REVIEW

Lung cancer screening: Should we be excluding people with previous malignancy?

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Abstract

The National Lung Screening Trial (NLST) was a large, randomized, controlled study showing a 20% reduction of lung cancer mortality and 7% reduction of all cause mortality using annual low dose computed tomography (LDCT) in a high risk population. NLST excluded people with a previous history of cancer treatment within the past 5 years and all people with a history lung cancer. The aim of this work is to review how lung cancer screening trials addressed the confounding effect of previous malignancy. We also review the subsequent recommendations by the United States Preventative Task Force Services, multiple professional societies and the Center for Medicaid and Medicare Services which defer either to NLST criteria or, clinician judgment or refrain from asserting any recommendation on the topic, respectively. Implications of lung cancer screening in the setting of previous malignancies, specifically lung, head and neck, esophageal, gastric, breast, colorectal cancer and lymphoma are also discussed. With lung cancer screening, an antecedent malignancy introduces the possibility of discovering metastasis as well as lung cancer. In some circumstances diagnosis and treatment of oligometastatic disease may confer a survival benefit. The survival benefit of treating either lung cancer or oligometastatic disease as result of lung cancer screening has yet to be determined. Further studies are needed to determine the role of lung cancer screening in the setting of previous malignancy.

Key words: Lung cancer screening; Criteria; Previous malignancy; Antecedent malignancy; Lung metastasis; Guidelines; Head and neck cancer; Lung cancer; Low dose computed tomography; Gastric cancer; Breast cancer; Colorectal cancer; Lymphoma; Esophageal cancer

Core tip: Most lung cancer screening trials, including the National Lung Screening Trial, exclude those with a history of a previous malignancy as it may introduce confounding factors that influence survival. However,

people with previous malignancy may benefit from the discovery of treatable lung cancer as well as treatable metastasis. In this review, we summarize the consideration that studies and national guidelines give in regards to lung cancer screening in patients with previous malignancy. Furthermore, we address the implications of lung cancer screening in the setting of specific malignancies, namely lung, head and neck, esophageal, gastric, breast, colorectal cancer and lymphoma.

INTRODUCTION

According the National Cancer Institute, lung cancer is the most common cause of cancer death among both men and women, accounting for more deaths than breast, colorectal, prostate and pancreatic cancer combined. Nearly 75% of lung cancers are diagnosed at stage III or IV[1], thus contributing to the dismal average five-year survival of 17.4% to 18.5%[2,3]. Though early detection through lung cancer screening should be expected to confer a survival benefit, several studies have failed to prove this, even in large randomized trials[4]. In 2011, the National Lung Screening Trial (NLST) compared a low dose computed tomography (LDCT) scan to chest radiography (CXR) as a modality of lung cancer screening. LDCT reduced the risk of lung cancer death by 20% and death from all causes by 7%[5]. This was a multi-institutional, randomized study of over 53000 patients. The NLST restricted eligibility to those with greater than 30 pack years of smoking, active smokers or those who quit smoking within the past 15 years who were between the ages of 55 to 74. In addition to including those at high risk of lung cancer, NLST excluded people who were not likely to benefit from lung cancer screening, namely those who were unwilling to undergo surgical resection, those with major health problems that would preclude lung cancer treatment, and those with obvious symptoms of lung cancer. The combination of a sufficiently powered study, inclusion of only those at highest risk of lung cancer and exclusion of people unlikely to benefit from early lung cancer detection contributed to the unprecedented mortality risk reduction of NLST. LDCT, applied to the United States population could potentially avert 12000 lung cancer deaths per year[6].

However, Pinsky *et al*[7] utilized data from Surveillance, Epidemiology and End Results (SEER), the United States Census and the National Health Interview Survey to determine that only 6.2% of the United States population over 40 years old was eligible for lung cancer screening. Additionally, only 26.7% of people with lung cancers would have been eligible for lung cancer screening by NLST criteria Farjah *et al*[8] used a risk-prediction model to review resected lung cancer patients. The authors concluded that NLST lung cancer screening criteria may exclude people who have a predicted risk greater than or equal to those who are currently eligible. Many people excluded by NLST criteria could benefit from lung cancer screening. This study prompts scrutiny of the exclusion criteria of lung cancer screening.

Looking at the design of NLST, is important to categorize the exclusion criteria into exclusion because people will not likely benefit from lung cancer screening, and exclusion that confounds a clinical trial. Patients presenting with symptoms of lung cancer such as, weight loss or, hemoptysis, and those who are unwilling to undergo lung cancer surgery are not likely to benefit from lung cancer screening[9]. However other NLST exclusion criteria such as "patients participating in another screening trial or cancer prevention study" may benefit from lung cancer screening, but were not included to avoid confounding scenarios. Similarly, the NLST exclusion of patients with metallic implants or devices in the chest or back, patients with a chest computed tomography (CT) within the past 18 mo, patients with a recent pneumonia or respiratory tract infection, or patients with removal of any portion of the lung excluding needle biopsy could all possibly benefit from the lung cancer mortality risk reduction of LDCT. More controversially, NLST excluded those on home oxygen and those with previous malignancy. Though unclear if these people will benefit from LDCT, they at least deserve further study.

