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Improved False-Positive Rates and the Overestimation of Unintended Harm from Lung Cancer Screening

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Abstract

Background Concern over high false-positive rates and the potential for unintended harm to patients is a critical component of the lack of widespread adoption of lung cancer screening.

Methods An institutional database was used to identify patients who underwent lung cancer screening between 2/2015 and 2/2018 at Rush University Medical Center and Rush Oak Park Hospital. Reads were executed by dedicated thoracic radiologists and communicated using the Lung Imaging Reporting and Data System (Lung-RADS V.1).

Results Six hundred and four patients were screened over the study period. We identified 21 primary lung cancers and 8 incidental cancers. We identified a false-positive rate of 17.5%. Only 9 patients underwent further investigative workup for benign disease (5.3%); however, only 4 (2.9%) of those patients were found to have inflammatory or infectious lesions, which are common mimickers of lung cancer. Excluding Lung-RADS category 3 for the purpose of quantifying risk of unintended harm from unnecessary procedures, we found a 6.9% false-positive rate, while diagnosing 25% of all Lung-RADS category 4 patients with primary lung cancer.

Conclusion False-positive rates in lung cancer screening programs continue to decline with improved radiologic expertise. Additionally, false-positive reporting overestimates the risk of unintended harm from further investigative procedures as only a percentage of positive findings are generally considered for tissue diagnosis (i.e., Lung-RADS category 4).

Keywords Lung cancer · Lung cancer screening · Lung-RADS · Lung nodule

Abbreviations

LCS	Lung cancer screening
LDCT	Low-dose computed tomography
NLST	National Lung Screening Trial
Lung-RADS	Lung Imaging Reporting and Data System
USPSTF	United Stages Preventative Services Task Force
VA	Veterans Administration
VATS	Video-assisted thoracoscopic surgery
NCCN	National comprehensive care network
CRT	Chemotherapy and radiation treatment
NND	Number needed to diagnose

Introduction

In 2011, the National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality, and a 6.7% reduction in all-cause mortality, by screening patients at high risk of lung cancer with annual low-dose CT scans (LDCT) [1]. Between 2013 and 2015, the U.S. Preventative Services Task Force (USPSTF) and the Center for Medicare Services approved recommendations for lung cancer screening, allowing access to patients at no cost. While lung cancer screening (LCS) is threefold to fivefold more efficient than other well-established cancer screening modalities [2], including breast and colon, the number of at-risk patients

This work has not been presented at any prior meeting.

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who have been screened is profoundly few. In 2015, according to the National Health Interview Survey, only 260,000 of 6.8 million eligible patients received lung cancer screening (3.8%) [3]. In addition to lack of patient and clinical awareness, central amongst the reasons for this is the perceived high false-positive rate, associated psychological stress, and potential for physical harm from unnecessary procedures [4]. In multiple published reports, more than half of surveyed patients and practitioners cite concerns over false-positive results as a barrier to adoption [5–7].

Despite the impact of major advances in radiological evaluation and reporting (Lung-RADS), one reason this concern persists is the published results of the Veterans Health Administration's lung cancer screening project. Although one of the largest post-NLST reports, this project was only designed to assess the feasibility of implementing lung cancer screening at the VA. With obsolete data reporting (i.e., Fleischner society guidelines), and no requirement for thoracic-trained radiologists, the authors reported a false-positive rate of 45% [8]. This garnered the attention of the media and the medical community, raising concerns over high false-positive rates, and casting doubt about the real world applicability of the NLST.

The LCS program at Rush University Medical Center was established in 2011 and is an American College of Radiology designated lung cancer screening center. It is supported by 2 dedicated lung screening nurses as well as 2 thoracic radiologists, and it is overseen by thoracic surgeons with expertise in minimally invasive techniques. In this review, we aim to underscore the applicability of the NLST to a real-world clinical practice and to illustrate the low rate, and marginal impact, of unintended harm stemming from false-positive findings in a modern lung cancer screening program.

