Lung Cancer Screening Overdiagnosis: 
Reports of Overdiagnosis in Screening for Lung Cancer Are Grossly Exaggerated

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The National Lung Cancer Screening Trial (NLST) demonstrated a mortality reduction benefit associated with low-dose computed tomography (LDCT) screening for lung cancer. There has been considerable debate regarding the benefits and harms of LDCT lung cancer screening, including the challenges related to its practical implementation. One of the controversies regards overdiagnosis, which conceptually denotes diagnosing a cancer that, either because of its indolent, low-aggressiveness biologic behavior or because of limited life expectancy, is unlikely to result in significant morbidity during the patient’s remainder lifetime. In theory, diagnosing and treating these cancers offer no measurable benefit while incurring costs and risks. Therefore, if a screening test detects a substantial number of overdiagnosed cancers, it is less likely to be effective. It has been argued that LDCT screening for lung cancer results in an unacceptably high rate of overdiagnosis. This article aims to defend the opposite stance. Overdiagnosis does exist and to a certain extent is inherent to any cancer-screening test. Nonetheless, the concept is less dualistic and more nuanced than it has been suggested. Furthermore, the average estimates of overdiagnosis in LDCT lung cancer screening based on the totality of published data are likely much lower than the highest published estimates, if a careful definition of a positive screening test reflecting our current understanding of lung cancer biology is utilized. This article presents evidence on why reports of overdiagnosis in lung cancer screening have been exaggerated.

Key Words: Lung cancer CT screening; randomized trials; overdiagnosis; cost effectiveness; risks; harms.

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WHY LUNG CANCER SCREENING MATTERS? THE CLINICAL CHALLENGE

Lung cancer is the leading cause of cancer-related deaths worldwide. In the United States, it causes more deaths than the next three most common cancers combined (colon, breast, and pancreatic). It kills nearly 160,000 Americans yearly, comprising 13% of all cancer diagnosis but 27% of all cancer deaths, denoting a substantially higher lethality than most other cancers (1–4). Among American women, although breast cancer affects circa 233,000 and lung cancer 108,000 annually, lung cancer kills 72,000 versus breast cancer 40,000 (1). Cigarette smoking is the single most important causative factor in lung cancer, with approximately 90% of lung cancers attributable to smoking and an average 20-fold increase in relative risk of lung cancer in smokers versus never smokers. [The lifetime risk of developing lung cancer ranges from 0.2–1.4% in never smokers to 18.5–24.4% in “heavy” smokers (1,3,5,6)]. There are estimated 1.1 billion active smokers in the world, and about 50% of them will die from the health consequences of their smoking habit. The cumulative risk of developing lung cancer in former smokers markedly decreases over time but never reaches that of a lifetime nonsmoker (5,6).

Once diagnosed, lung cancer requires multimodality therapy that is complex, potentially morbid, and very expensive. The National Institutes of Health estimate that direct costs related to lung cancer treatment reached over $12 billion and indirect costs related to lost productivity and years of life reached over $36 billion, making it the costliest cancer to society (7). Nonetheless, in spite of all the advances in surgery, radiation therapy, and chemotherapy, the overall 5-year survival rate of lung cancer patients remains an average dismal 16.8% in the United States (<10% in the United Kingdom), in comparison to 89% for breast, 91% for melanoma, and 65% for colon and rectum. More importantly, the survival likelihood drops precipitously once the neoplasm has spread to regional lymph nodes or distant sites (eg, metastasized). Local lung cancer carries a 5-year survival of 54%, whereas it drops to 26% once it has spread to regional lymph nodes or neighboring tissues and to a dismal 4% once it has metastasized to distant sites (1,3,4,6).

These numbers demonstrate that lung cancer is a major global health care problem accounting for substantial suffering and premature deaths. To make a meaningful impact in reducing lung cancer deaths, society has to aim primarily at prevention, not just at treating manifested lung cancers. A concerted effort must involve both primary and secondary prevention strategies.
Primary prevention relies on smoking control and cessation, and several countries have introduced smoking bans, educational programs, and heavy taxation, with varied degree of success. Secondary prevention involves detection of cancers in the preclinical phase, also called screening. Given that the statistics show that the chances of cure are only significant when lung cancer is detected at an early stage (eg, has not spread regionally or to distant sites), there is a strong conceptual argument that screening for lung cancer may allow a greater detection of early-stage cancers, and this may lead to increased long-term survival and increased rates of cure.

