Commentary

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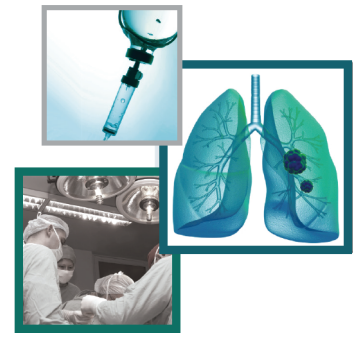
Lung Cancer Management



Lung cancer screening guidelines are clear but are they being followed?

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"We believe there should be an open discussion between physicians and high-risk patients regarding lung cancer screening with LDCT. Physicians should discuss with patients the risks and benefit to reach a shared decision making."

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Lung cancer is the second most common cause of cancer worldwide and the leading cause of cancer death in the USA [1]. The American Cancer Society (NY, USA) estimated a total of 228,150 new cases of lung cancer with 142,670 deaths from lung cancer in the USA for 2019 [1]. Smoking is the main cause of lung cancer and contributes to 80% of lung cancer deaths in women and 90% in men [2].

Lung cancer is typically diagnosed at advanced stages and carries a high mortality rate, with a 5-year survival rate of only 18% [3]. Randomized controlled trials targeted toward lung cancer screening started in the 1970s when the US National Cancer Institute (NCI; MD, USA) sponsored several clinical trials to evaluate the benefit of adding sputum cytology to annual chest radiography (CXR) [4,5]. However, none of the trials showed a reduction in lung cancer mortality (Supplementary Table 1). Decades later, the NCI initiated the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), a large randomized controlled trial that aimed to reduce disease-specific cancer mortality by evaluating the use of CXR for screening [6]. The study found that 2% of participants that had a positive radiographic findings were diagnosed with lung cancer within 12 months of the screen, 44% of whom were diagnosed with stage I disease [6]. Pertinent findings that paved the road for future guidelines included the discovery that high incidences of lung cancer were noted in active smokers or those that had quit within 15 years of randomization [6].

In the 2000s, prospective studies were created throughout the world to evaluate the role of low-dose computed tomography (LDCT) for screening. The Lung Screening Study compared LDCT and CXR as screening modalities and revealed that LDCT was twice as effective as CXR in detecting lung cancer [7]. It also showed that 48% of lung cancers detected by LDCT screening were diagnosed at stage I [7]. Inspired by the Lung Screening Study, a large scale study called the National Lung Screening Trial (NLST), which enrolled 53,456 participants, was created. Participants were randomized to LDCT or CXR at a 1:1 ratio. The study demonstrated a 20% relative reduction in mortality in patients screened with LDCT compared with CXR [8]. Results from this trial were updated in 2013 and confirmed the benefit of LDCT for lung cancer screening in specific patient populations [9]. Similar results were showcased from The Dutch–Belgian Randomized Lung Cancer Screening Trial (NELSON) which began in Europe in 2003 [10]. More than 15,000 participants were enrolled and assigned to either computer tomography (CT) screening or to the control group with no screening [10]. The study reported a 41% positive predictive value with screening and 50% of the cancers diagnosed in the screening arm were found at early stages of the disease [10]. During a 10-year follow-up, there was a 26% mortality rate reduction in men and 39% in women [10]. Updated results published in the *New England Journal of Medicine* in 2020 confirmed that lung cancer mortality was significantly lower in patients who underwent CT screening compare to those in the control arm [11].

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Based on the data strongly supporting lung cancer screening, the US Preventive Services Task Force (USPSTF; MR, USA) and the National Comprehensive Cancer Network (NCCN; PA, USA) created screening guidelines recommendations for high-risk patients in 2014. While both these guidelines focus on high-risk groups, there are some differences in the screening criteria. USPSTF recommends annual screening for lung cancer in adults aged 55–80 years who have a smoking history of 30 packs a year, are current smokers or have quit within 15 years [12]. The NCCN classifies high-risk patients as those ages 55–74 with >30 packs a year history of smoking with <15 years since quitting, smoking cessation; or >20 packs a year history of smoking and additional risk factors that increased the risk of lung cancer to >1.3% [13]. The goal of screening is to detect the disease at earlier stages which allows for curative surgical resection and an increase in overall cure rates in patients with lung cancer. Unfortunately, despite these clear recommendations and coverage of services by Medicare, Medicaid and most commercial insurances, the adherence to screening guidelines remains low.