Methods

Data Source and Eligibility

An institutional database was used to identify patients who underwent LCS between 2/2015 and 2/2018 at Rush University Medical Center and Rush Oak Park Hospital. Screening eligibility was determined by age (≥55 years) and smoking history (≥30 pack/years). Patients were asymptomatic and underwent a documented shared decision making visit. Duration of screening was determined by reimbursement criteria; 77 years of age for those with Medicare and 80 years of age for private insured patients in accordance with USPSTF guidelines. A pack-year was defined the number of packs of cigarettes smoker per day multiplied by the number of years the person has smoked. If not actively smoking, all patients must have quit no more than 15 years prior to initial screen to be eligible. Patients enrolled were offered smoking cessation counselling. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This project was approved by the Rush University Institutional Review Board (18013102-IRB01) and waived the requirement for individual consent.

Technique

Low dose CT scans were performed according to the guidelines set forth by the American College of Radiology and the American Association of Physicists in Medicine. Reads were executed by dedicated thoracic radiologists and communicated using the Lung Imaging Reporting and Data System (Lung-RADS V.1). A positive scan was defined as a Lung-RADS category 3 or 4 lung nodule, and a negative scan includes category 1 and 2. Management recommendations for lung nodules were made in accordance with Lung-RADS guidelines. Lung nodules with Lung-RADS score 1–3 were followed with serial LDCTs (12 months for category 1 and 2, and 6 months for category 3), and multidisciplinary review was required for any category 4 lesion or at the discretion of the interpreting radiologist or treating physician. Results and patient outcomes were reported to the Centers for Medicare and Medicaid Services approved national registry maintained by the American College of Radiology.

Variables and Outcomes

In addition to patient demographics, radiology, pathology, and operative reports were collected from the electronic medical record. Histologic classification of tumors was determined by a board certified pathologist. All lung resections were performed by board-certified cardiothoracic surgeons.

Results

Patient Characteristics

In total, 604 patients who met USPSTF eligibility criteria for lung cancer screening underwent low dose CT scan between February 2015 and February 2018. This included 299 females (49.5%) and 305 males (50.5%). The median patient age was 65 years at first scan. In total, 331 patients (54%) were active smokers and the remaining 273 (46%) were former smokers who had quit within 15 years of the initial scan. Our screening population included 58% Caucasians, 35%

African Americans, 5.8% unknown, and 0.8% other. The demographic features are summarized in Table 1.

Results of Screening

In our 604 patient cohort, we identified 21 primary lung cancers (3.5%) over the study period, with 68% diagnosed on the initial CT scan. The average duration from screen detected finding to diagnosis was 27 days. The number needed to screen in our series was 29, meaning that only 29 at-risk patients needed to be screened to make one diagnosis of primary lung cancer. Of the total number of low-dose CT chest screening studies ($n=842$), 169 (28%) were classified as positive, defined as either category 3 or 4 Lung-RADS lesion. Of the 842 total screens performed, 148 were positive screenings which did not lead to a diagnosis of lung cancer, giving an overall false-positive rate of 17.5% (Table 2).

However, the rate of intervention for patients with a false-positive result was 5.3% ($n=9$). Interventions included bronchoscopy, thoracoscopy, and mediastinoscopy (Table 3). A third of these patients ($n=3$) were found to have infectious etiologies for which treatment was initiated, and one patient was diagnosed with pulmonary sarcoidosis. Only 5 patients (2.9%) underwent procedural interventions that led to either no diagnosis ($n=1$), or diagnosis of non-inflammatory/non-infectious benign disease ($n=n=4$). Procedural complications in this group included only one prolonged air leak, which was managed successfully with chest tube drainage alone.