**LUNG CANCER IS A HETEROGENEOUS DISEASE: INSIGHTS FROM CANCER BIOLOGY**

When lung cancer is discussed, especially in the lay press, there is a common misconception that it is a single, well-defined entity. This could not be farther from the truth. Cancer comprises a large heterogeneous group of diseases, which are related by the presence of uncontrolled, progressive growth and spread of abnormal cells that if unchecked for a long enough period of time will ultimately lead to morbidity and may lead to death. It is known that for a cell to become cancerous, it must acquire several changes in its genome and proteome. Rarely will a single mutation suffice. Several genes that control cell cycle regulation, cell-to-cell and cell-to-matrix interactions, and angiogenesis must be altered for a single cell to become cancerous, denoting a multistep route for cancer induction, which is different for each cancer. Furthermore, the cancerous cell must evade immune surveillance to be allowed to proliferate. These interactions are complex and happen over the course of years or decades, amidst continued exposure to environmental and internal carcinogenic factors. The myriad of possible pathways and different types of cells involved accounts for the range of variation of biologic behavior, from very indolent cancers that are highly unlikely to cause clinically significant harm in one end of the spectrum to aggressive cancers that are typically lethal within months on the other, with an entire spectrum of cancers lying in between. There is no binary distinction of “indolent” versus “aggressive” cancers as those are just opposite ends of a continuum spectrum of biologic aggressiveness.

Therefore, a more accurate picture emerges of lung cancer as a set of heterogeneous but related diseases that generally develop nonlinearly over a long span of time, with wide variation of biologic resilience and aggressiveness. These concepts will be crucial when discussing overdiagnosis (8,9).

**LUNG CANCER SCREENING TRIALS AND RESULTS: BENEFITS OF LUNG CANCER SCREENING**

Given that lung cancer is a major global public health problem, there have been multiple research efforts to prove whether screening for lung cancer is effective. Several multi-institutional trials have taken place in the United States and Europe in the past two decades, involving chest radiography, sputum samples, and low-dose computed tomography (LDCT). The largest trial ever performed was the National Lung Screening Trial in the United States. In the NLST, 53,454 high-risk patients (based on age 55–74 years and smoking history >30 pack-years) were randomized to either LDCT or radiography and screened annually between 2002 and 2009. The trial demonstrated a 20.0% relative reduction in mortality from lung cancer in the LDCT arm, statistically significant (relative risk [RR], 0.80; 95% confidence interval [CI], 0.70–0.92, \(P = .002\)), after 6.5 years of follow-up. The absolute risk reduction was approximately 0.4% (17 of 1000 deaths in the chest x-ray arm vs. 13 of 1000 deaths in the LDCT arm). For each lung cancer death avoided, 320 individuals underwent LDCT screening, which compares favorably with the number needed to screen of diagnostic mammography in the age range of 50–59 years, which is 1339 (ie, number of women who need to undergo screening to avert one breast cancer–related death). Using the NLST definition of a positive screen, the sensitivity of LDCT was 93.1% and the specificity of LDCT was 76.5% (10–12).

Among those screened with LDCT after two rounds of screening, 227 of 24,102 (cumulative incidence of 0.94%) had confirmed lung cancers, of which 211 (93%) were detected by LDCT, whereas in the control x-ray arm, 122 of 23,346 (cumulative incidence of 0.52%) had confirmed lung cancers, of which 78 (64%) were detected by chest x-ray. The number of false positives, defined as a positive screening study in which further confirmatory tests fail to demonstrate the presence of lung cancer (ie, the finding that prompted the screening study to be called positive was found not to be a lung cancer), was high, varying between 95% and 98% for the LDCT arm. Because of the large number of false positives, the positive predictive value of a positive screening study is low, varying between 5.2% and 6.7%. The first two incidence screenings of the NLST (round T1 and T2) demonstrated a stage shift in comparison to the radiography arm, as most LDCT detected cancers were stage IA (47.5%), whereas most radiography detected cancers were stage III or IV (59.1%). This stage shift is the most likely reason the trial was able to demonstrate diminished lung cancer–specific mortality in the LDCT arm (13,14).