In 2016, we conducted a study to evaluate compliance for LDCT screening in an outpatient Internal Medicine clinic [14]. Based on our observations and reports in literature, we anticipated a low baseline LDCT compliance and hypothesized that by providing an educational program, overall compliance would increase [15]. The educational program consisted of lectures provided to primary care physicians and internal medicine trainees. Following the lectures, consecutive patient visits were reviewed to assess compliance with screening. We studied the differences in LDCT adherence comparing rates of referral for screening pre-intervention and post-intervention [15]. We also assessed the differences in physicians' understanding of the screening program using paired pre-and post-tests. Screening rate at baseline was 27% and improved to 78% after intervention (odds ratio: 9.98, 95% CI: 5.87–16.4; $p < 0.0001$) [15]. Many other investigators have reported similar findings of poor adherence to screening guidelines across the USA. In 2017, one study evaluated the incidence of patients who met screening criteria over a 5-year period from 2010 to 2015 to assess the incidence of screening with LDCT in patients that met the criteria [16]. Out of the 6.8 million smokers eligible for LDCT screening in 2015, only 3.9% received it and there was no significant increase in compliance with screening from 2010 to 2015 [16]. Another study evaluated the lung cancer screening inconsistencies with the established guidelines and showed how only 4.4% of patient who met criteria for screening in 2015 received a LDCT for lung cancer screening [17].

It is known that lung cancer screening tendencies can vary across geographic distribution. For example, a study revealed how across all states, 28.1% of patients aged 55–79 years did not have access to a lung cancer screening center within a 30-min drive [18]. Urban residents are more likely than rural residents to have access to a designated LDCT screening center within 30 miles (47.5% rural vs 93.7% urban) or a 30-min drive (22.2% rural vs 83.2% urban) [18]. Based on these findings, it is not surprising that most of the patients referred for treatment of lung cancer present at late stages. In our thoracic oncology clinic, we find many incidences of missed opportunities for early diagnosis. For instance, we recently met a 68-year-old woman who presented to us with stage IV adenocarcinoma of the lung. Upon reviewing her history, we discovered that she had a history of smoking 75 packs a year in addition to a history of chronic obstructive pulmonary disease and a personal history of a prior malignancy. This patient met high-risk criteria for screening under both USPSTF and NCCN guidelines but was unaware that screening for lung cancer was available, as it was never mentioned or discussed by her primary care physician. Real life stories like this led us to investigate barriers for screening adherence and reasons for lack of referral of appropriate patients for lung cancer screening. A common barrier is physicians' lack of knowledge regarding lung cancer screening guidelines. This has been demonstrated in multiple studies. For instance, one recent article regarding screening knowledge and practices among primary care physicians (PCPs) in an academic center showed that only 47% had knowledge of three or more of the criteria for screening and 24% did not know any component of the guidelines [19]. Few PCPs reported ordering lung cancer screening: chest x-ray (21%), LDCT (12%) and sputum cytology (3%) [19]. Another study assessed the tendencies for family medicine physicians to refer their patients to lung cancer screening in 2015 after the screening guidelines were established. Less than half knew that organizations such as the USPSTF or NCCN recommended screening and an average of 48% incorrectly recommended screening with CXR or LDCT [20].

To understand the practices at a national level, a survey of PCPs was performed in 2019 to assess the perception and practices of LDCT lung cancer screening, where 75% agreed that the benefits of LDCT screening outweigh the risks [21]. However, only 50% believed there is enough evidence to suggest that screening reduces mortality (50%) [21]. Common barriers reported in that study were prior authorization requirements (57%), lack of insurance coverage (53%) and coverage denials (31%) [20]. Oftentimes, physicians are unaware that LDCT for screening are covered by Medicare and Medicaid services [20]. However, contrary to general belief, the comprehensive lung cancer

screening registry is considered a metric for reimbursement from Medicare and Medicaid services [22]. Another factor that has been brought up as a reason for low referrals to LDCT is patients' competing health priorities.