Table 1 Demographics

	Rush	NLST	VA	
Age	65	Unknown	65	
Male	305 (50.5%)	15,770 (59%)	2028 (96.3%)	
Female	299 (49.5%)	10,952 (41%)	78 (3.7%)	
White	352 (58.3%)	24,289 (90.0%)	1520 (72.2%)	
African American	212 (35.1%)	1195 (4.5%)	312 (14.8%)	
Other	5 (0.8%)a	1075 (4.2%)	30 (1.4%)	
Unknown	35 (5.8%)	163 (0.6%)	244 (11.6%)	Aberle (2011) [1]
Current Smoker	331 (54%)	12,862 (48.1%)	1192 (56.6%)	Kinsinger (2017) [8]
Former Smoker	273 (46%)	13,860 (51.9%)	914 (43.4%)	

[a]Includes Asian ($n=4$) and Native Hawaiian/Pacific Islander ($n=1$)

Table 2 Summary results for lung cancer screening compared to NLST and VA

	Rush	NLST	VA
Total patients	604	26,309	2106
Total screening CTs	842	75,126	2694
Total positive screens	169 (27.9%)	18,146 (24.2%)	1257 (59.6%)
Cancer detection rate	21 (3.5%)	1060 (4%)	31 (1.5%)
Number needed to diagnose (NND)	29	38	68
False positive rate	148 (17.5%)	17,497 (23.3%)	1226 (45.5%)
Intervention rate for false positives	9 (5.3%)	457 (2.58%)	42 (3.3%)
Clinically significant abnormality not suspicious for lung cancer	9 (5.3%)	5622 (7.4%)	Unknown

Table 3 Interventions for false-positive lesions

Diagnosis	No. of patients ($n=9$)	Lung-RADS category	Thoracoscopy or mediastinoscopy ($n=7$)	Bronchoscopy ($n=2$)
Infectious	3 (33%)	4B, 4A, 4AS	3	
Inflammatory	1 (11%)	4X	1	
Non-diagnostic	1 (11%)	4A		1
Other[a]	4 (44%)	4A, 4X, 4A, 4X	3	1

[a]Includes a hamartoma, subpleural scar, squamous metaplasia, and mesothelial hyperplasia

Histopathology

Of the 21 primary lung cancers that were identified, 19 (90%) were non-small cell lung cancers (NSCLC), including 17 adenocarcinomas and 2 squamous cell carcinomas. Additionally, 2 small cell carcinomas were identified (10%). Of the 19 non-small cell lung carcinomas, we identified 8 stage I (44%), including 5 pT1a (<T2 cm) and 3 pT1b (2–3 cm) tumors. All stage Ia tumors benefited from VATS sublobar resection and all stage Ib tumors underwent VATS lobectomy. We found 5 stage II NSCLCs (28%), including 4 stage IIa and 1 stage IIb. Two of 5 patients underwent VATS lobectomy, 1 open sleeve resection, and the remaining 2 patients were deemed non-operable and underwent SBRT. Four patients were diagnosed with stage III disease (22%); 4 stage IIIa and 1 stage IIIB. Of the 4 stage IIIa patients, 2 were diagnosed on invasive mediastinal staging procedures and both patients opted for definitive chemotherapy and radiation. The remaining stage IIIa diagnosis was made on final pathology when either T4 or N2 disease was discovered. The patient with stage IIIb disease underwent definitive chemotherapy and radiation treatment (CRT) in accordance with NCCN guidelines (Table 4). Of the 18 non-small cell lung cancers, we identified with screening, only 1 (6%) was stage IV (Table 2). In total, 13 of 19 patients were managed with definitive operations, 2 patients were medically non-operable and underwent stereotactic body radiation therapy, 2 patients refused surgery and underwent definitive CRT, and 2 patients were advanced stage with no indication for surgery.

Furthermore, 8 incidental malignancies were identified in our series. This included a poorly differentiated sarcoma, a renal cell carcinoma, a thymic carcinoma, two breast carcinomas, a lymphoma, a metastatic prostate cancer, and a follicular thyroid cancer. When the number needed to screen is broadened to include incidental malignancies, it decreases to 21.

