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Resected Lung Cancer Patients Who Would and Would Not Have Met Screening Criteria

Farhood Farjah, MD MPH[1,2], **Douglas E. Wood, MD**[1], **Megan E. Zadworny, MHA**[2], **Valerie W. Rusch, MD FACS**[3], and **Nabil P. Rizk, MD MS**[3]

[1]University of Washington, Department of Surgery, Division of Cardiothoracic Surgery

[2]University of Washington, Department of Surgery, Surgical Outcomes Research Center

[3]Memorial Sloan Kettering Cancer Center, Department of Surgery, Thoracic Service

Abstract

Background—Current eligibility criteria for lung cancer screening may underestimate the risk of malignancy for some individuals. We compared the predicted risk of lung cancer among patients who would have met screening criteria to those who would not have despite being at moderate-risk.

Methods—A retrospective cohort study was performed of resected lung cancer patients. The screen eligible group was based on criteria provided by the United States Preventive Services Task Force—age 55–80 and a ≥30 pack-year smoking history. The screen ineligible group was based on criteria provided by the National Comprehensive Cancer Network for a moderate-risk individual not recommended screening—age >50 years, >20 pack-year smoking history, and no history of asbestos exposure or chronic obstructive pulmonary disease. A recently validated risk-prediction model was used to compare the risk of lung cancer across eligibility groups based on measured and imputed patient-level variables.

Results—Screen ineligible patients (n=88) had a lower estimated probability of lung cancer than screen eligible patients (n=419)—1.3% versus 3.1%, p<0.001. However, 20% of screen ineligible patients had a predicted probability of lung cancer greater than or equal to the prevalence of lung cancer (3.7%) among National Lung Screening Trial participants; 17% of screen ineligible patients had a predicted probability of lung cancer greater than or equal to the American Association for Thoracic Surgery threshold (5%) defining high-risk individuals.

Conclusions—Current eligibility criteria for lung cancer screening underestimate the risk of lung cancer for some individuals who might benefit from lung cancer screening.

Keywords

Lung cancer, diagnosis (incl staging, imaging, fiducials); Lung cancer surgery; Computed tomography, CAT scan; Practice guidelines (lung cancer)

Corresponding Author Farhood Farjah, MD MPH, University of Washington, Department of Surgery, Division of Cardiothoracic Surgery, 1959 NE Pacific St, Seattle, WA 98195, Phone: 206-685-7547, Fax: 206-543-0325, ffarjah@uw.edu.

Introduction

The National Lung Screening Trial (NSLT) demonstrated a significant reduction in lung cancer mortality attributable to screening high-risk individuals with low-dose computed tomography (LDCT) [1]. People eligible for study were 55 to 74 year old current or former smokers who quit within the last 15 years and had at least a 30 pack-year smoking history. In 2013, the United States Preventive Services Task Force (USPSTF) recommended screening of high-risk individuals as defined by NLST inclusion criteria, but extended the age range to 80 years based on modelled analyses of risks and benefits [2]. As a result, commercial insurers are required (by law) to fully cover the costs of LDCT screening for this high-risk population starting in 2015. The availability of lung cancer screening is one of the most significant advances in thoracic oncology in a generation. Yet most guidelines for screening, including the USPSTF, have limited themselves to the inclusion criteria of the NLST, which were developed in order to accomplish a randomized clinical trial and do not assert that they represent an exclusive risk profile for development of lung cancer. The NLST utilized only age and smoking exposure in order to simplify patient recruitment and did not study other known risk factors for lung cancer. Since it is unlikely that large randomized trials will assess other at-risk populations, it is important to consider whether there are opportunities to extend the benefits of early-detection to other high-risk individuals.

The current approach to determining screen eligibility omits other known risk-factors for lung cancer and imposes arbitrary bounds on age and tobacco exposure. In response to this criticism, investigators developed a risk-prediction model for lung cancer among smokers enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), and validated model performance in NLST participants [3]. One can use the publicly available prediction model to estimate the risk of lung cancer for a hypothetical individual under various assumptions about their risk profile. This exercise demonstrates that an individual can be ineligible for screening based on USPSTF criteria, but have a similar or even higher risk of lung cancer than NLST participants. Current eligibility criteria for screening may underestimate the risk of lung cancer for some individuals.