EXCLUSION OF PATIENTS WITH PREVIOUS MALIGNANCY

NLST excluded people with a history of lung cancer and those who were treated for a malignancy within five years of the initial screen. People with non-melanomatous skin cancer were still eligible for lung cancer screening. From the perspective of study design, previous malignancy introduces confounding challenges to the study of lung cancer screening: (1) A lung nodule has a 40%-60% chance of being a metastasis from a previous malignancy. Radiologists may interpret a nodule differently with the knowledge of a previous malignancy[10,11]; (2) The management of a lung nodule in a patient with a previous cancer history varies from that in patients without a cancer history. For instance, a lung nodule in the setting of previous cancer may prompt a PET scan to look for other metastasis or recurrence of the primary cancer. The recommendation for management of the same nodule in a patient without previous malignancy may be a follow up CT scan. It is difficult to establish the benefit and harms of screening when work-up and treatment varies within the study group; (3) The etiology of a malignant nodule

cannot always be determined. For instance, a squamous cell cancer found in the lung may be a lung primary or a metastasis from a head and neck cancer. Even immunohistochemistry and genetic analysis may not be able to distinguish the cancer's origin; (4) Previous malignancy introduces wide variability in survival. The type, stage and disease free interval of a previous malignancy all influence overall survival. It would be difficult to interpret if screening for lung cancer with a LDCT improved survival in these patients; and (5) It can be challenging to determine the contribution a lung cancer, another distinct malignancy or the combination of the two has on mortality.

Previous studies of lung cancer screening had similar concerns about including patients with previous malignancy. We have summarized findings of index trials in lung cancer screening in Table 1. In 1993, Henschke and colleagues concluded that CT screening for lung cancer detected disease at an earlier stage than CXR in their Early Lung Cancer Action Project (ELCAP)[12]. Patients with prior cancer were excluded from the study. The ongoing International I-ELCAP study continues to limit enrollment to people with no previous history of lung cancer[13]. The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) was a longitudinal, population-based study of 335441 people proved that lung cancer screening with CT scanning and a volumetric lung nodule management algorithm was feasible[14]. The NELSON trial excluded persons with current or past renal cancer, melanoma or breast cancer were not included, "because these tumors give rise to lung metastasis even after long follow up. People with lung cancer within 5 years of diagnosis, and lung cancer diagnosed greater than 5 years from randomization, but still undergoing treatment were also excluded[15]. The Detection and Screening of Early Lung Cancer with Novel Imaging Technology (DANTE) Trial published their results comparing lung cancer mortality in those undergoing LDCT compared to no screening in May of 2014[16]. Unlike NLST, there was no reduction in lung cancer or all cause mortality in 2532 patients randomized to LDCT *vs* no screening. Similar to NLST and NELSON, persons with a previous malignancy within 10 years of recruitment were ineligible. The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial was a population study of over 154000 patients looking at lung cancer death as a primary outcome[17]. There was no reported difference in lung cancer mortality with CXR as a screening modality[4,18]. This study excluded patients with prior cancer of the colon, rectum, lung, prostate, ovary or individuals undergoing treatment for cancer at the time of the study, excluding basal-cell and squamous-cell skin cancer.

At the time of this writing, 15 studies of lung cancer screening are registered as "active" with ClinicalTrials.gov. Of these 15 studies, 13 have exclusion criteria for people with a history of previous malignancy, including lung cancer. These studies have varying exceptions, but all allowed people with non-melanomatous skin cancer

to be eligible for lung cancer screening. Only two studies made no mention of excluding people with previous malignancy. Only one study aims to look at lung cancer screening in the setting of previous malignancy, namely Hodgkin's lymphoma[19].

RECOMMENDATIONS FOR LUNG CANCER SCREENING

Though the exclusion of a previous malignancy makes sense in the setting of a randomized trial, it does not necessarily translate to the logic of excluding these patients as a policy. In 2014, the United States Preventative Services Task Force (USPSTF) updated their recommendations regarding lung cancer screening[20]. The previous recommendation, published in 2004, found insufficient evidence to recommend LDCT for lung cancer screening. With compelling evidence from four randomized controlled studies NLST, DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays)[13,21], DLCST (Danish Lung Cancer Screening Trial)[22], and MILD (Multicentric Italian Lung Detection)[23] the USPSTF "concludes with moderate certainty that annual screening for lung cancer with LDCT is of moderate net benefit[16]".

Interestingly, USPSTF departed from the NSLT in its recommendations by expanding eligibility. Based on comparative modeling studies calibrated to both NLST and PLCO Cancer Screening Trial data, de Koning *et al*[24] found that annual LDCT has a favorable benefit-harm ratio for individuals aged 55 through 80, not 55 to 74 as defined by NLST. USPSTF does not mention excluding people with a history of previous malignancy. Even though both NLST and PLCO had exclusion criteria of lung cancer and restrictions on any previous malignancy, USPSTF did not recommend including or excluding people with previous malignancy from lung cancer screening. This leaves clinicians to interpret the USPSTF recommendation to screen patients in a fashion "similar to NLST".

The American Lung Association (ALA) in 2012 published guidance on lung cancer screening addressing both patients and physicians in 2012[25]. Though the ALA did not specifically address screening people with previous malignancy, they did acknowledge that lung cancer screening requires future refinement of the criteria. In the absence of randomized control data for all clinical scenarios of criteria, they suggest relying on risk stratification models. They cite Tammemagi and colleagues' use of PLCO participants to develop a lung cancer risk prediction model[26] which performed better than the NLST criteria. Unfortunately, risk prediction models rely on existing data about lung cancer screening, which excludes those with a history of previous malignancy.