Table 4 Stage at diagnosis (NSCLC)

	Rush ($n=19$)	NLST all enrolled ($n=1040$)	NLST all screened ($n=679$)[a]	VA ($n=30$)
I	8 (42%)	520 (50%)	407 (60%)	20 (64.5%)
II	5 (26.3%)	73 (7.1%)	51 (7.5%)	2 (6.4%)
III	5 (26.3%)	221 (21.2%)	126 (18.5%)	6 (19.3%)
IV	1 (5.3%)	226 (21.7%)	95 (14%)	2 (6.4%)

[a]Of the 1040 lung cancers diagnosed in the NLST, only 679 were identified after either a positive or negative screen; 367 lung cancers were diagnosed without a screening chest CT, or outside of the screening phase

Discussion

Considering every prior innovation in the multimodal management of lung cancer, the survival benefit associated with early detection represents perhaps the single greatest advancement in the treatment of lung cancer. However, lung cancer screening has not been widely adopted. Amongst other contributing factors, reasons most commonly cited for this include concerns over the unintended harm from high false-positive rates, with the attendant negative psychological impact for patients, as well as perceived rates of unnecessary interventions and their associated morbidity [4–7].

When developing a screening test, balancing rates of detection with the unintended harm of the test require substantial consideration. In the case of lung cancer screening, the high false-positive rates presented by the NLST (23%) and VA (45%) have been used to suggest that the harm associated with screening may outweigh the benefits [1, 8]. Since the NLST was published, a new system for radiologic reporting was developed (Lung-RADS), and is currently considered best practice. Nodules smaller than 6 mm (previously 4 mm) are now deemed negative findings. Employing the Lung-RADS reporting system, as well as trained and experienced radiologists and thoracic surgeons, we demonstrate an overall false-positive rate of 17.5%.

Similar to the NLST and VA, very few patients with false-positive results were subjected to unnecessary procedures in our series. Additionally, not all procedures which do not lead to a cancer diagnosis are unnecessary. We identified 3 infectious and 1 inflammatory lung lesion, which are common mimickers of lung cancer. Only 5 patients (2.9%) underwent an intervention that did not identify treatable lung disease. All of these patients had lesions with Lung-RADS 4 designation and underwent either VATS biopsy ($n=4$) or bronchoscopy ($n=1$), with minimal attendant morbidity (i.e., one prolonged air leak). Even considering the 45% false-positive rate in the Veteran's project, only 3.3% of their patients underwent any additional evaluation that did not result in a lung cancer diagnosis [8], underscoring the rarity of unintended harm from lung cancer screening.

Furthermore, it is critical to note that while Lung-RADS category 3 is a positive finding, the management recommendation is shorter interval follow-up, not diagnostic intervention. Category 4 lesions are generally the only finding considered for tissue sampling. Thus, the pool of patients truly at risk from unnecessary procedures is significantly smaller than what is depicted by overall false-positive reporting. In our series, 20 of 21 lung cancers were diagnosed in patients with Lung-RADS category 4

results. Only one patient underwent diagnostic intervention for a Lung-RADS category 3 lesion, and this was secondary to new mediastinal lymphadenopathy, which lead to a lung cancer diagnosis. Excluding Lung-RADS category 3 as a positive finding purely for the purpose of better quantifying risk of unintended harm, we found only a 6.9% false-positive rate, while diagnosing 25% of all Lung-RADS 4 patients with primary lung cancer.

As previously discussed, critics of lung cancer screening also cite the psychological impact of false-positive screening. While the effect of this is difficult to quantify, multiple analyses counterintuitively suggest that the psychological impact may provide some benefit, owing to increased rates of smoking cessation and associated improvement in quality of life in screened smokers [9, 10]. Compared to those with a negative screening CT, a significant and proportional increase in smoking cessation has been demonstrated in patients who had minor and major findings not suspicious for lung cancer, and findings suspicious for lung cancer, including false-positives. These differences persist up to 5 years after the last screen [10].