To provide empirical evidence of this concern, the goal of this investigation was to compare the predicted risk of lung cancer among operatively managed lung cancer patients who would and would not have met screening eligibility criteria. Screen eligibility was based on the USPSTF criteria. A meaningful comparator group would ideally consist of individuals at risk for lung cancer but not recommended screening. Accordingly, we identified a group based on criteria provided by the National Comprehensive Cancer Network (NCCN) for individuals at moderate risk not recommended to undergo screening [4].

Methods

A retrospective study was conducted of lung cancer patients treated with pulmonary resection between 1999 and 2008 with follow-up through 2012. Subjects included in this study were asymptomatic adults with solitary, primary lung cancer detected by computed tomography and meeting screen eligibility or ineligibility criteria as defined in the next

paragraph. The source of patient information was a single-institution surgical quality improvement database maintained by Memorial Sloan-Kettering Cancer Center. This database contains information on patient, cancer, and treatment characteristics; early post-operative events; and long-term survival available through a linkage with the Social Security Death Index. An institutional review board approved this investigation and waived the need for consent.

Patients considered screen eligible were 55 to 80 years of age and had a ≥ 30 pack-year smoking history. This group was based on eligibility criteria provided by the USPSTF. Former smokers in this database had information on number of years quit recorded as a categorical variable: 1–4 weeks, 1–6 months, 6–12 months, 1–5 years, 6–10 years, and ≥ 10 years. Since it was not possible to measure the number of years quit more granularly, the number of years quit was re-coded assuming the following: quit 1 year ago if quit 1–4 weeks, 1–6 months, or 6–12 months ago; quit 5 years ago if quit 1–5 years ago; quit 10 years ago if quite 6–10 years ago; and quit 15 years ago if quit > 10 years ago. Patients considered screen ineligible were ≥ 50 years of age, had a ≥ 20 pack-year smoking history, and no additional documented risk factor. Selection of this comparator group was based on criteria outlined by the NCCN for an individual at moderate risk for lung cancer but not recommended screening, yet excluding clearly low-risk patients that would not provide a legitimate comparison. Lung cancer risk factors routinely recorded in the database were a documented history of chronic obstructive pulmonary disease (COPD) and asbestos exposure. The screen eligible and ineligible groups were mutually exclusive. For instance, a 57 year old 32 pack-year current smoker was classified as screen eligible.

The primary aim of this study was to compare the predicted risk of lung cancer across eligibility groups using a validated prediction model [3]. Tammemägi and associates developed and validated a risk-prediction model among 80,375 patients enrolled in the PLCO trial based on the following variables: age, race, education, body mass index, COPD, personal history of cancer, family history of lung cancer, smoking status (current versus former), duration of smoking intensity, and smoking quit time. The performance of this model was validated in an independent cohort of individuals from the NLST. Published coefficients from this model were used to estimate the probability of lung cancer for each subject in our study based on his/her unique set of risk factors [3]. Variables recorded in our database and allowed to vary at the patient-level included age, race, smoking status, average number of cigarettes smoked per day, years smoked, and years quit. The database recorded pack-years of cigarette exposure. In order to use this information for risk-prediction—as specified by the model with two different variables for cigarette exposure—pack-years was disaggregated to cigarettes per day and years smoked under the assumption that all patients smoked one pack per day. Variables not recorded in the database were imputed and set to the same value for all patients as such: body mass index of 27, some college education, no personal history of malignancy, and no family history of lung cancer. In order to anchor risk estimates to an external reference, we calculated the proportion of patients with an estimated risk of lung cancer equal to or above several thresholds including 1) the prevalence of lung cancer among NLST participants [1], 2) the thresholds for detecting 80% and 90% of lung cancers as reported by the authors of the validated risk-prediction model [3], and 3) the threshold for a high-risk individual proposed by the American Association of Thoracic

Surgery (AATS) lung cancers [5]. STATA/SE 12.1 was used for all analyses (StataCorp LP, College Station, Texas). Median values were compared using the Kruskal-Wallis equality-of-populations rank test; categorical variables were compared using the Fisher's exact test; and survival rates were compared using Kaplan-Meier methods and a log-rank test. Confidence intervals [CI] for binary variables were estimated using binomial exact methods. P-values <0.05 were considered significant.