The American College of Chest Physicians (ACCP) released their evidence-based clinical practice guidelines in 2013[27]. Regarding the inclusion and exclusion

Table 1 Index trials of lung cancer screening

Ref.	Participants	Exclusion criteria	Design	Results
Aberle *et al*[5]	53454 participants	Previous lung cancer diagnosis	Randomized Control Trial	Rate of positive screening was 24.2% in LDCT and 6.9% with CXR group
	Age 55 to 74			
	At least 30 pack-year smoking history	CT scan within previous 18 mo	Participants randomized to three annual screenings with LDCT (26722) *vs* single view PA CXR (26732)	The majority of positive screening results were false positives, 96.4% in the LDCT group and 94.5% in the CXR group
	Former smokers must have quit within previous 15 yr			Lung cancer mortality decreased by 20% (P = 0.004) and all cause mortality decreased by 6.7% in LDCT group (P = 0.02)
van Iersel *et al*[14]	15822 participants	Hemoptysis or unexplained weight loss of 15 lbs or more in last year	Randomized Control Trial	Ongoing - 10 yr follow up planned
	Age 50-74	Current or past diagnosis of renal cancer, melanoma or breast cancer		
	Determined to be high risk based on answers to heath questionnaire	Lung cancer diagnosis within last 5 yr or current treatment	Participants randomized to either LDCT screening (7915) or no screening (7907)	
	Good overall health (able to climb 2 flights of stairs, weight less than 140 kg)	CT scan within past year		
Infante *et al*[16]	2472 participants	History of previous malignancy treated within 10 yr (exceptions: Early laryngeal cancer and nonmelanoma skin cancer with a 5-yr disease-free interval)	Randomized Control Trial	Ongoing. 3 yr results: Lung cancer detected in 4.7% of patients in LDCT group and 2.8% in controls (P = 0.016)
	Males aged 60-74	Comorbid conditions with life expectancy less than 5 yr	Randomized to 5 yr of annual screening with LDCT (1276) or clinical follow up (1196)	There was a 1.6% lung cancer mortality in the LDCT group and 1.7% in the control group (P = 0.84). No difference in all cause mortality (P = 0.83) to this point in the study
	20 pack-year smoking history			
Saghir *et al*[22]	4104 participants	Previous cancer diagnosis and treatment	Randomized control trial	There was a higher rate of invasive procedures performed in the LDCT group compared with controls (P < 0.0001)
	Age 50-70			Ongoing. 5 yr results:
	At least 20 pack-year smoking history	Comorbid illness that would shorten life expectancy to < 10 yr	Participants randomized to five annual LDCT screenings (2052) or no screening (2052)	Lung cancer was diagnosed in 69 patients in the LDCT group, compared with 24 in the control group (P < 0.001)
	Former smokers who quit after age 50 and quit less than 10 yr prior	CT scan within previous year		Stage Ⅰ - Ⅱ B lung cancer was diagnosed more frequently in the LDCT group (P = 0.002), however there was no difference in frequency of Stage ⅢA-Ⅳ lung cancer (P = 0.509)
	FEV1 of at least 30% predicted value			There was no difference in mortality from lung cancer (P = 0.428) or overall mortality (P = 0.059) to this point of follow up
	Good overall health (able to climb 2 flights of stairs, weight less than 130 kg)			
Pastorino *et al*[23]	4099 participants	History of cancer within the previous 5 yr	Randomized Control Trial	The cumulative 5-yr lung cancer incidence rate was 0.0031% in the control group, 0.0046% in the biennial, and 0.0062% in the annual LDCT group (P = 0.036)
	Age 49 or older			
	At least 20 pack-year smoking history - current smoker or had quit within 10 yr		Randomized participants to annual LDCT screening (1190), biennial LDCT screening (1186), or observation alone (1723)	Rates of mortality from lung cancer were 0.0011% in the control group, 0.0011% in the biennial group, and 0.0022% in the annual group (P = 0.21) There was also no difference in all cause mortality between the three groups (P = 0.13)

LDCT: Low dose CT; CXR: Chest radiography; CT: Computed tomography.

criteria of the NLST, the authors state, "Expanding screening to cohorts other than those included in the NLST is probably not warranted at this time unless it is in the context of a research study". They also look

to risk prediction models to assist with establishing screening criteria, however they must account for competing causes of death. More specifically, for those with a previous malignancy, further studies are needed to understand how a previous malignancy impacts lung cancer death. Though there are no clear recommendations about lung cancer screening in those with previous malignancy, the ACCP and their collaborative, multi-society statement with the American Cancer Society (ACS), the American Society of Clinical Oncology (ASCO) and the NCCN emphasizes the need to balance the benefits and harms of lung cancer screening on an individual basis[28].

The Centers for Medicare and Medicaid Services released their final national coverage determination for lung cancer screening with LDCT in February of 2015[29]. The supporting data cites the Cochrane Database Systematic Review[30] and a systematic review by Prosch and Schaefer-Prokop[31]. Both of these reviews included studies like NLST, DANTE, DLCST and PLCO which all excluded people with previous malignancy. However there is no recommendation on either including or excluding patients with previous malignancy.