Despite only 3 years of data and follow-up in this series, our 3.5% detection rate compares favorably to the NLST and far outperforms the VA project. Notably, of the 1060 diagnoses of lung cancer in the NLST, only 693 were found after either a positive ($n=649$) or negative ($n=44$) screening CT (Table 4) [1]. Excluding the 367 participants diagnosed without a screening CT scan, or outside of the screening phase, the rate of diagnosis in the NLST falls to 2.6%, and the number of at-risk patients needed to be screened to diagnose one primary lung cancer (NND) increases to 38 (Table 2). The VA detection rate was even lower at 1.5%, with a NND of 68 [8]. The reason for the higher detection rate in our screening program is likely multifactorial, but may be accounted for by improvements in radiological evaluation and experience, careful evaluation of patients by lung screening RNs to ensure they meet screening guidelines, as well as from selection bias owing to differences in patient demographics. Reflective of the patient population we serve, our program screened a disproportionate number of African Americans (35%) compared to the NLST and VA series (4.5% and 14.8%, respectively [1, 8]). The increased risk of lung cancer in African Americans has been well established [11], and they represent 52% of the patients diagnosed with lung cancer in our series.

Of the 21 lung cancers diagnosed in our LCS program, 18 were found after a positive initial screen (category 3 or 4 lesions), and 68% were diagnosed after the initial scan. The average interval from screen detected finding to diagnosis was 27 days in our series. In comparison, of the 649 lung cancers diagnosed by the NLST after a positive screen, only 41.6% were found after the initial scan (25.8%, and 32.5% were found after the second and third, respectively) [1]. While the NLST did not report the interval from screen detected finding to diagnosis, the VA reported an average of 137 days from initial screen to diagnosis [8]. These are both critical improvements, as higher rates of cancer detection on initial screen, as well as minimizing delays from screen to diagnosis, has the potential to further improve the survival benefit imparted by lung cancer screening and minimize the risk of unintended harm. This must be assessed in future analyses.

In conclusion, improvements in radiological expertise and reporting, along with dedicated multidisciplinary oversite, result in higher detection rates, decreased false-positive findings, and minimize delays from screening to diagnosis. Furthermore, reporting of false-positive rates overestimates the risk of unintended harm from unnecessary procedures as only a percentage of positive scans is generally considered for tissue biopsy (i.e. Lung-RADS category 4). A better understanding of the true risks and benefits of lung cancer screening is critical to achieve wide-spread adoption.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest

References

1. Aberle DR, Adams AM, Berg CD et al (2001) Reduced lung-cancer mortality with low-dose computed tomographic screening. New Engl J Med 365(5):395–409
2. Gotzsche PC, Nielsen M. Screening for breast cancer with Mammography. *Cochrane Database Syst Rev*. 2011;(1)CD001877
3. Jemal A, Fedewa SA (2017) Lung cancer screening with low-dose computed tomography in the United States-2010 to 2015. JAMA Oncol 3(9):1278–1281
4. Amer RR, Yasky AF, Zawaki AH (2017) Lung cancer screening: beliefs and recommendations of primary care physicians at the National Guard Hospital (NGHA). Glob J Medi Res 17(2):7–15
5. Lewis JA, Pety J, Tooze JA et al (2015) Low-dose CT lung cancer screening practices and attitudes among primary care providers at an Academic Medical Center. Cancer Epidemiol Biomark Prev 24(4):664–670
6. Ersek JL, Eberth JM, McDonnel KK et al (2016) Knowledge of, attitudes toward, and use of low-dose computed tomography for lung cancer screening among family physicians. Cancer 122:2324–2331
7. Crothers K, Dross EK, Reisch LM et al (2016) Patients' attitudes regarding lung cancer screening and decision aids. A survey and focus group study. Ann Am Thorac Soc 13(11):1992–2001
8. Kinsinger LS, Anderson C, Kim J et al (2017) Implementation of lung cancer screening in the Veterans Health Administration. JAMA Intern Med 177(3):399–406
9. Cressman S, Peacock SJ, Tammemagi MC et al (2017) The Cost Effectiveness of High-Risk Lung Cancer Screening and Drivers of Program Efficiency. J Thorac Oncol 12(8):1210–1222

10. Tammemagi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL (2014) Impact of lung cancer screening results on smoking cessation. J Natl Cancer Inst 106(6):dju084
11. Haiman CA, Stram DO, Wilkens LR et al (2006) Ethnic and racial differences in the smoking-related risk of lung cancer. New Engl J Med 354(4):333–342