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Review Artical on beneficial effect of CT screening in lung cancer

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ABSTRACT

Context: Lung cancer is the leading cause of cancer death. Most patients are diagnosed with advanced disease, resulting in a very low five-year survival rate. Screening may reduce the risk of death from lung cancer.

Objective:A multi-society collaborative initiative (involving the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network) was undertaken to conduct a systematic review of the evidence regarding the benefits and harms of lung cancer screening using low dose computed tomography (LDCT), in order to create the foundation for development of an evidence-based clinical guideline.

Data Sources:MEDLINE (OVID: 1996 to April 2012), EMBASE (OVID: 1996 to April 2012), and the Cochrane Library (April 2012).

Study Selection: Of 591 citations identified and reviewed, eight randomized controlled trials and 13 cohort studies of LDCT screening met criteria for inclusion. Primary outcomes were lung cancer mortality and all-cause mortality, and secondary outcomes included nodule detection, invasive procedures, follow-up tests, and smoking cessation.

Data Extraction: Critical appraisal using pre-defined criteria was conducted on individual studies and the overall body of evidence. Differences in data extracted by reviewers were adjudicated by consensus.

Results: Three randomized studies provided evidence on the impact of LDCT screening on lung cancer mortality, of which the National Lung Screening Trial was the most informative, demonstrating that among 53,454 enrolled, screening resulted in significantly fewer lung cancer deaths (356 vs 443 deaths; lung cancer-specific mortality, 247 vs 309 events per 100,000 person-years for LDCT and control groups, respectively; Relative Risk [RR] = 0.80, 95% Confidence Interval [CI] 0.73–0.93; Absolute Risk Reduction [ARR] = 0.33%, P=0.004). The other 2 smaller studies showed no such benefit. In terms of potential harms of LDCT screening, across all trials and cohorts, about 20% of individuals in each round of screening had positive results requiring some degree of follow-up, while approximately 1% had lung cancer. There was marked heterogeneity in this finding and in the frequency of follow-up investigations, biopsies, and the percent of surgical procedures performed in those with benign lesions. Major complications in those with benign conditions were rare.

Conclusions:LDCT screening may benefit individuals at an elevated risk for lung cancer, but uncertainty exists about potential harms and the generalizability of results.

I. BACKGROUND

Lung cancer is the leading cause of cancer death in the United States (and worldwide), causing as many deaths as the next four most deadly cancers combined (breast, prostate, colon and pancreas).[1] Despite a slight decline since 1990 in the US, lung cancer will claim >160,000 American lives in 2012.[2] Most patients diagnosed with lung cancer today already have advanced disease (40% are stage IV, 30% are stage III), and the current five-year survival rate is only 16%.[3]

Earlier randomized controlled trials (RCT) involving chest radiographs (CXR) and sputum cytology for lung cancer screening found that these strategies detected slightly more lung cancers, smaller and more stage I tumors, but the detection of a larger number of early stage cancers was not accompanied by a reduction in the number of advanced lung cancers or lead to a reduction in lung cancer deaths.[4–14] Renewed enthusiasm for lung screening arose with the advent of low dose computerized tomography (LDCT) imaging, which is able to identify smaller nodules than can CXR.

This systematic review focuses on the evidence regarding the benefits and harms of LDCT screening for lung cancer. Other potential screening methods (e.g. CXR, sputum cytology or biomarkers, exhaled breath) are not addressed. This review is a collaborative initiative of the American Cancer Society (ACS), the American College of

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Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN), and forms the basis for the clinical practice guideline of the ACCP and ASCO (Box xx – link to full guideline in box?). This work will be re-assessed when pertinent new data become available, consistent with the Institute of Medicine's recommendations for guideline development.

Benefits of screening

Results of randomized control trials

The NLST randomized almost 55,000 subjects aged 55–74 years to three annual rounds of screening with either LDCT or chest radiograph [8]. Eligibility criteria included 30-plus pack-years of smoking and current smoking or having quit smoking within the last 15 years. Overall, approximately 50% of NLST subjects were current smokers, and the mean pack-years was 56. A noncalcified nodule (NCN) of at least 4 mm in greatest diameter constituted a positive LDCT screen; other suspicious abnormalities (e.g., adenopathy) could also trigger a positive screen. Subjects were followed for a median of 6.5 years from randomization.

The NLST initially reported a statistically significant 20% reduction in lung cancer mortality for LDCT versus chest radiograph [8]. Subsequent publications examined a slightly longer follow-up period for lung cancer deaths and reported a 16% lung cancer mortality reduction, or a rate ratio (RR) of 0.84 (95% CI: 0.75–0.95) [10]. Approximately 60% of LDCT-arm lung cancers were screen detected, and of these, 62% were diagnosed in stage I.