Results

Compared to screen eligible patients, screen ineligible patients were more frequently women, had fewer pack-years of tobacco exposure, were less likely to have cardiac comorbid conditions, and had higher median predicted DLCO levels (Table 1). The distribution of screen eligible and ineligible patients did not change over time (p=0.585).

As expected, the median predicted probability of lung cancer was significantly lower among screen ineligible versus screen eligible patients (1.3% [range 0.3–14%] versus 3.1% [range 0.7–15%], p<0.001). The distributions of the predicted probability lung cancer by eligibility status are shown in Figure 1. Among patients in the screen ineligible group, 20% (95% CI 13–30%) had a similar or higher predicted risk of lung cancer than the prevalence of lung cancer (3.7%) among NLST participants [1] (Table 2). Using published thresholds for detecting 80% and 90% of lung cancers using the risk-prediction model [3], 43% (95% CI 33–54%) and 68% (95% CI 57–78%) of screen ineligible patients, respectively, would have been considered high-risk. Finally, using the probability cut-off recommended by the AATS for defining a high-risk patient (≥5%), 17% (95% CI 7–25%) of individuals would have been considered high-risk.

There were no significant differences across eligibility groups in terms of clinical or pathologic stage (Table 3). There was a significant difference in the distribution of histologic types of lung cancer. Compared to screen eligible patients, carcinoid tumors were more common (5.7% versus 0.7%, p=0.005) and squamous cell carcinomas were less common (6.8% versus 19%, p=0.004) in the screen ineligible group.

Discussion

The goal of this study was to better understand the relationship between eligibility criteria for lung cancer screening and an individual's predicted risk of lung cancer. We provide evidence that a significant proportion of individuals who would have been considered ineligible for screening were in fact at high-risk for developing lung cancer.

Several lines of evidence suggest that there is substantial concern about using NLST inclusion criteria to determine screen eligibility. The previously validated risk-prediction model adopted by our study was motivated by concerns over omitted predictors of lung cancer and arbitrary bounds for age and tobacco exposure [3]. Similarly, modelled analyses of the risks and benefits of lung cancer screening were motivated by a desire to understand alternative screen eligibility criteria [9]. This modelled analysis, initiated by the USPSTF, demonstrated benefit up to age 80 years and was intended to inform the decision to recommend for or against screening—a decision that has resulted in a legal obligation

among commercial insurers to fully cover the costs of LDCT. In addition to the USPSTF decision to provide a B recommendation for screening patients age 55–80 with a 30 pack-year smoking history [2], the Society of Thoracic Surgeons advocated strongly that the USPSTF should consider even broader screen eligibility criteria [10]. Several professional organizations—including the NCCN and AATS—have provided recommendations for expanding lung cancer screening criteria above and beyond both the NLST inclusion criteria and USPSTF recommendations [4–5]. It is evident that many are concerned that current policy may restrict access to the benefits of early-detection.

Findings from our study lend strength to these concerns by demonstrating that many individuals at substantial risk of lung cancer may not currently be eligible for screening. What constitutes “substantial” is in the eye of the beholder, and therefore we used several external references to anchor our understanding of risk, including the prevalence of lung cancer among NLST participants [1], risk thresholds expected to identify upwards of 80–90% of lung cancer patients [3], and a threshold for high-risk recommended by the AATS [5]. Beyond demonstrating that some individuals ineligible for screening are in fact at substantial risk for lung cancer, our findings also challenge the NCCN’s approach to risk stratification [4]. The screen ineligible patients in our study were defined using NCCN’s criteria for moderate-risk individuals, and yet a substantial proportion of patients would be considered high-risk across several thresholds. The AATS recommended a threshold for high-risk patients, but could not advocate for the use of a risk-prediction model because the validation study for that model was published one year later after the AATS guidelines [3, 5]. Practice guideline organizations that recommend expanded criteria for lung cancer screening should consider recommending the use of a risk-prediction model to guide selection *and* define a threshold that confers the status “high-risk.”