Other trials that tested the efficacy of chest radiography screening alone have failed to demonstrate a survival benefit in the screened arm, such as the National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian trial (RR, 0.98; 95% CI, 0.96–1.01) (15,16). The International Early Lung Cancer Action Project (ELCAP) trial results suggest a similar stage shift as demonstrated by the National Lung Screening Trial (NSLT), with 85%–92% of LDCT screen detected cancers found not to be associated with metastatic disease, and hence potentially curable. Smaller European trials have not replicated the NSLT results but were not sufficiently statistically powered. Several European trials are currently underway, the largest of which being the...
NELSON trial in the Netherlands and should report final results in the next few years (15,17–19).

HARMS AND LIMITATIONS OF LUNG CANCER SCREENING

The NSLT results are extraordinary because of the controlled randomized nature and the statistical power of the study, allowing it to prove a mortality benefit where other trials failed. For example, screening for breast cancer with mammography has been performed much longer and at a much larger scale worldwide; yet, no such comparable high-quality data exist to evaluate the benefits and harms of mammographic screening, which is estimated to improve disease-specific mortality by 10%–15% but at a probably higher overdiagnosis/overtreatment rate (20–22). The Cochrane collaboration graded the NLST evidence quality higher overdiagnosis/overtreatment rate(20–22).T h e disease-specific mortality by 10%–15% but at a probably higher overdiagnosis/overtreatment rate (20–22). The Cochrane collaboration graded the NLST evidence quality as high (15). The United State Preventive Services Task Force (USPSTF) issued a recommendation in favor of lung cancer screening (“The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.”) and assigned it a grade B, indicating “There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial” (23,24).

Notwithstanding, as it is often the case, the devil is in the details. First, as impressive as a 20% mortality reduction in the LDCT screened arm is, it still means that the most patients diagnosed with lung cancer will die from lung cancer. Early detection will save lives, but still a minority of them. It must nevertheless be emphasized that the mortality benefit of lung cancer screening could be considerably >20% as the NLST trial was designed to evaluate whether a significant reduction of mortality of lung cancer could be attained, not to define optimal benefit. The trial was terminated when a 20.3% reduction was demonstrated because it would be unethical to proceed with the trial if a mortality reduction of such magnitude was statistically demonstrated in the LDCT arm. The proven effectiveness of LDCT would support offering LDCT to the control arm and to the general population (25).

Second, because LDCT screening has high sensitivity but low specificity, the positive predictive value of a positive study is very low (5.2%), whereas the negative predictive value (NPV) is very high (99.9%). This introduces a large number of false positives, which have to be dealt with, and is probably the most important problem to be addressed when implementing an LDCT screening program and a crucial factor impacting cost-effectiveness. To prove that a positive screening study is a false positive, it is necessary to establish at least 2 years of stability (for small solid nodules) or obtain pathologic confirmation of the diagnosis via an invasive procedure, either a biopsy or a surgical resection. The very high NPV means that false negatives are not a significant problem of LDCT screening.

Third, there is the conceptually related risk of overdiagnosis, which will be addressed in detail further in this article. Finally, there is a risk associated with radiation exposure because of the LDCT, which is outside the scope of this article. Suffice it to state that at the current average LDCT dose of 1–2 mSv, which is less than the annual background exposure, the radiation exposure effects are negligible in comparison to the other risks associated with screening, with estimated additional risk of fatal radiation-induced cancer in the same range as mammography, between 1 in 10,000 and 1 in 100,000 (25–28).