In the 2015 review of current ACS guidelines for cancer screening in the United States, the authors advise that clinicians should initiate a discussion about lung cancer screening in people who meet the criteria of the NLST. "Clinicians should not discuss LDCT lung cancer screening with patients who do not meet the recommended criteria", including those with previous malignancy. The ACS allows for judgment of the clinician to discuss lung cancer screening when the risk "seems to approximate" NSLT eligibility criteria. They note that the uncertainty of harms and benefits outside the NLST criteria are too great to recommend screening.

In contrast, in the most recent 2015 update of the National Comprehensive Cancer Network (NCCN) guidelines for lung cancer screening[32], the panel members do not exclude patients with previous cancer from lung cancer screening. In fact, the NCCN guidelines include a personal cancer history as a significant risk factor for developing lung cancer. The guidelines highlight that those who survive lung cancer, lymphomas, cancers of the head and neck and other smoking-related cancers such as esophageal cancer. The panel recommends that with one additional risk factor (category 2A), like previous malignancy, lung disease, family history of lung cancer, radon exposure and occupational exposure to carcinogens, individuals aged 50 or older with a 20 pack-year history of smoking tobacco should undergo lung cancer screening.

The most comprehensive evaluation of lung cancer screening in patients with previous malignancy is found in the American Association for Thoracic Surgery guidelines[33]. These guidelines note that people with previous cancer, lung cancer in particular, are at increased risk of developing a lung malignancy. Complex environmental and genetic factors that predispose someone to the first malignancy are still relevant for the development of a second lung cancer. Additionally, treatment with radiation therapy or alkylating agents for a previous cancer may also contribute to the risk of developing lung cancer. The consensus opinion is that a previous malignancy should not exclude patients from lung cancer screening. Furthermore, a previous malignancy is an indication to start lung cancer screening at an earlier age and in those with less tobacco exposure than currently recommended by NLST criteria. With regard to patients who have been successfully treated for lung cancer, they should receive high resolution CT scans for 4 years followed by annual LDCT screening for the rest of their life, or until functional status or refusal to undergo lung cancer treatment precludes the potential benefit of lung cancer screening. Jaklitsch *et al*[33] recommend lung cancer screening in patients with level 2 evidence (*i.e.,* data from case-controlled or nonrandomized clinical trials).

In the absence of specific data about lung cancer screening in the setting of previous malignancy, risk prediction models can guide recommendations. Tammemägi *et al*[26] have developed a lung cancer risk prediction model (www.brocku.ca/lung-cancer-risk-calculator). This model incorporates multiple variables including smoking (intensity, duration, quit time), social circumstances and personal health history[34,35]. Selecting individuals for lung cancer screening based on accurate lung cancer risk prediction models can increase sensitivity (83.0% *vs* 71.1%; $P < 0.001$) and positive predictive value (4.0% *vs* 3.4%; $P = 0.01$) without loss of specificity (62.9% and 62.7%; $P = 0.54$) compared to NLST or USPSTF criteria[36]. Accurate modeling can lead to smaller numbers of individuals being screened, identification of more lung cancers and an increased positive predictive value[37]. Early data of lung cancer screening in patients with antecedent malignancy suggests that such screening may contribute to developing personalized risk prediction models.

LUNG CANCER SCREENING IN PATIENTS WITH HISTORY OF SPECIFIC MALIGNANCY

The benefit that lung cancer screening can confer on a patient with previous malignancy depends on the antecedent cancer. Benefit may be in the form of finding lung cancer in a high risk population, or in the form of finding treatable metastasis. We summarize the existing knowledge of lung cancer screening in the setting of previous lung, head and neck, esophageal, gastric, breast, colorectal cancer and lymphoma (Table 2).

Lung cancer

A history of lung cancer is one of the strongest risk factors for developing a new lung cancer. In a study of 1294 patients undergoing resection for early stage