Three smaller randomized controlled trials (RCTs) of high-risk current and former smokers – all in Europe – have also reported mortality outcomes [5–7]. Each offered five rounds of LDCT screening, and in contrast to NLST, compared LDCT screening with no screening. These RCTs reported RRs for lung cancer-specific mortality of 0.83 (95% CI: 0.45–1.54), 1.37 (95% CI: 0.63–2.97) and 1.99 (95% CI: 0.80–4.96). The wide confidence intervals indicate the lack of precision of the RR estimates; combined, these studies only had 10% of the number of lung cancer deaths as NLST.

Metrics of screening benefit

In cancer screening RCTs, the generally accepted primary outcome is cancer-specific mortality, and the standard metric for measuring this is the RR cited above (i.e., the ratio of cancer-specific mortality rates in the two trial arms). From a public health perspective, a more informative measure of screening effectiveness is the number needed to screen (NNS), which is defined as the reciprocal of the difference in (cancer-specific) mortality rates between trial arms [11]. The NNS denotes the number of subjects needed to be screened in order to prevent one death from the cancer of interest. As such, and in contrast to the mortality RR, it is directly interpretable in terms of the required resources that need to be expended in order to obtain a given health benefit.

Although often left unstated, any NNS estimate refers to a given scenario involving the number and frequency of screens. In the NLST, where an NNS of 320 was computed, this estimate implicitly refers to three annual LDCT screens (i.e., 320 subjects need to be screened over three annual rounds [and followed for a total of 6.5 years] in order to prevent one lung cancer death) [10]. In addition, the study population from which the estimate was derived is also critical. In populations with lower risk than the NLST, the NNS would likely be greater since, assuming the same lung cancer mortality RR, the NNS increases as the population lung cancer risk decreases. Even within the NLST, former smokers had twice the NNS as current smokers (462 vs 230), due primarily to their lower risk level [10].

In terms of minimizing NNS, LDCT screening is favorable for several reasons. Although the percentage mortality benefit is modest at 16–20% (corresponding to an RR of 0.80–0.84), not only does lung cancer have a high overall mortality rate, but also a high-risk group can be easily identified and targeted for screening. A useful contrast is with mammography. In their respective intended screening populations, which for mammography is women aged 50–74 years based on the most recent USPSTF recommendations, the mortality rate from breast cancer is less than a fifth of the mortality rate from lung cancer for the LDCT recommended screening population. Because the percentage mortality reductions for their respective cancers for LDCT and mammography are similar, this translates into a NNS that is approximately five-times as large for mammography as for LDCT screening.

Screening benefits in the population setting

Since the NLST was conducted only over three rounds of screening and other LDCT trials or observational studies were also of limited duration,

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there is little direct evidence as to the long-term benefits (and harms) of continued screening in the population over the periods recommended by the USPSTF. For now, one has to rely on modeling efforts in order to estimate long-term effects. The Cancer Intervention and Surveillance Modeling Network (CISNET) lung consortium consists of five independent groups who developed microsimulation models for lung cancer natural history and screening [12]. All five groups modeled a number of LDCT screening scenarios for a hypothetical cohort of US subjects followed from 45 to 90 years of age. Based on the USPSTF screening guidelines and assuming 100% compliance, the CISNET models showed (on average) a 14% population reduction in lung cancer mortality, with 19% of the entire cohort undergoing at least one round of LDCT screening [12]. As with any modeling exercise, these results must be viewed with caution, as they are based (largely) on extrapolating the findings from the three screening rounds of NLST to 25 rounds in the population setting. To this point, the variability of the five model predictions was wide, with a range of estimated population lung cancer mortality reductions of 4.8 to 23% [12].

Indirect measures of screening efficacy

In contrast to the direct mortality benefit metrics of screening efficacy estimable from a randomized screening trial as described above, a number of indirect measures of screening efficacy are widely utilized outside of the randomized trial setting. Two common such measures are survival statistics and stage distribution (i.e., comparing the survival and stage distribution of cancers detected under a screening program with those of cancers detected in a nonscreening environment). Each of these measures alone or in combination is not sufficient to conclude that screening has any mortality benefit, due to the widely known biases of lead time, length-biased sampling and overdiagnosis, and to the fact that a 'stage shift', or a more favorable stage distribution observed with screening, is a necessary but not sufficient condition for a mortality reduction [13]. Another metric of screening efficacy is test sensitivity, although again, high sensitivity does not necessarily translate into a mortality benefit of screening.