HARMS: FALSE POSITIVES

In the NLST, approximately 24% of LDCT studies were considered positive, but the vast majority (over 90%) of these were deemed false positives. Having a positive scan triggered additional tests, such as short-term repeat diagnostic CT, positron emission tomography/CT, biopsy (percutaneous, bronchoscopic, or surgical), or surgical resection. All these tests carry some risks, including emotional stress, morbidity from interventional procedures, and even mortality from complications. Furthermore, there is a substantial associated cost, which ultimately drives the cost-effectiveness of screening downward.

Total incidence of complications in the NLST was 1.4% in the LDCT arm and resulted from additional evaluation of suspicious findings. Of the patients with a lung nodule that eventually was deemed benign (false positives), 1.2% underwent an invasive procedure such as a needle biopsy or bronchoscopy, whereas 0.7% of false positives underwent a surgical procedure (thoracoscopy, mediastinoscopy, or thoracotomy). Major complications were rare (0.06%) in the false-positive group. In contrast, major complications occurred in 11.2% of screen-detected true-positive cancers, most related to surgical procedures (26–28).

Even when the additional work-up of false positives only entails obtaining more frequent chest CTs without any invasive procedure, as is often the case for small pulmonary nodules, it can still potentially lead to psychological impact. However, published data suggest this may not be the case. An analysis of the NLST data assessed short-term (1 month) and long-term (6 months) anxiety and health-related quality of life in patients receiving a false-positive result, significant incidental results, or a negative screen. There were no differences in anxiety or health-related quality of life at 1 or 6 months on false-positive or significant incidental finding screens relative to the negative screens of statistical significance. For example, at 6 months, the anxiety score (mean and standard deviation) in the LDCT arm was 32.76 (12.04)
in the negative group, 33.92 (12.77) in the false-positive group, and 33.19 (12.41) in the significant incidental findings group (29).

LIMITATIONS: COST-EFFECTIVENESS AND FINANCIAL COSTS

A detailed analysis of economic implications of LDCT screening programs and cost-effectiveness of such programs is beyond the scope of this article. A brief summary will be presented. The current models vary widely in their results because of different assumptions regarding definition of the screened population, definition of a positive scan, price of the scans, algorithm to manage positive scans, cost of work-up of positive results, and adherence rate. It cannot be overemphasized that the cost-effectiveness threshold is arbitrary—it depends on what society is willing to pay for each additional quality-adjusted life year (QALY), which measures not only how much time a specific medical intervention adds to a patient's life but also factors in quality of life. For example, an intervention that adds years of life to a patient who is otherwise bedridden and unconscious in the intensive care unit would score very low using a QALY metric.

Before the NLST, a study modeled on the results of the ELCAP trial suggested that the incremental cost-effectiveness ratio of a single baseline LDCT scan was approximately $2500 per year of life saved; however, that figure was very sensitive to the overdiagnosis rate, varying from $2500 at an overdiagnosis rate of 5% up to $>50,000 at an overdiagnosis rate of 50% (30). Another model using ELCAP data suggested a cost of $19,000 per life year saved under optimal conditions in a high-risk cohort of individuals aged between 60 and 74 years (31).

More recent analyses have arrived at different results. It has been proposed that offering LDCT lung cancer screening to the entire high-risk population in the United States (using NLST criteria) would cost between $2.2 and $3.3 billion a year (adherence rate of 50% or 75%, respectively), but the cost would climb to $19.1 billion if all individuals in the NLST age range (55–74 years) were included, irrespective of smoking history, dramatically showcasing the need for strict inclusion criteria. Given the estimate that 320 patients need to be screened to avoid one death, a national US screening program would potentially save 18,000 lives a year at an average cost of $170,500 per life saved. Multiple studies using observational data to estimate the cost-effectiveness of LDCT screening and employing different assumptions concluded that the cost per QALY gained ranged from $4000 to $250,000, a wide dispersion indicating the sensitivity of the proposed models to different basic premises (32). It is widely accepted that the threshold of cost-effectiveness is $50,000 per QALY gained; consequently, a definitive conclusion about cost-effectiveness of LDCT screening will require additional assessment of data from the NLST and other trials (27,28,32,33).

