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Follow-up of incidental pulmonary nodules and association with mortality in a safety-net cohort

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Abstract

Background: Though incidental pulmonary nodules are common, rates of guideline-recommended surveillance and associations between surveillance and mortality are unclear.

Objective: Describe adherence (categorized as complete, partial, late and none) to guideline-recommended surveillance among patients with incidental 5 to 8 millimeter pulmonary nodules and assess associations between adherence and mortality.

Methods: Retrospective cohort study of 551 patients (≥35 years) with incidental pulmonary nodules conducted from September 1, 2008 to December 31, 2016, in an integrated safety-net health network.

Results: Of the 551 patients, 156 (28%) had complete, 87 (16%) had partial, 93 (17%) had late and 215 (39%) had no documented surveillance. Patients were followed for a median of 5.2 years (interquartile range, 3.6 to 6.7 years) and 82 (15%) died during follow-up. Adjusted all-cause mortality rates ranged from 2.24 (95% CI, 1.24 to 3.25) deaths per 100 person-years for complete follow-up to 3.30 (95% CI, 2.36 to 4.23) for no follow-up. In multivariable models, there were no statistically significant associations between levels of surveillance and mortality (p>0.16 for each

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comparison with complete surveillance). Compared with complete surveillance, adjusted mortality rates were non-significantly increased by 0.45 deaths per 100 person-years (95% CI, −1.10 to 2.01) for partial, 0.55 (95% CI −1.08 to 2.17) for late and 1.05 (95% CI −0.35 to 2.45) for no surveillance.

Conclusions: Although guideline-recommended surveillance of small incidental pulmonary nodules was incomplete or absent in most patients, gaps in surveillance were not associated with statistically significant increases in mortality in a safety-net population.

Keywords

adherence; ambulatory care; care management; guidelines; underserved populations; diagnosis

INTRODUCTION:

Incidental pulmonary nodules are an increasingly common finding in clinical practice with estimates of 1.5 million new cases each year in the United States.(1) Fleischner Society guidelines recommend longitudinal non-urgent radiographic surveillance for indeterminate pulmonary nodules to document stability and identify and accurately diagnose nodules which may harbor malignancy.(2, 3) Surveillance can extend up to two years, depending on nodule size and patient characteristics. While revised guidelines(3) published in 2017 recommend less aggressive surveillance of pulmonary nodules, prior and more aggressive Fleischner guidelines(2) were the standard for clinical practice from 2005 through 2017. Though most incidental nodules are benign, failure to provide appropriate and timely longitudinal follow-up can lead to delayed cancer diagnoses, poor patient outcomes and costly malpractice claims.(4, 5)

Incidental pulmonary nodules present unique barriers to longitudinal evaluation and care coordination. By definition, these nodules are detected on radiographic imaging ordered for unrelated reasons such as evaluation of trauma or pulmonary embolism.(6–8) It follows that incidental nodules are often discovered in acute care hospital settings where the physician ordering the study is unlikely to be the physician following up incidental findings once the patient leaves the hospital. Responsibility for longitudinal surveillance generally falls on the primary care physician, and prior studies demonstrate that communication of test results is often inadequate during the transition from acute to outpatient settings.(9–11)

The few studies(6, 12) that have assessed the adequacy of guideline-adherent nodule surveillance in usual care settings demonstrate highly variable results, and little is known about levels of adherence to Fleischner guidelines or associations between adherence and patient outcomes such as mortality, where earlier detection and treatment of lung cancer could potentially have an impact. In addition, rates of adherence in safety-net health systems, where patients may be at higher risk for lung cancer compared with the general population due to higher smoking rates, are unclear. Patient characteristics such as limited English proficiency and health literacy, which are more prevalent among patients cared for in safety-net settings, and limited institutional resources may further complicate longitudinal care. Thus, we aimed to evaluate levels and rates of adherence to guideline-recommended

surveillance and associations between guideline adherence and mortality in a safety-net cohort of patients with incidental pulmonary nodules.