Nevertheless, if there is already evidence of a mortality benefit from a well-conducted randomized trial, as there is with LDCT and lung cancer screening from the NLST, then these surrogate outcome measures may serve as important benchmarks for monitoring the performance of screening in clinical practice, since it is difficult for a variety of reasons (including self-selection of who chooses to be screened) to assess actual reductions in cancer-specific mortality outside of a randomized trial setting. In the NLST, 62% of LDCT-arm screen-detected cancers were stage I; furthermore, 59% of all LDCT-arm cancers diagnosed during the screening phase of the trial were stage I [8]. LDCT test sensitivity was 93.7%. All-cause 5-year survival of screen-detected cancers was 55% for subjects over 65 years of age and 64% for subjects under 65 years of age [14].

Methods

ACS, ACCP, ASCO and NCCN assembled a panel of experts, representing the relevant clinical disciplines and the consumer's perspective. All members cleared all organizations' conflict of interest policies for participation in guideline development; none received compensation for participation. The sponsoring organizations donated staff time supported by their general administrative funds. No industry funds were used in the support of this endeavor. The panel defined a process for selection, data extraction and outcomes assessment to produce a thorough evaluation of LDCT screening relative to patient-centered outcomes, including quantifying potential benefits and harms. The target patient population for this initiative is individuals at elevated risk of developing lung cancer due to age and smoking history; and the target audience includes physicians, allied professionals and policy makers. The panel was divided into evidence review and writing sub-committees, focusing on the following key questions:

1. What are the potential benefits of screening individuals at elevated risk of developing lung cancer using LDCT?
2. What are the potential harms of screening individuals at elevated risk of developing lung cancer using LDCT?
3. Which groups are most likely to benefit or not benefit from screening?
4. In what setting is screening likely to be effective?

The literature search was developed and conducted by an experienced systematic reviewer using MEDLINE (OVID: 1996 to April 8, 2012), EMBASE (OVID: 1996 to April 8, 2012), and the Cochrane Library (April 20, 2012). Additional citations were gleaned from the reference lists of

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related papers and review articles. The literature search included MeSH and Emtree headings and related text and keyword searches in a manner that combined terms related to lung cancer, population screening and LDCT (eAppendix 1). The search was limited to published data only because it was felt that any unpublished preliminary data identified would add little to inform the primary outcomes of interest.

Studies were eligible for inclusion if they involved either a RCT using LDCT screening for lung cancer in one arm, or a non-comparative cohort study of LDCT screening, provided they reported at least one of the following outcomes: lung-cancer-specific or all-cause mortality, nodule detection rate, frequency of additional imaging, frequency of invasive diagnostic procedures (e.g. needle or bronchoscopic biopsy, surgical biopsy, surgical resection) complications from the evaluation of suspected lung cancer, and the rate of smoking cessation or re-initiation. For lung-cancer-specific and all-cause mortality endpoints, only RCT data were considered eligible for inclusion; for other endpoints, data from the LDCT arm of both RCTs and cohort studies were included. Exclusion criteria include studies that only assessed screening among those with risk factors other than smoking (e.g. asbestos), those not published in English, and meta-analysis or case-series reports of outcomes only among patients diagnosed with lung cancer.

The above exclusion criteria were determined a priori and guided whether data identified by the systematic literature review was judged to have been reported in a manner appropriate for inclusion. Articles were selected and data were extracted independently by a minimum of two reviewers. At the point of abstract review, if one of two reviewers indicated that a citation may be relevant, the full text article was retrieved. Upon full text review, if there was a discrepancy among the two reviewers, a third reviewer determined eligibility and the reviewers came to consensus. In addition, the third reviewer also verified that articles deemed ineligible did not actually meet eligibility criteria. Between the three reviewers, discrepancies occurred in approximately 12% of cases and were resolved through consensus. Most notably, the small RCT by Garg et al and the smoking cessation study by Schnoll et al were originally excluded, but the decision was reversed upon further review.[16, 17] Common reasons for exclusion included the identification of narrative reviews, studies that did not involve high risk smoking populations or studies that only followed patients diagnosed with lung cancer. A full list of the studies excluded from the systematic review and the reasons for exclusion is available from the authors.

The risk of bias was assessed by a minimum of two reviewers using pre-specified criteria (eAppendix 2) and discrepancies were resolved through consensus.

The frequency of nodule detection across studies was analyzed both unadjusted and stratified by multiple study design characteristics (e.g. CT collimation, minimum smoking exposure criteria for study enrollment, stated threshold for labeling a finding “positive” or “suspicious”).