Nonetheless, it is encouraging to note that adding smoking cessation can not only be highly beneficial to the population screened but also would improve cost-effectiveness of LDCT screening. A study simulating 15 years of screening in a hypothetical high-risk cohort of adults aged between 50 and 64 years with >30 pack-years of smoking history yielded 20%–45% improvement in cost-effectiveness when smoking cessation initiatives were added, with the cost–utility ratio ranging from $16,198 to $21,185 per QALY gained, more cost effective than breast cancer screening with mammography ($24,100 per QALY gained) and colon cancer screening with colonoscopy ($127,700 per QALY gained) (27,34).

HARMs: OVERDIAGNOSIS AND OVERTREATMENT

Overdiagnosis refers to the ability to detect a neoplasm that would neither result in clinical symptoms nor lead to death during the patient’s remainder lifetime. This concept is distinct from false positive as an overdiagnosed cancer is a confirmed cancer from a pathologic standpoint (eg, confirmed by biopsy), not a benign lesion. However, because it lacks the capacity to grow and spread quickly, an overdiagnosed cancer presents such an indolent biologic behavior that it will remain subclinical for the remainder of the patient’s life. This is particularly relevant in elderly patients. For example, a low-grade adenocarcinoma in situ may never develop into an invasive carcinoma and may grow so slowly that it will never cause symptoms. If this cancer is detected by screening, it is an overdiagnosed cancer. Another example would be an aggressive cancer, such as a small-cell carcinoma, that is screen detected in a patient who has advanced dementia, severe congestive heart failure, and coronary artery disease, whose life expectancy is <6 months. In this latter scenario, even an aggressive cancer is considered an overdiagnosed cancer because of the patient’s very limited life expectancy due to comorbidities.

There has been considerable debate regarding overdiagnosis as it applies to population screening for cancers, not only in the realm of LDCT for lung cancer screening. Earlier lung cancer screening strategies were tested on randomized population trials using annual chest radiography and sputum samples versus no screening. These studies were interpreted as having failed to demonstrate effectiveness (eg, no mortality reduction) in the screened arm, although excess lung cancers were detected, because these were attributed to overdiagnosis (35), which was estimated as ≥25% of chest x-ray–detected cancers (36). Patz el al. (37) have reported their analysis of overdiagnosis using NLST data. Their estimate of the probability of any lung cancer detected by screening LDCT being an overdiagnosed cancer was 18.5% (95% CI, 5.4%–30.6%), with this number increasing to 78.9% in the case of “bronchioalveolar lung cancer” (BAC; please note that this terminology is no longer accepted, as the term BAC has been
replaced by adenocarcinoma–spectrum lesion in the new International Association for the Study of Lung Cancer classification of adenocarcinomas, which reflects better understanding of the pathology of these malignancies, but will be used throughout this article for consistency with the published references). The authors conclude that 320 participants needed to be screened to prevent one death from lung cancer, but this would also generate 1.38 overdiagnosed cancers. Other estimates arising from the differential incidence of lung cancer in the two arms of the NLST suggest an overdiagnosis rate of 10%–15%, which is derived from the 13% greater incidence of lung cancer in the LDCT arm, although this is likely overestimated because of the potential lead time bias associated with the LDCT arm (32).

In a response to Patz et al., Couraud et al. (38) argued that an accurate assessment of overdiagnosis must take into account lead time and length time biases and therefore would require a longer follow-up period extending up to 9–10 years, versus the 7 years used by Patz et al. They excluded BAC from their analysis arguing that these are mostly small ground-glass opacities that should not be considered positive screens, if a volumedoubling time approach is used (such as in the NELSON trial). They also argued that if only non-BAC lung cancers are included, the fact that the number of non-BAC lung cancers in the chest radiography (CXR) arm eventually became higher than in the LDCT arm suggests that cancers not previously diagnosed by CXR due to lead time or length time biases ultimately became symptomatic. Their estimate of overdiagnosis of non-BAC lung cancers is a much lower 5.3%. Gelbman and Libby (38) argued that available NLST data do not allow distinction between beneficial lead time (eg, early detection of a cancer that would ultimately prove harmful) and overdiagnosis (eg, early detection of a cancer that would never become clinically relevant). They also argued that Patz et al. own convolution-type model attempted to remove the lead time effect and arrived at much lower estimates of 9% of excess lung cancers that would be ultimately discovered with lifetime follow-up (for all lung cancers), versus only 1.2% if BAC is excluded, numbers that more likely reflect the true overdiagnosis rate.