Table 2 Prior malignancy and lung cancer			
Prior malignancy	**Ref.**	**Method**	**Results**
Lung	Lou *et al*[38]	1294 participants with early-stage NSCLC underwent resection and then were followed with surveillance CT screening	Recurrence was diagnosed in 20% of patients and second primary lung cancer was diagnosed 7% of patients. The risk of second primary lung cancer diagnosis did not decrease over time. Of the second primary cancers that were diagnosed, 93% were identified by scheduled surveillance CT. Of the recurrences that were diagnosed, 61% were identified by surveillance CT. Twenty five percent of patients required additional invasive testing, but less than 1% experienced complications from these procedures
Head and Neck	Milano *et al*[50]	61883 patients with SCC of the head and neck were identified *via* the SEER database. Of those, 4522 developed a second primary lung cancer. A retrospective data analysis was performed	The risk of developing a primary lung cancer after HNSCC was 5.8%, 11.4%, and 16.4% at 5, 10, and 15 yr. These rates are higher compared to the general population
Head and Neck	Baxi *et al*[51]	35958 three-year survivors of SCC of the head and neck were identified *via* SEER database. A competing-risks proportional hazards regression was used to estimate probabilities of death from different causes	Second primary malignancy was the second leading cause of death (second only to primary head and neck squamous cell carcinoma) in this population. Of these, 53% of second primary malignancies were lung cancer
Head and Neck	Pagedar *et al*[54]	Data was collected and retrospectively analyzed. Survival estimates were generated for patients with lung cancer with and without a history of head and neck cancer	The median survival of patients with only primary lung cancer was 38 mo, compared to 22 mo in those with a history of head and neck cancer with lung cancer as a second primary malignancy. This statistically significant difference suggests that survival outcomes after lung cancer diagnosis are worse in patients who have a history of head and neck malignancy
Breast	Kitada *et al*[63]	Data was collected an analyzed on 1226 patients who underwent surgical resection of breast cancer, 49 of whom were found to have at lease one pulmonary lesion during or after workup	14 patients underwent surgical resection of the pulmonary lesion. Primary lung cancer was the diagnoses in 3 of these patients, metastases in 8 cases. Of those diagnosed with second primary lung cancer, the stage was I A in all
Breast	Kerendi *et al*[67]	35 patients with breast cancer and second primary lung cancer were identified and retrospective analysis of survival was performed	More than half of patients had their lung cancer diagnosed during workup or follow-up. 54% of these patients were successfully treated with surgery. There was a statistically significant survival benefit when the cancer was detected early (stage I A, asymptomatic)
Breast	Milano *et al*[68]	3529 women with NSCLC diagnosis after breast treatment were identified in the SEER database. Data on these patients was retrospectively analyzed and compared to data on 151628 women diagnosed with NSCLC alone	Patients with a history of breast cancer were diagnosed at significant earlier stage, although surgical resection was used more frequently in the NSCLC only group. History of breast cancer history did not affect overall survival in localized NSCLC. Overall survival was significantly greater in patients with regional and distant NSCLC that had a history of breast cancer
Bladder	del Rey *et al*[72]	Data from 231 patients with non-muscle invasive bladder cancer were retrospectively analyzed	Lung cancer was the most common second primary malignancy in this population. The risk of lung cancer in patients with non-muscle invasive bladder cancer is 10 fold higher than the regional general population
Lymphoma	Das *et al*[75]	Authors used a decision-analytic model to estimate potential benefits of annual low-dose CT screening *vs* no screening in a hypothetical cohort of patients (early stage lymphoma diagnosed at age 25, lung cancer screening starting at age 30). Model parameters were generated from SEER	In this simulated model, annual CT screening increased survival by 0.64 yr for smokers and 0.16 yr for non-smokers. The difference in quality of life and cost effectiveness was also more pronounced in smokers
Lymphoma	Milano *et al*[77]	Survival data of 187 patient with history of Hodgkins lymphoma diagnosed with NSCLC was compated to data from 178431 patients diagnosed with NSCLC only	Hodgkins lymphoma survivors had significantly inferior overall survival across all lung cancer stages (estimated to be between 30% to 60% decrease in overall survival). Patients with younger age at lymphoma diagnosis, younger age at lung cancer diagnoses, and those with longer latency between cancer diagnoses were more likely to be diagnosed with late stage disease
Colorectal	Hattori *et al*[34]	A retrospective analysis of lung cancer patients with (123) or without (4431) a previous history of colorectal cancer treated with surgical resection	There is no statistically significant difference in overall survival comparing patients with lung cancer *vs* lung cancer with a history of surgery for colorectal cancer. Prior history of colorectal cancer was not a poor prognostic indicator on multivariate analysis. Of those patients who had been diagnosed with both lung and colorectal cancer, those who are older and those who underwent treatment with adjuvant chemotherapy had poorer outcomes

CT: Computed tomography; NSCLC: Non-small-cell lung cancer; SEER: Surveillance, epidemiology and end results; SCC: Squamous cell cancer; HNSCC: Head and neck squamous cell cancer.

lung cancer, 7% presented with a second primary lung cancer within a median follow up of 35 mo[38].

People with lung cancer have a 3%-6% risk per year of developing a second lung cancer, a risk that actually

increases with time[31,39,40]. This increased risk of a second lung cancer persists to even 10 years after the initial diagnosis[41]. By comparison, in the NLST high-risk population, the incidence of lung cancers was less than 1% per patient year[5]. Screening lung cancer patients should be at least as successful in discovering a new lung cancer as screening those who fit the NLST criteria. Second primary lung cancers found during surveillance are diagnosed in stage I (92%) or stage II (4%), suggesting a survival benefit[31]. However, the survival benefit of long term, annual LDCT to screen for second primary lung cancers is unknown. Special consideration should be given to the possibility of false positives (25%) and unnecessary invasive procedures (3%) and complications from unnecessary invasive procedures (0.3%) from nodules found in the setting of CT scanning after lung cancer treatment[31].

Surveillance following the treatment of lung cancer consists of a history and physical and chest CT every 6 to 12 mo for two years, then a history and physical with a LDCT annually, according to NCCN guidelines[31]. Locoregional recurrence occurs in 10%-30% of patients[42], and metastatic spread occurs in 15%-39% of patients[33]. A majority of these occur within the first 2 years of diagnosis[43]. For the first 4 years after surgery, the risk of recurrence is 6% to 10% per patient year but decreases thereafter to 2%[31]. In a review of 9 studies looking at lung cancer recurrence following surgical resection[44], Mollberg *et al*[44] found that only 0.9% to 4.4% of patients with lung cancer recurrence were candidates for repeated resection. A more recent study by Crabtree *et al*[45] showed that 40%-41% of subsequent malignancies were treated with curative intent. Data on five-year survival following recurrence varies widely from 8.3% to 40.0% with improved survival in those receiving curative treatment[37,38]. Though it would seem that early detection of recurrent lung cancer would improve survival, several studies comparing intense surveillance for lung cancer with clinic visits and CT scans failed to demonstrate a survival benefit[38,46]. A randomized trial in France comparing lung cancer surveillance with CXR *vs* CT and bronchoscopy is underway. Hopefully these results will clarify which surveillance techniques improve survival[47]. Regardless of whether a CT following lung cancer treatment is for surveillance for recurrence or early diagnosis of a new lung cancer, the impact on survival is still unclear. Advances in targeted therapy, novel chemotherapeutic regimens and palliative care give promise toward improved survival, even with a diagnosis of metastatic disease.