SUBJECTS AND METHODS:

Study design

We performed a retrospective cohort study of patients with indeterminate incidental pulmonary nodules. We queried our health system's radiology database to identify eligible patients and reviewed medical records to collect patient and clinical data. The University of California, San Francisco Institutional Review Board reviewed and approved this study (15–18436).

Setting

The study took place within a publicly-funded, urban, integrated health network which includes the largest safety-net hospital in San Francisco, serving approximately 106,000 patients annually, with nearly 600,000 outpatient visits. The patient population is predominately publicly insured or uninsured and racially and ethnically diverse with the majority of patients being Hispanic, Asian, and non-Hispanic African-American. Patients cared for in the San Francisco Health Network (SFHN) experience a higher prevalence of homelessness, psychiatric comorbidity, and smoking compared to the general state population.(13)

Participants

We included adults age 35 years and older with 5 to 8 millimeter pulmonary nodules discovered incidentally between September 1, 2008 and December 31, 2014 for whom guidelines recommend longitudinal CT surveillance. We chose 2008 as the initial time point because the hospital had recently installed new CT scanners and it provides a 3-year buffer period for dissemination of recommendations following publication of Fleischner guidelines for nodule surveillance in 2005. We assessed adherence to the 2005 guidelines(2) as opposed to more recent guidelines(3) because the 2005 guidelines were applicable during the study period. The 2005 Fleischner guidelines recommend follow-up CT scans within at least 1 year for all patients with nodules of this size. We chose the age cutoff to match guideline criteria and the end time point to allow for at least 2 years of follow-up. We excluded patients with smaller nodules (4 millimeters or less) that would not necessarily require follow-up and larger nodules (greater than 8 millimeters) that would likely trigger immediate referral for advanced studies such as positron-emission tomography (PET) scans and biopsies based on guideline recommendations. We excluded patients with a history of active or previous cancer for whom guidelines would not apply, patients who died within 3 months of the index CT scan, and patients without any primary care, specialty care, or non-trauma emergency department visits with the health system within 24 months after the index scan. We aimed to evaluate surveillance for patients engaged with the health system who would represent true missed opportunities for appropriate follow-up. To our knowledge, no systematic interventions to track, communicate or improve pulmonary nodule surveillance were implemented or in effect during the study period, and no standard institutional guidelines for radiologists' reporting of recommended surveillance existed.

To identify eligible patients, we searched all CT radiology reports within the Radiology Information System database for the keyword “nodule” using Microsoft SQL Server Reporting Services software. We developed a natural language processing tool in Python as an initial screen to identify nodule size and to exclude non-pulmonary nodules and CT scans performed for malignancy staging. We performed medical chart review of the remaining patients to confirm eligibility.

Data collection

We queried the electronic health record to obtain structured patient data including sex, race/ethnicity, and primary language. We developed an abstraction protocol and standardized data collection form using REDCap (version 8) and performed chart review to capture patient (history of smoking, homelessness and psychiatric comorbidity) and nodule (size, upper lobe location, consistency, reason for exam) characteristics, and nodule evaluation including CT scans, PET scans and biopsies. We abstracted radiology recommendations for surveillance and reviewed primary care notes following the index scan, when available, abstracting medical decision making to not pursue recommended follow-up. We abstracted nodule evaluation until reaching one of the following endpoints: 1) nodule stability as defined by Fleischner guidelines or radiology recommendation that no further follow-up was needed; 2) diagnosis of lung or other cancer; 3) patient death or lost to follow-up from the health system; or 4) documentation of a decision to not pursue follow-up. Five trained researchers performed medical record abstraction. Two researchers abstracted each record until they reached inter-rater agreement of 0.88, measured by Cohen’s Kappa coefficient. Discrepancies in coding were resolved by consensus among senior study investigators. We excluded patients who were found to meet previously defined exclusion criteria during medical record review.