The truth is that it is not feasible to quantify overdiagnosis accurately because the vast majority of lung cancer patients with access to medical care in the developed world will be offered treatment; therefore, there is no ethical way to determine the natural history of untreated lung cancers, which would provide an accurate rate of overdiagnosis. Furthermore, the concept of overdiagnosis is complex as it can only be defined in retrospect, and it is not a simple binary construct. As detailed previously, cancers are a heterogeneous group of diseases. There is a continuum spectrum of aggressiveness from premalignant to indolent malignant to aggressive malignant lesions. Even state of the art pathology using the entire armamentarium of molecular genomics and proteomics oftentimes is unable to draw the line between indolent and aggressive cancers. Furthermore, biologic behavior is nonlinear. Cancers can spontaneously regress, remain in a subclinical localized state for a very long time, or evolve to aggressive lesions with potential to spread locally and to distant sites. The latter may lead to death if the patient's life expectancy is long enough—even an aggressive cancer can be an overdiagnosis cancer in patients with very limited life expectancy because of comorbidities. Different cancers have a very different potential for overdiagnosis because of differences in average biologic behavior, with thyroid and prostate malignancies having much higher rates than lung or pancreatic malignancies, given a higher proportion of neoplasms with indolent biologic behavior in the former group (9,39,40).

It has been suggested that the excess-incidence approach (eg, the excess number of cancers detected in the screening arm vs. the control arm) is preferable to a lead time approach to estimate overdiagnosis in cancer screening (41) and that the two approaches yield quite different results, with the excess-incidence approach being more accurate. Nonetheless, in a testament to the degree of controversy in the scientific literature, it has been argued otherwise (42), that the lead time models can provide a better estimate of overdiagnosis as long as there exist good quality data on disease incidence with and without screening, on risk of progression from latent to clinical disease and on the sensitivity of the screening test. Overdiagnosis is such an elusive concept that there is not even consensus on how to measure it; hence, any estimate of overdiagnosis must be taken with a grain of salt and with careful attention to methodology.

In another rebuttal to the article by Patz et al., Detterbeck (43) emphasizes that the retrospective estimates of overdiagnosis on LDCT lung cancer screening vary widely according to screening duration (3–5 years), follow-up duration (5–7 years vs. lifetime), and histologic type of cancer (BAC vs. non-BAC), from 2.6% to >80%, with the estimated rate of overdiagnosis decreasing as the screening duration increases. Naturally, these widely dispersed numbers are not terribly helpful for the clinician who has to make decisions prospectively for an individual patient. He contends that, nevertheless, the focus should be on the low overdiagnosis rate for non-BAC non–small-cell lung cancer, which almost always (97%–98% of the times) will require intervention to prevent cancer-related death and also on the empirical fact that most BAC can be managed very conservatively to minimize harms from screening.

**CONCLUSIONS**

Faced with the breadth of conflicting data in the scientific literature regarding benefits and harms of lung cancer screening, one can identify two diametrically opposed stances. The optimist would say "LDCT lung cancer screening is highly beneficial and should be offered to every eligible individual, as it is the only effective way to save lives from lung cancer deaths." The nihilist would say "LDCT lung cancer screening is hampered by an unacceptably high rate of false positives and overdiagnosis, therefore should not be offered to the population." The truth (or at least the more rational stance) lies somewhere in between.
Lung cancer is one of the most important health problems worldwide. Any effort to reduce its morbidity and mortality is commendable. The NLST provides high-quality scientific evidence that LDCT lung cancer screening does impact outcomes by reducing lung cancer–specific mortality in the LDCT screened arm, and it does so because of a stage shift in the screen-detected cancers from likely noncurable stage III and IV cancers to potentially curable stage I and II. However, lung cancer screening is not a panacea. Although we, taxpayers, have indirectly spent millions of dollars funding trials such as the NLST and therefore shall not ignore its results, we must implement lung screening wisely. What this means is maximizing its benefits and minimizing its harms, at a sustainable cost. What follows is a prescription of what this would entail and how this might happen in the future.