Perhaps the greatest value of surveillance and screening in lung cancer survivors is ensuring that patients are smoke free. Parsons *et al*[48] found that continued smoking following treatment for lung cancer was associated with a significant increased risk of recurrence and an almost threefold increase risk of all cause mortality. Even recent quitters enjoy a significant improvement in disease free and overall survival compared to those who continue to smoke[49]. Smoking cessation confers a benefit for lung cancer patients at any time.

Head and neck cancer

Head and neck cancer and lung cancer share the risk factors of smoking and age. Up to 15%-20% of head and neck cancer patients develop a second primary malignancy[50]. Lung cancer accounts for 50% of these second primary malignancies and 50% of second primary malignancy-related deaths in patients with head and neck cancer[51]. With proactive follow up with a CT scan, oro-nasopharyngeal and esophageal endoscopy, Wolf *et al*[52] found a second primary malignancy in 18% of head and neck squamous cell cancer patients. Almost half of the second primary malignancies turned out to be primary lung cancer. Of the patients found to have a second primary malignancy, 86% were diagnosed at an early stage and were able to undergo therapy with curative intent. Though this study demonstrated that a lung cancer can be found and treated in patients with head and neck cancer, they did not study the influence of lung cancer treatment on survival.

To date, there are no controlled trials of head and neck cancer patients comparing survival with and without LDCT screening for lung cancer. In the absence of controlled trials, a recent survey of Canadian Head and Neck Surgeons showed that a majority of surgeons believe lung screening can improve patient mortality, and 31% currently screen high-risk patients for lung cancer with a LDCT[53]. However, Pagedar *et al*[54] found that the median survival of patients with lung cancer was 38 mo compared to 22 mo in patients with an antecedent history of head and neck cancer. These authors suggest that screening patients with a history of head and neck cancer with LDCT may not have the same survival benefit as those without this cancer history.

Additional questions arise when screening head and neck cancer patients for lung cancer. For instance, it is not always possible to determine if a pulmonary nodule is a primary lung cancer or a metastasis. Previously, Geurts *et al*[55] found that there is no difference in overall survival between patients who had surgical resection of a metastasis *vs* a lung cancer[55]. This would argue for screening in the setting of head and neck cancer. However a directed study looking at survival in the setting of screening has yet to be done. As second question is when to start screening head and neck cancer patients, at the time of diagnosis or some interval following successful treatment? Patients presenting with synchronous second primary lung cancer are more likely to have treatable, early-stage disease, as compared to patients with metachronous malignancy[56]. Five-year survival is higher in patients with synchronous head and neck and lung cancer compared to metachronous malignancies[57]. The improved 5-year survival is likely due to increased detection of early stage disease and earlier intervention.

It is possible that lung cancer screening may aid in detecting metachronous malignancy at an earlier stage and thus may improve survival, but this is yet to be demonstrated in the literature. These questions and controversies will hopefully lead to controlled trials looking at lung cancer screening in the setting of head and neck cancer. Clinicians must evaluate the value of lung cancer screening in head and neck cancer survivors on an individual basis, taking into consideration the patient's expected survival, risk of lung cancer, and potential benefit of treatment for either lung primary or metastasis. As with all cancer patients with a smoking history, a discussion of lung cancer screening should also include a discussion about smoking cessation.

Esophageal cancer and gastric cancer

Patients with esophageal cancer, gastric cancer and lung cancer share smoking as a common risk factor. In a study of 116 consecutive cases of esophageal cancer, 19% had a solitary pulmonary nodule[58]. Of these, 68% were benign nodules, 18% were new primary lung cancers and none were metastatic esophageal cancer. In patients with gastric cancer, 9.2% had secondary primary malignancies, of which lung was the most common (18.4%)[59]. In this same study, logistic regression analysis failed to show a significant association between age, gender, smoking, alcohol and *Helicobacter pylori* infection and the development of a second primary malignancy. The authors propose that clinicians consider the possibility for secondary primary malignancies during diagnosis and surveillance. However, there are no studies addressing the value of lung cancer screening. Furthermore, there are no evidence-based guidelines on who to screen and when to screen for lung cancer in those with previous esophageal and gastric cancer. Clinicians have to judge on an individual basis if the risk of lung cancer is great enough to screen, and if treatment of a discovered lung cancer will favorably impact survival. In sharing this decision with active smokers, clinicians must emphasize that risk reduction achieved by smoking cessation will likely surpass any risk reduction from lung cancer screening.