One finding from this study that may raise concern is the higher prevalence of carcinoid tumors in the screen ineligible group. Importantly, the higher frequency of carcinoid in our study reflects how we group patients rather than the effect of a screening intervention. Some may erroneously conclude that a higher prevalence of carcinoid tumors is synonymous with overdiagnosis. A secondary analysis of the NLST suggests that overdiagnosis might occur in up to 18% of people undergoing LDCT [12]. However, this study did not directly evaluate overdiagnosis; rather, it measured excess cases of lung cancer attributable to screening. Overdiagnosis is defined as the detection of cancer that, in the absence of treatment, would not be expected to impact a person’s life-expectancy or health-related quality of life. Approximately 6–8% of NLST participants diagnosed with lung cancer did not receive any treatment, but the reasons for not undergoing treatment have not been described. Accordingly, one cannot evaluate overdiagnosis using NLST data. Regardless, although carcinoid tumors tend to have a better prognosis than other histologic types of NSCLC, the current standard of care is to treat carcinoid tumors rather than observe them.

An important limitation of this study is that it was restricted to patients diagnosed incidentally with a diagnostic CT and treated for lung cancer. Accordingly, we cannot conclude that there are benefits of using a prediction model to guide the selection of at-risk individuals to undergo LDCT screening. Furthermore, we cannot identify an optimal threshold of risk that maximizes the benefits and risks of lung cancer screening. It is

erroneous to assume that patients with similar predicted probabilities of lung cancer would derive equal benefit. Consider two individuals with a predicted risk of lung cancer of 3.7%, but one is highly functional without comorbid conditions and the other is in a wheelchair, requires supplemental oxygen, and is on dialysis. The latter would not be expected to benefit from screening because he or she would be unlikely to receive curative-intent treatment and/or may have a limited life-expectancy independent of a lung cancer diagnosis. We also cannot conclude that risk-prediction would have resulted in early-detection of disease among our patients, because an overwhelming majority presented with early-stage disease in the absence of a screening intervention. There are also concerns that use of a risk-prediction model may be associated with increased risks of radiation exposure and invasive diagnostic tests; however, these concerns are not supported by any available evidence. When validating the risk-prediction model, investigators demonstrated that the prediction model in fact had a higher sensitivity and positive predictive value than NLST criteria without loss of specificity or an estimated decrement in benefit [3]. To the extent that use of a prediction model increases the number of individuals eligible for screening, the number of people exposed to radiation and potentially invasive diagnostics will increase. However, their diagnostic-related risks would be unaltered or even lower because of the superior diagnostic accuracy of the prediction model. Another limitation of our study is the use of a common data point to impute missing values for variables included in the prediction model. We used this simple approach to highlight the limitation of current screening criteria. Had lung cancer screening and a prediction model actually been used in clinical practice during the study, a better approach to handling missing data would have been to use multiple-imputation.

Investigating the short-comings of the current approach to determining screen eligibility is extraordinarily challenging for several reasons. There are no population-based registries of smokers that routinely measure lung cancer risk factors with longitudinal follow-up on cancer occurrence, healthcare utilization, and outcomes. Administrative data lack sufficient detail about lung cancer risk factors (e.g. tobacco exposure) to be useful. The Cancer Research Network (CRN)—a National Cancer Institute funded network of integrated health systems—links longitudinal administrative data, cancer registry data, and electronic medical records, and therefore holds the greatest promise as a population-based source of information for at-risk individuals [13]. Registries such as these can be used to evaluate the incidence of cancer, the frequency of diagnostic tests and related complications, and survival. Accordingly, these registries may also be used to explore the risks and benefits of using risk-prediction to select individuals to undergo screening. However, the feasibility of measuring lung cancer risk factors retrospectively within the CRN is uncertain and currently under investigation [14]. The development of prospective registries for the purposes of quality assurance could be used to study expanded eligibility criteria for lung cancer screening. However, creation of these registries must be thoughtful and at least include all current and former smokers and systematically measure tobacco-related and other risk-factors for lung cancer. The Center for Medicare and Medicaid Services has proposed mandatory registry participation for institutions seeking reimbursement for lung cancer screening among Medicare beneficiaries [15]. A perusal of the data elements of this proposed registry reveal that it is limited because the registry would only identify and follow individuals who strictly adhere to NLST inclusion criteria. Finally, defining a risk-threshold

to trigger screening will likely be controversial and is probably best approached through multi-stakeholder engagement. The optimal cut-point would ideally maximize the benefits (i.e. early-detection and cure) and risks (i.e. radiation exposure, invasive diagnostic tests, anxiety) of screening. These examples highlight the challenges and opportunities of evaluating screen eligibility in the general population.