Categorization of nodule surveillance

We categorized patients as high risk if they were current or former smokers. We treated ground glass nodules as solid nodules because the 2005 Fleischner guidelines do not give a specific recommendation for duration of follow-up for sub-solid nodules. We defined evaluation as “complete” if all recommended CT/PET scans or biopsies were completed, timely, and a nodule stability or cancer diagnosis endpoint was reached. We defined scans as timely if they occurred within 3 months of recommended follow-up at 6–12 months and within 2 months for recommended follow-up at 3–6 months to allow for scheduling and other delays encountered in usual care, similar to definitions used by previous studies.(6, 14) We defined evaluation as “partial” if the first follow-up scan was completed and timely but any subsequent recommended evaluation was not completed or not timely. We defined evaluation as “late” if the first follow-up scan was completed but was not timely regardless of subsequent evaluation. We categorized patients who had no surveillance evaluation as “none.”

Patient outcomes

We abstracted cancer diagnoses and death from the medical record. To account for patients lost to follow-up or no longer cared for in the SFHN, we supplemented our analysis using

mortality and cause of death data through 2016 from the National Center for Health Statistics' National Death Index.

Statistical analysis

We used multiple imputation by iterative chained equations to impute missing data.(15) Using the resulting 20 completed datasets, we used logistic and multinomial models to compare baseline patient characteristics across follow-up categories, combining results according to Rubin's rules.(16) In addition, for each category, we calculated unadjusted mortality rates per 100 person-years, then used a Poisson model,(17) with the log time from the index scan until death or the end of 2016 as an offset, to estimate adjusted between-category mortality rate ratios, controlling for patient and nodule characteristics. Regression standardization was then used to obtain marginal adjusted rates and rate differences, based on the Poisson model. In two sensitivity analyses, we first repeated the assessment of between-category differences using Cox models, to check sensitivity to the Poisson assumption of a constant baseline mortality rate, and then repeated the Poisson analysis using observed complete-case data. For both sensitivity analyses, results were similar to the primary multiple imputation analysis and are not reported. We performed all statistical analyses using Stata 15.1 (StataCorp, LLC, College Station, Texas). Two-sided P values <.05 were considered statistically significant.

RESULTS:

Study population and nodule surveillance

Our natural language processing algorithm identified 1365 patients with possible pulmonary nodules detected on CT scans during the study period. We excluded 666 patients after initial review, primarily related to nodule size and patients who were not engaged in care within 24 months of the index scan (Figure 1). We conducted complete medical record review of the remaining 699 patients and excluded 148 for a final cohort of 551 patients with 5 to 8 millimeter pulmonary nodules requiring follow-up. We categorized 156 (28%) patients as complete, 87 (16%) as partial, 93 (17%) as late and 215 (39%) as no surveillance.

Overall, the mean age was 59 years (SD 11), 58% of patients were male and over half (58%) were non-Hispanic African-American, Hispanic or Asian (Table 1). Most patients (66%) were current or former smokers. Over one-quarter (27%) of patients had a history of homelessness, 40% had a history of substance abuse and 34% had a history of psychiatric illness. Nearly three-quarters of nodules (72%) were 5 to 6 millimeters in size and 39% were located in upper lobes of the lung. Nearly two-thirds of patients (61%) had multiple nodules on index CT scans.

The average number of surveillance CT scans was 2.2 for complete, 3.1 for partial and 1.8 for late follow-up groups. For patients with complete surveillance, 2 (1%) were diagnosed with lung cancer during follow-up. Among those with less than complete surveillance, 7 (2%) were diagnosed with lung cancer during follow up. For patients with partial surveillance, the vast majority (85, 98%) completed two or more surveillance scans while only 2 (2%) patients had no further surveillance after the first follow-up scan. For patients

with late surveillance, 51% with 5 to 6 millimeter nodules had a delay of at least 24 months (vs guideline recommended 6 to 12 months for high or low risk), 67% of low-risk patients with 7 to 8 millimeter nodules had a delay of at least 24 months (guideline recommended 6 to 12 months), and 82% of high-risk patients with 7 to 8 millimeter nodules had a delay of at least 12 months (guideline recommended 3 to 6 months) between the index and first surveillance scan.

