid nodules where observation on an annual basis is now considered acceptable practice under certain conditions. Again, both the I-ELCAP database and NLST database have been used to confirm this approach (25,26). In the future, continued accrual of screening cases is needed in order to remain current with state-of-the-art technology. The imaging from the NLST is now over a decade old. However, the I-ELCAP does continue to accrue new cases.

The process of shared decision making by necessity includes a discussion of risks and benefits. As we continue to advance our knowledge about findings made on lung cancer screening studies, discussion of these various additional findings will become more important for both the screen and the physician to understand. This knowledge base will be greatly enhanced by collecting image data along with more comprehensive clinical data in an organized registry. CMS has now begun this type of process and hopefully it will continue to expand so as to fully leverage the information that is available.

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Footnote

Conflicts of Interest: Dr. David Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents; Dr. Yankelevitz is a consultant and shareholder for Accumetra LLC; Dr. Henschke gave her disclosure in the other article that she was first author on and you can use

that one here as well.

References

1. Elwyn G, Laitner S, Coulter A, et al. Implementing shared decision making in the NHS. BMJ 2010;341:c5146.
2. Oshima Lee E, Emanuel EJ. Shared decision making to improve care and reduce costs. N Engl J Med 2013;368:6-8.
3. Grade Definitions. Available online: http://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions
4. Lung Cancer: Screening. Available online: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening
5. Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N). Available online: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274
6. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
7. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012;307:2418-29.
8. Harris RP, Sheridan SL, Lewis CL, et al. The harms of screening: a proposed taxonomy and application to lung cancer screening. JAMA Intern Med 2014;174:281-5.
9. Yankelevitz DF, Smith JP. Understanding the core result of the National Lung Screening Trial. N Engl J Med 2013;368:1460-1.
10. A Foundation for Evidence-Driven Practice: A Rapid Learning System for Cancer Care - Workshop Summary. Available online: http://www.nationalacademies.org/hmd/Reports/2010/A-Foundation-for-Evidence-Driven-Practice-A-Rapid-Learning-System-for-Cancer-Care.aspx
11. Fontana RS, Sanderson DR, Woolner LB, et al. Screening for lung cancer. A critique of the Mayo Lung Project. Cancer 1991;67:1155-64.
12. Shemesh J, Henschke CI, Farooqi A, et al. Frequency of coronary artery calcification on low-dose computed tomography screening for lung cancer. Clin Imaging 2006;30:181-5.
13. Shemesh J, Henschke CI, Shaham D, et al. Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. Radiology 2010;257:541-8.
14. Budoff MJ, Hamirani YS, Gao YL, et al. Measurement of thoracic bone mineral density with quantitative CT. Radiology 2010;257:434-40.
15. Gondrie MJ, Mali WP, Jacobs PC, et al. Cardiovascular disease: prediction with ancillary aortic findings on chest CT scans in routine practice. Radiology 2010;257:549-59.
16. Lee CI, Forman HP. What we can and cannot see coming. Radiology 2010;257:313-4.
17. Htwe Y, Cham MD, Henschke CI, et al. Coronary artery calcification on low-dose computed tomography: comparison of Agatston and Ordinal Scores. Clin Imaging 2015;39:799-802.
18. Chiles C, Duan F, Gladish GW, et al. Association of Coronary Artery Calcification and Mortality in the National Lung Screening Trial: A Comparison of Three Scoring Methods. Radiology 2015;276:82-90.
19. ACR NRDR – LCSR Registry. Available online: http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/NRDR/Lung%20Cancer%20Screening%20Practice%20Registry/Exam%20Form.pdf
20. Lung-RADS™ Version 1.0 Assessment Categories Release date: April 28, 2014. Available online: https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/LungRADS/AssessmentCategories.pdf
21. Hecht HS, Henschke C, Yankelevitz D, et al. Combined detection of coronary artery disease and lung cancer. Eur Heart J 2014;35:2792-6.
22. Henschke CI, Yip R, Yankelevitz DF, et al. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med 2013;158:246-52.
23. Yip R, Henschke CI, Yankelevitz DF, et al. CT screening for lung cancer: alternative definitions of positive test result based on the national lung screening trial and international early lung cancer action program databases. Radiology 2014;273:591-6.
24. Lung cancer screening. Available online: http://www.nccn.org/patients/guidelines/lung_screening/
25. Yankelevitz DF, Yip R, Smith JP, et al. CT Screening for Lung Cancer: Nonsolid Nodules in Baseline and Annual Repeat Rounds. Radiology 2015;277:555-64.
26. Yip R, Yankelevitz DF, Hu M, et al. Lung cancer deaths in the National Lung Screening Trial (NLST) attributed to nonsolid nodules. Radiology 2016. In Press.

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