In summary, there is great interest in using prediction models to improve cancer care [15]. The current approach to determining lung cancer screen eligibility may deny some high-risk individuals an opportunity to reap the benefits of early-detection and cure. Further studies are needed to understand the benefits and risks of using risk-prediction to determine screen eligibility. Practice guidelines and policy-makers who currently endorse expanded screen eligibility criteria should consider recommending the use of a risk-prediction model and define a threshold for what constitutes a high-risk individual.

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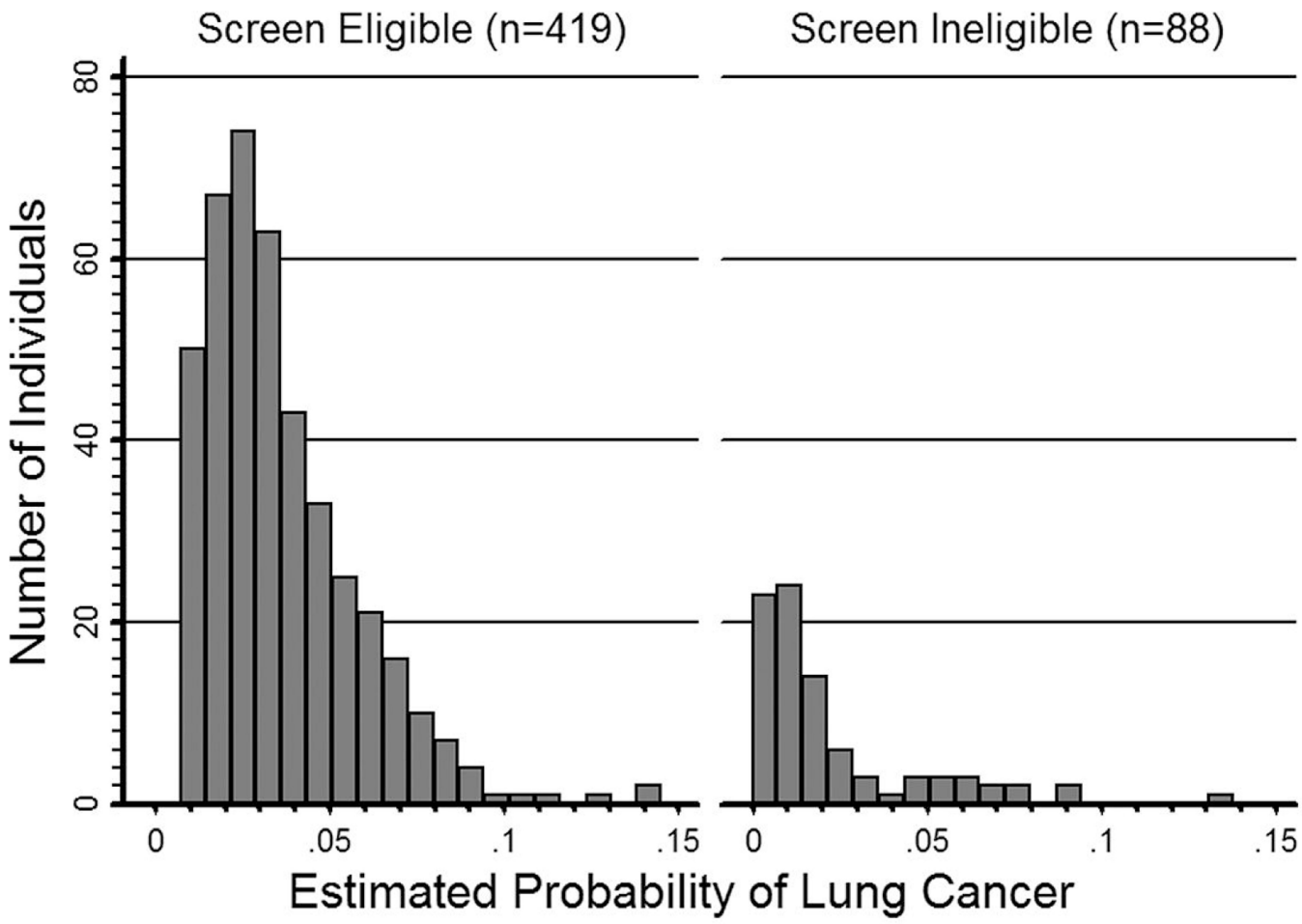