II. DISCUSSION

This paper summarizes the systematic review conducted by a multi-society collaborative effort examining the risks and benefits of LDCT screening for lung cancer, and forms the basis of the American College of Chest Physicians and the American Society of Clinical Oncology clinical practice guideline (Box, link to full practice guideline). The guideline is based on the finding that a reasonable amount of data has been reported regarding the outcomes for LDCT screening for lung cancer and that some conclusions can be drawn regarding its risks and benefits despite many areas of uncertainty.

A recent large, high quality RCT (the NLST) found that annual LDCT screening reduced the relative risk of death from lung cancer by 20%, and the absolute risk by 0.33% in a population with a substantially elevated risk for lung cancer. Two smaller RCT’s (DANTE and DLSCT) comparing LDCT to usual care found no benefit of LDCT screening, but are best interpreted as neither confirming nor contradicting the NLST findings. Because studies a recent large (N=154,901) RCT demonstrated no lung cancer mortality difference between CXR screening and usual care, the interventions in these three studies are reasonably comparable.[56]

The literature supports the conclusion that LDCT screening can lead to harm. It identifies a relatively high percentage of subjects with nodules (average ~20%), the vast majority of which are benign. The additional imaging that these nodules trigger increases radiation exposure. The rates of surgical biopsy are also variable (<1–4%) as are the percentage of surgical procedures performed for benign disease. The rate of major, and sometimes

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fatal, complications among those with benign conditions is low.

The unexplained heterogeneous rates of nodule detection, additional imaging and invasive procedures that occurred within the structured settings of the controlled trials of LDCT raise concerns about how easily LDCT can be more broadly implemented. There is already substantial variability in the US in the rates and complications of pulmonary needle biopsy[57] and outcomes of lung cancer surgery, being considerably better in dedicated centers (such as those conducting LDCT trials).[58, 59] Furthermore, compliance with screening is consistently lower in cohort studies than in the NLST, and could be worse with unstructured implementation, with resulting diminished benefits. Analogous concerns in breast cancer screening led to the Mammography Quality Standards Act. The position statement by the International Association for the Study of Lung Cancer recommends demonstration projects to evaluate implementation of LDCT screening, establishment of quality metrics, and multiple task forces to address the many critical areas of uncertainty.[60] Given all of these issues, performing a LDCT scan outside of a structured organized process appears to be beyond the current evidence base for LDCT lung cancer screening.

III. RESULTS

Bronchial wall thiekeing can be seen on lung CTs, the ratio of the bronchial wall thekness and the bronchial diameter is between 0.17 and 0.23.CT angiography of the chest is becoming the primary method for detecting pulmonary embolism and aortic dissection. CT is the standard method of evaluating abnormalities seen on chest X-ray and follows a significance finding in lungs cancer detection.

Three randomized studies provided evidence on the **impact** of LDCT **screening** on **lung cancer** mortality, of which the National **Lung Screening** Trial was the most informative, demonstrating that among 53,454 enrolled, **screening** resulted in significantly fewer **lung cancer** deaths (356 vs 443 deaths; **lung cancer**-specific.

A formal assessment of the risk of bias in the RCTs (eTable 1) discloses a low risk in NLST and DLCST, and variable results and an incomplete ability to assess the risk in other studies (often because only preliminary reports of ongoing studies are available). The risk of bias in the cohort studies is variable and often high (usually because justification of sample size, definition of a primary endpoint or funding sources was lacking).

Across the RCTs, the minimum smoking history required for enrollment ranged from 15–30 pack years (i.e. cigarette packs smoked per day multiplied by years of smoking), with a maximum time since quitting smoking ranging from 10 years to an unlimited number of years. The lower age limit ranged from 47 to 60 years, and the upper limit from 69 to 80 years. There was greater variation in entry criteria in the cohort studies. Thus, the underlying risk for lung cancer varies substantially. Generally speaking, the NLST, LSS and Garg studies focused on higher risk, DLCST, ITALUNG and DANTE on both higher and intermediate risk and NELSON and Depiscan on a broad range of risk among participants.[16, 18, 20–24, 38] Although estimating the average risk of all participants in any of these studies is difficult due to lack of granular data, the minimum risk level in each study can be approximated using established formulas.[39,40] Over 10 years, the risk of being diagnosed with lung cancer for participants meeting minimum entry criteria of each study, assuming they had quit smoking at time of study entry, are approximately 2% for NLST, 1% for DLSCT and considerably less than 1% for NELSON. The nodule size deemed large enough to investigate further ranged from “any size” to >5 mm; the size that triggered an invasive intervention (when specified) ranged from 6–15 mm.