It behooves on us to offer lung cancer screening only to high-risk patients using strict entry criteria as these patients are most likely to benefit from screening (44,45). These criteria should be modified and evolve with the latest scientific evidence. Aggressive smoking cessation programs should be an integral part of lung cancer screening because this strategy would not only improve its cost effectiveness but also result in the greatest health benefit (34). Furthermore, it makes no sense to screen a patient who does not have access to high-quality, comprehensive lung cancer care, which is more likely to achieve optimal outcomes with minimal morbidity and complications. Having lung cancer screening integrated with pulmonary nodule management programs is crucial to optimize outcomes and cost-effectiveness.

Better risk stratification models will be crucial to allow a reduction in the rate of false positives, which is probably a more pressing issue than overdiagnosis, in the setting of LDCT screening for lung cancer. This can be achieved via updating the definitions of a positive screen and adjusting thresholds of nodule size and growth rate to increase specificity in light of evolving evidence. Another approach is to have a more conservative algorithm regarding recommendation of invasive procedures, to minimize the risk of harm associated with detection of false positives. Finally, there is great potential to augment LDCT screening with molecular biomarkers that can substantially increase specificity without reducing sensitivity (46,47).

Finally, it is important to appraise that overdiagnosis of lung cancer is not a simple concept and that it depends on the definition of cancer, the phenotypic and genotypic characteristics of the lesion, and the patient’s overall clinical status and life expectancy. Some degree of overdiagnosis in LDCT lung cancer screening is unavoidable, and we must accept it. In a certain sense, overdiagnosis in screening is a consequence of our not knowing the future. Even if we knew the likely biologic behavior of every screen-detectable lung cancer, which we of course do not, we would still be unable to predict whether any specific cancer would lead to symptoms and death with certainty because random future events such as mutations can potentially transform an indolent lesion into an aggressive cancer, even in a short time frame.

How do we navigate this uncertainty? We cannot discern for sure the lesions that will evolve into aggressive cancers during the patient’s expected lifetime from those that will not. Nonetheless, we can devise a more nuanced strategic approach that incorporates probabilistic thinking and stratifies management based on the best available information. One proposal (48) is to reclassify indolent adenocarcinoma spectrum lesions (formerly BAC), which are currently classified as cancers, as indolent lesions of epithelial origin. This would have the benefit of shifting medical-legal notions and perceived risk to better reflect biological behavior and allow more conservative management approaches, which would focus on surveillance and reduce the likelihood that an interventional procedure would be performed, avoiding potential harm. From the perspective of LDCT screening, these lesions would no longer be classified as cancers and may not even be considered positive screens, which would reduce overdiagnosis and improve specificity simultaneously, besides improving cost effectiveness and increasing patient safety. Better non-invasive surveillance strategies coupled to risk stratification models may also allow for lesser risk of overtreatment of these indolent lesions, avoiding the potential morbidity associated with current multi-modality cancer therapy.

In conclusion, overdiagnosis in lung cancer screening certainly exists and cannot be completely eliminated, but its extent has been exaggerated. The consensus estimates vary widely but are likely not anywhere close to 18–19%, but most probably in the 2–10% range, which is substantially better than most other cancers for which there are accepted screening tools. There is evidence that the number of overdiagnosed cancers can be further reduced to less than 5% with careful exclusion of indolent lesions based on CT imaging features and growth-rate (47). More importantly, a nuanced, probabilistic approach to overdiagnosis that takes into account the variability and non-linearity of biological behavior of pre-malignant and malignant lesions will lead to better screening programs, which will offer holistic, risk-based nodule management protocols and decrease not only the rate of overdiagnosis, but also the rate of false positives, ultimately allowing successful implementation of LDCT lung cancer screening that will be maximally beneficial to society at large.

REFERENCES