Figure 1.
Distributions of the Predicted Probabilities of Lung Cancer by Screening Eligibility Group

Table 1

Cohort characteristics

	Screen Eligible n=419	Screen Ineligible n=88	p-value
Median age, years [range]	70 [55–80]	69 [50–89]	0.3951
Men	51%	36%	0.019
Race			0.224
White	97%	94%	
Black	2.4%	5.7%	
Other	0.7%	0.0%	
Median pack-years, [range]	55 [30–250]	25 [20–100]	<0.001
Time Since Quit			0.164
0 (current smokers)	17%	16%	
1 year	18%	10%	
5 years	14%	10%	
10 years	9.3%	8.1%	
15 years	41%	55%	
Comorbid conditions			
Cardiac	60%	48%	0.043
Renal	2.9%	3.4%	0.732
Endocrine	13%	8.0%	0.212
Nodule detected through screening	26%	23%	0.421
DLCO, % predicted [range]	73 [31–135]	85 [27–154]	<0.001
Complications	26%	22%	0.420
Operative mortality	0.9%	0.0%	1.000
5-year overall survival [95% CI]	49% [43–55%]	47% [34–61%]	0.859

Confidence interval (CI), diffusion capacity of carbon monoxide (DLCO)

Table 2

Variation in Predicted Risk of Lung Cancer across Screen Eligibility Groups

	Screen Eligible n=419	Screen Ineligible n=88	p-value
Median predicted probability of lung cancer	3.1%	1.3%	<0.001
Proportion with an estimated probability of lung cancer equal to or higher than the:			
Prevalence of lung cancer in NLST participants (≥3.7%)	39%	20%	0.001
AATS threshold for high-risk individuals (≥5%)	22%	17%	0.319
Threshold to detect 80% of lung cancers (≥1.6%)	85%	43%	<0.001
Threshold to detect 90% of lung cancers (≥0.9%)	96%	68%	<0.001

* Lung cancer risk was estimated [3] allowing measured risk factors (age, race, tobacco exposure) to vary at the patient-level while holding imputed unmeasured risk factors constant across all subjects (assume body mass index=27, some college education, no personal history of malignancy, and no family history of lung cancer).

National Lung Screening Trial (NLST), American Association for Thoracic Surgery (AATS)

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Table 3

Cancer Characteristics by Eligibility Groups

	Screen Eligible n=419	Screen Ineligible n=88	p-value
Clinical Stage			0.976
IA	66%	70%	
IB	11%	8.0%	
IIA	6.0%	5.7%	
IIB	2.4%	3.4%	
IIIA	11%	10%	
IIIB	1.7%	1.1%	
IV	1.4%	1.1%	
Pathologic Stage			0.942
0	1.0%	1.1%	
IA	53%	53%	
IB	14%	13%	
IIA	8.8%	8.0%	
IIB	2.6%	2.3%	
IIIA	13%	16%	
IIIB	4.8%	2.3%	
IV	3.1%	4.6%	
Histology			0.003
Adenocarcinoma	70%	76%	
BAC	1.4%	1.1%	
Squamous	19%	6.8%	
NSCLC NOS/Large cell	2.6%	3.4%	
Carcinoid	0.7%	5.7%	
Small cell	2.4%	1.1%	
No tumor identified	1.4%	1.1%	
Other	1.9%	5.7%	

Bronchioalveolar carcinoma (BAC); non-small cell lung cancer (NSCLC); not-otherwise-specified (NOS)