Complications of Diagnostic Procedures Stemming from Screening

The only study reporting on complications resulting from LDCT screening is the NLST. Overall, the frequency of death occurring within 2 months of a diagnostic evaluation of a detected finding was 8 per 10,000 individuals screened by LDCT, and 5 per 10,000 individuals screened by CXR. Some of the deaths after a diagnostic evaluation were presumably unrelated to follow-up procedures, as 1.9 and 1.5 per 10,000 occurred within 2 months when the diagnostic evaluation involved only an imaging study. Deaths most clearly related to follow-up procedures were those occurring within 2 months when the most recent procedure was a bronchoscopy or needle biopsy (3.4 per 10,000 screened by LDCT and 2.2 per 10,000 screened by CXR). Approximately one third of the deaths occurred within 2 months of a surgical procedure in both arms, and the vast majority of these were in the patients with cancer, suggesting perhaps that the surgical procedures in

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those with cancer were more extensive (i.e. resection rather than biopsy; such details were not reported). The 60-day perioperative mortality for patients with lung cancer who underwent a surgical procedure was 1% for the LDCT arm and .2% for the CXR arm.

Overall, the frequency of a major complication occurring during a diagnostic evaluation of a detected finding was 33 per 10,000 individuals screened by LDCT, and 10 per 10,000 individuals screened by CXR. The rate of (presumably unrelated) complications following imaging alone was similar and low (1.1 and 1.5 per 10,000 screened); the complication rate after a bronchoscopy or needle biopsy was also low (1.5 and 0.7 per 10,000 for LDCT and CXR, respectively). The vast majority of major complications occurred after surgical procedures, and in those patients with lung cancer. The rate of major complications in those patients with lung cancer who underwent surgery was 14%.

Focusing only on those patients who had nodules detected by LDCT that turned out to be benign, death occurred within 60 days among 0.06%, and major complications occurred among 0.36%. About half of the deaths occurred after imaging alone, whereas the majority of major complications occurred after a surgical procedure (details unknown). Calculating these numbers for an entire screened population, the risk of death or major complications following diagnostic events (including imaging) for what turns out to be a benign nodule is 4.1 and 4.5 per 10,000. This is higher than in the CXR arm (1.1 and 1.5 per 10,000).

Overdiagnosis

Overdiagnosis refers to histologically confirmed lung cancers identified through screening that would not impact the patient's lifetime if left untreated. This includes patients who are destined to die of another cause (e.g. a co-morbidity or an unexpected event).[44] Earlier studies suggested that CXR screening may have an overdiagnosis rate of roughly 25%.[45, 46] The overdiagnosis rate for LDCT screening cannot yet be estimated; NLST data shows a persistent gap of about 120 excess lung cancers in the LDCT vs. the CXR arm, but further follow-up is needed.

Radiation Exposure

The effective dose of radiation of LDCT is estimated to be 1.5 mSv per examination, but there is substantial variation in actual clinical practice. However, diagnostic chest CT (~8 mSv)[47] or PET-CT (~14 mSv)[47–49] to further investigate detected lesions rapidly increases the exposure and accounts for most of the radiation exposure in screening studies. We estimate that NLST participants received ~8 mSv per participant over the three years, including both screening and diagnostic examinations (averaged over the entire screened population). Estimates of harms from such radiation come from several official bodies and commissioned studies,[50, 51] based on dose extrapolations from atomic bombings and also many studies of medical imaging.[52, 53] Using the NLST data these models predict approximately one cancer death caused by radiation from imaging per 2500 subjects screened. Therefore, the benefit in preventing lung cancer deaths in NLST is considerably greater than the radiation risk – which furthermore only becomes manifest 10–20 years later. However, for younger individuals or those with lower risk of developing lung cancer the tradeoff would be less favorable. Preliminary modeling studies suggest that potential risks may vastly outweigh benefits in non-smokers or those ≤ age 42.[54] Further study, including the effects of ongoing annual LDCT beyond three successive years, is needed.

Impact on Quality of Life

The impact of LDCT screening on quality of life (QOL) is unclear. We found only one study, in which 88–99% of 351 subjects reported no discomfort, but 46% reported psychological distress while awaiting results.[55] One can speculate about QOL benefits due to lower morbidity from advanced lung cancer, but there are also potential detriments due to anxiety, costs, and harms from the evaluation of both false positive scans and overdiagnosed cancers.

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International Journal of Pharmaceutical Research and Applications
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