Breast cancer

Breast cancer is the most commonly diagnosed malignancy in females. Current recommendations in breast cancer surveillance recommend frequent physical exams and post-treatment yearly mammograms[60]. Given the rarity of lung metastasis, the ASCO guidelines do not recommend routine CT screening for metastatic disease of the lung[61]. Even during initial breast cancer workup, routine use of CT staging is thought to have limited value, low sensitivity, and considerable rate of false positives, and thus is recommended only in the setting of symptoms concerning for distal metastases[62]. However, excluding women with a history of breast cancer from LDCT lung cancer screening eliminates a large number of women who may otherwise benefit from early detection of malignancy. Almost 4% of breast cancer patients have pulmonary lesions during workup or identified during follow up[63]. In addition, while radiation therapy is an effective treatment for breast malignancy, it leads to a well-documented increase in risk for second primary malignancy of the lung[64,65]. This risk of treatment related lung cancer is significantly higher in patients with a smoking history[66].

Earlier diagnosis of lung cancer in a patient with a history of breast cancer carries an improved prognosis. Kerendi *et al*[67] reviewed the records of 35 patients with known breast cancer found to have a second primary malignancy of the lung. Of these patients 54% were asymptomatic at the time of diagnoses, and the malignancy was found during workup or routine follow up. Pre-operative biopsy yielded a diagnosis in 82% of cases and 54% of these lung cancers were successfully treated with surgery. They documented an improved prognosis if the lung cancer was diagnosed when the patient was asymptomatic and if the patient was a non-smoker. In addition, it has been demonstrated that treatment of non-small cell lung cancer in the setting of a history of breast cancer paradoxically may convey an improved prognosis compared to patients diagnosed with non-small cell lung cancer alone. Data gathered from the SEER-18 registry indicated that non-small cell lung cancer was diagnosed at an earlier stage in patients with a breast cancer history, and these patients were more likely to undergo surgical resection[68]. Breast cancer history did not affect overall survival in local disease, but portended an improved overall survival in regional or distant lung cancer. Thus, it appears as though this patient population would certainly be ideal for inclusion in a LDCT lung cancer screening program.

While CT screening may identify a solitary pulmonary nodule, it is notoriously difficult to distinguish between primary lung malignancy and breast metastasis radiologically. Evidence suggests that over 50% of solitary pulmonary nodules detected in the setting of treated breast malignancy are primary lung cancer[69]. Kinoshita *et al*[70] reviewed records of 64 breast cancer patients who had undergone surgical resection of a pulmonary nodule. Of these, 37 patients (58%) were found to have a primary lung cancer. Retrospectively reviewing pre-operative CT scans after surgical diagnosis suggested that primary lung malignancy was significantly associated with the following radiologic findings: Air bronchograms, increased size, and ill defined nodule border. However, these can still be non-specific findings and radiologic diagnosis continues to be a challenge.

This begs the question, does survival differ between patients with a solitary pulmonary nodule found to be lung cancer *vs* breast metastasis? Tanaka *et al*[69] studied 30 patients who underwent surgical resection for a solitary pulmonary nodule after curative surgery for breast cancer. They found that 93% of pulmonary nodules were malignant, 67% of these being primary lung cancer. Five-year survival after surgical resection was 100% in cases of breast metastasis and 61%

in cases of primary lung cancer[62]. In another study, 84% of patients found to have a solitary breast cancer metastasis to the lung were able to undergo complete metastatic resection[71]. Thus, in the setting of a history of breast cancer a Solitary pulmonary nodule is almost uniformly malignant. Again, given high 5-year survival rates regardless of pathologic diagnosis, LDCT screening is likely to be beneficial in breast cancer survivors who meet all other NLST criteria.

Bladder cancer

Lung cancer also shares an association with bladder cancer. A recent study examined 231 patients with non-muscle-invasive bladder cancer and found that 4% of these patients were found to have a second primary lung malignancy during follow up, a rate 10-fold higher than the local population[72]. Of those found to have a lung malignancy, 9 were found at late stage and only 1 was found at an early stage. In the 5 years following diagnosis, all patients with late stage lung cancer died; however the patient with early stage lung cancer was still alive after undergoing chemotherapy. In those patients with both primary lung and primary bladder cancer, the cause of death was uniformly attributed to lung cancer. Thus, the authors suggest early detection of a primary lung malignancy in a patient with history of non-invasive bladder cancer may contribute to improved survival. People with a history of bladder cancer who otherwise meet all other NLST criteria are likely to benefit from a discussion of lung cancer screening and smoking cessation, if applicable.

Lymphoma

Hodgkin's lymphoma is associated with a significantly increased risk of treatment related lung cancer. According to American College of Radiology (ACR) recommendations within the first 5 years of follow up, the imaging goal is to detect lymphoma recurrence. After this time the focus shifts towards detecting complications of treatment. The current ACR recommendations state that after 5 years there is no longer a need for follow up imaging, although mammography and LDCT can be considered despite a lack of evidence of their benefit[73]. The incidence of lung cancer in patients with a history of Hodgkin's lymphoma is over 1% by 15 year follow up, with a relative risk of 4.62 (95%CI: 3.18-6.70)[74]. The risk is greater in patients diagnosed and treated for Hodgkin's lymphoma at an earlier age, especially 15-24.