Major socio-economic and geographic differences in referral for LDCT suggest the role of multiple other factors in low lung cancer screening rates across the US [18]. Concerns about risks to patients because of unnecessary invasive procedures, radiation exposure from multiple LDCT procedures and emotional stress resulting from abnormal test results of unknown significance are some concerns that have been raised by both providers and patients. While these are valid issues, available the literature does not support the level of concern. In the NLST, 24.2% of LDCT scans and 6.9% of CXR had abnormal results from which 96% were false positives [9]. However, only 11% of the positive results led to an invasive study. Most positive studies are resolved with imaging and proven to be false-positive exams [9]. To overcome some concerns and aim to achieve similar results from the NLST, the USPSTF recommends limiting referrals to patients at high risk, using LDCT and standardizing the imaging findings to avoid false positives and minimize the need for unnecessary invasive procedures [12]. Radiation exposure of LDCT is approximately five-times less than radiation doses of one diagnostic chest CT [23]. A study specifically evaluated the risk of radiation exposure and subsequent development of secondary malignancies in high-risk patients undergoing LDCT. After 10 years of screening, they found an additional risk of only 0.05% for major cancers [24]. Considering the high mortality from lung cancer and very minimal risk for major cancer, LDCT is acceptable given the significant reduction in mortality associated with screening.

Future perspective

Besides highlighting the common barriers to screening, an important step in the discussion is to create possible solutions that can be created to strengthen the adherence for lung cancer screening. We believe there should be an open discussion between physicians and high-risk patients regarding lung cancer screening with LDCT. Physicians should discuss with patients the risks and benefit to reach a shared decision making.

Since PCPs play a critical role in increasing the rates of lung cancer screening, methods to improve adherence include educating them about the literature available to support lung cancer screening and the criteria that place patients at high risk for lung cancer. Creating an outreach approach for a lecture series education can help to increase adherence to lung cancer screening via educational online videos or real-life PowerPoint lectures discussing the guidelines for screening and the low tendencies for referral. It is also important to make physicians aware of the access to screening programs so that they know where to refer their patients after undergoing screenings. Additionally, distributing pamphlets to primary care and pulmonary practices highlighting screening guidelines and steps the following LDCT would be beneficial. Another potential option is to create a screening process through a survey in order to identify eligible patients who meet criteria for screening prior to their visit. This would facilitate physicians to target those that meet criteria for screening referral. At last, incorporating lung cancer screening to medical records that can flag high-risk patients and set a reminder to providers to discuss potential for screening.

Equally of importance is creating awareness for patients. Patients should be aware of the guidelines to support lung cancer screening and the characteristics required to be eligible. A way of targeting patients is creating billboards in different languages to bring awareness to patients and provide brochures for patients in the lobby or waiting rooms of primary care practices to encourage them to start the conversation. This can be used as a tool for patients to inquire about lung cancer screening and start a discussion with their primary care providers. Motivated patients can help ease the gap and increase PCPs tendencies for screening referrals.

The conversations with patients should not only rely on LDCT for screening, since smoking cessation remains a powerful intervention to decrease the risk for lung cancer. We believe that smoking cessation should be incorporated into lung cancer screening programs, as it has been established that tobacco cessation alone has more impact in reducing mortality than screening. Lung cancer screening techniques can be amplified and more cost effective when combined with tobacco cessation.

With an increase in knowledge about lung cancer screening among providers, improved radiological techniques and standardization of reporting, we expect adherence to LDCT to increase over the next few years. As ongoing efforts for tobacco cessation continue, the population of smokers and amount of cigarette smoking is expected to continue to decrease. If these trends continue, there will be an overall decrease in the incidence of tobacco-related lung cancer and progressively fewer patients diagnosed with advanced lung cancer.

Currently, improvised technologies and noninvasive and minimally invasive biomarker testing that could complement LDCT and improve diagnostic accuracy are being studied in clinical trials [25]. Circulating biomarkers is

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one such intervention which is currently being tested [26]. There are ongoing Phase III studies assessing the value of this assay in detecting preclinical and early-stage disease.

Conclusion

LDCT saves lives in patients who adhere to screening guidelines. It is important to educate physicians and patients about the benefit of LDCT while continuing to strengthen diagnostic accuracy by improvising and standardizing radiological techniques and interpretations as well as developing novel biomarkers that can complement LDCT in accurately diagnosing preclinical and early-stage lung cancer. This should occur in tandem with aggressive smoking and vaping interventions in order to significantly impact mortality from lung cancer.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/lmt-2020-0015

Financial & competing interests disclosure

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