Das *et al*[75] performed a cost-effectiveness estimate of annual lung cancer screening in patients with Hodgkin's lymphoma. Hypothetical patients for the model analysis were diagnosed with stage ⅠA-ⅡB Hodgkin's lymphoma at age 25, with screening starting 5 years after initial diagnosis. Annual CT screening was predicted to increase survival by 0.64 years for smokers and 0.16 years for non-smokers, with improvement in quality of life and cost effectiveness greater in the population of smokers with lymphoma. Wattson *et al*[76]

reported similar cost and survival benefits in smokers compared to non-smokers with Hodgkin's lymphoma. While non-smokers were predicted to experience a slightly improved survival and quality of life, LDCT scanning does not appear to be cost effective in this population.

In clinical practice it is unclear if this survival benefit of lung cancer screening is observed. Milano *et al*[77] examined overall survival in patients with Hodgkin's lymphoma diagnosed with NSCLC compared to controls diagnosed with only NSCLC. Lung cancer stage at diagnosis did not differ significantly between the groups. Despite this, Hodgkin's lymphoma survivors had a 30%-60% decrease in overall survival. This suggests that annual LDCT lung cancer screening may aid in identifying a second lung malignancy in this high-risk population, especially in current or heavy smokers. However, lung cancer screening may not provide as robust of a survival benefit in patients with a history of Hodgkin's lymphoma compared to the general population. There is currently a trial looking at lung cancer screening in people with a history of Hodgkin's lymphoma, which is expected to conclude by 2015[78]. Hopefully these results will define the benefit of lung cancer screening in this population.

Colorectal cancer

Low-dose CT may have a role in both colon cancer surveillance and screening for lung cancer. There have been many studies of postoperative surveillance programs following surgical resection of colon cancer. Aside from screening colonoscopy and CEA testing, there is little consensus opinion on the use of additional modalities that may detect colorectal cancer recurrence[79]. The purpose of these surveillance programs is to detect asymptomatic recurrences so intervention may occur at an earlier stage. A meta-analysis of 11 studies looking at intensity of surveillance determined that overall survival was significantly improved in patients who underwent more intense follow up (more frequent, additional imaging modalities). CT scanning of the pelvis and frequently the chest, lead to improved overall survival[80]. Thus, while not currently part of the surveillance guidelines, patients with a history of colorectal cancer would likely benefit from more frequent imaging of the chest.

Additionally, patients with colorectal cancer are more likely to be diagnosed with a primary lung cancer then the general population[81]. There is no difference between lung cancer incidence in patients with a history of colon or a history of rectal cancer[73]. A recent multicenter study in Japan examined whether a history of surgically resected colorectal cancer affected prognosis in patients diagnosed with lung cancer[34]. They compared 123 lung cancer patients with a history of colorectal cancer to 4431 controls with lung cancer alone. Patients with a history of colorectal cancer were more likely to be diagnosed at stage ⅠA, however there was no difference between the groups in overall survival

or lung cancer mortality. This relationship did not vary with colorectal cancer stage. Thus, a previous history of surgically resectable colon cancer does not portend an improved nor diminished overall survival in patients diagnosed with a primary lung malignancy. These patients may still benefit from LDCT screening similar to the general population, so long as they fulfill all other accepted criteria for lung cancer screening. As with the majority of the previous malignancies discussed, there is a great need for prospective studies to examine clinical disease features, treatment response, and overall survival in these patients after lung cancer is detected by screening exam.

CONCLUSION

NLST demonstrated a reduction of lung cancer mortality and all cause mortality with annual screening LDCT. With regard to lung cancer screening in people with previous cancer, there is no data, as most lung cancer screening trials have excluded this population. Implementation of LDCT in the general population has proven complicated as USPSTF, professional societies and CMS have published slightly different recommendations on this and other criteria. The potential benefit of diagnosing early stage lung cancer or treatable metastatic disease is at least compelling enough to justify future study. Future directions include defining which malignancies at which stage are likely to benefit. The type of screening (routine CT dose or low dose), the interval of screening, and when to initiate and end screening after previous cancer treatment remain unanswered questions.

Until randomized, controlled studies can direct recommendations on lung cancer screening for people with antecedent malignancy, clinicians will need to consider screening on an individual basis. To be eligible for lung cancer screening, patients with previous malignancy should at least fulfill other lung cancer screening eligibility criteria. The previous malignancy, like any comorbidity, "should not substantially limit life expectancy or the ability or willingness to have curative (lung cancer) surgery" as defined by USPSTF. The prediction of survival benefit of lung cancer treatment and metastatic cancer treatment should outweigh the risks of screening. Clinicians should have a detailed, personalized discussion about these survival benefits of annual LDCT, as wells as the risks of false positive, overdiagnosis, anxiety, radiation, and the possibility what we know from all existing data may be insufficient to guide any individual decision. As with all lung cancer screening LDCT, a shared decision making tool should be used to address the issues of lung cancer screening that matter most to the individual. As patients with previous malignancy present complex scenarios, screening should be done within a setting with access to multidisciplinary evaluation and treatment. Most importantly, lung cancer screening in the setting of previous malignancy should include a discussion of smoking cessation in active smokers and a discussion with previous smokers of

staying smoke free. Smoking cessation is critical in this population as these patients face the increased risk of recurrence, metastasis as well as lung cancer. When available, lung cancer screening of patients with previous malignancy should be done within a clinical trial.

In conclusion, though patients with previous malignancy have been excluded from lung cancer screening trials, they are a unique population that may enjoy a survival benefit from diagnosis of not only lung cancer, but of metastatic disease. Hopefully future clinical studies in this population will clarify the risks and benefits of lung cancer screening in the setting of antecedent malignancy.

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