Association between nodule follow-up and mortality

In multivariable regression models, there were no statistically significant associations between levels of surveillance and mortality ($p>0.16$ for each comparison with complete surveillance). Adjusted mortality rate ratios were non-significantly elevated for partial (adjusted rate ratio [ARR] 1.20; 95% CI, 0.64 to 2.25), late (ARR 1.24; 95% CI, 0.65 to 2.36) and no (ARR 1.47; 95% CI, 0.86 to 2.52) surveillance when compared with complete surveillance (Table 2). Nodule size of 7–8 millimeter (vs 5–6 millimeter) was associated with greater mortality (ARR 2.19; 95% CI, 1.51 to 3.20).

Mortality rates and differences by nodule follow-up

Patients were followed for a median of 5.2 years (interquartile range, 3.6 to 6.7 years) and 82 (15%) died during follow-up. There were few deaths attributed specifically to lung cancer (1 in each surveillance group) based on chart review and National Death Index cause of death data. Adjusted all-cause mortality rates were similar to unadjusted rates and ranged from 2.24 (95% CI, 1.24 to 3.25) deaths per 100 person-years for complete follow-up to 3.30 (95% CI, 2.36 to 4.23) deaths per 100 person-years for no follow-up (Table 3). Compared with complete surveillance, adjusted mortality rates were non-significantly increased by 0.45 deaths per 100 person-years (95% CI, −1.10 to 2.01) for partial, 0.55 (95% CI −1.08 to 2.17) for late and 1.05 (95% CI −0.35 to 2.45) for no surveillance.

DISCUSSION:

In this study of 551 patients with incidental 5 to 8 millimeter pulmonary nodules, we found significant gaps in recommended surveillance with only 28% of patients completing all follow-up and 39% with no documented follow-up. However, gaps in surveillance were not associated with statistically significant differences in mortality in this safety-net population. Stated another way, complete adherence to guidelines was not associated with reduced mortality. To our knowledge, this is one of few studies of usual care settings to assess the completeness of adherence to pulmonary nodule guidelines and the only study to assess associations between adherence and mortality.

Our finding of large gaps in pulmonary nodule surveillance is consistent with existing studies evaluating follow-up for patients in usual care settings. In two single-center studies, only 29% and 48% of patients completed at least one recommended surveillance scan.(6, 12) However, neither of these studies assessed surveillance up to nodule stability or diagnosis of lung cancer. A study conducted within the Veterans' Administration health system found that 92% of patients underwent some degree of nodule surveillance with 11% of patients undergoing surveillance across multiple facilities.(18) These impressive follow-up rates may

not be generalizable to other usual care settings, such as in this study, that lack a standard electronic health record accessible by any facility within the integrated health system.

Despite a high proportion of patients with incomplete or no surveillance, we found no associations between the completeness of surveillance and mortality. One likely explanation for this discrepancy is that deaths from lung cancer were outweighed by deaths from other causes. Amongst patients in our study with complete follow-up, only 1% were diagnosed with lung cancer, a lower proportion than other studies evaluating nodules 5 to 8 millimeters in size.(5, 18, 19) Larger nodule size, which is associated with increased lung cancer risk, was also associated with increased mortality in our study. However, few deaths in any group were attributed to lung cancer. It is possible that the level of surveillance may be associated with reduced mortality amongst patients diagnosed with lung cancer due to earlier detection but we were not able to assess this. A longer duration of follow-up may also be required to detect associations between nodule surveillance and mortality. The National Lung Screening Trial(20) followed high-risk patients for a median of 6.5 years to demonstrate reduced lung cancer and all-cause mortality compared with a median follow-up of 5.2 years in our study.

Our study has important implications for patients, clinicians and health systems. First, though validation of the 2005 Fleischner guidelines was not our primary objective, our findings support a less aggressive approach to surveillance of pulmonary nodules 5 to 8 millimeters in size than recommended by these guidelines given the demonstrated lack of association between follow-up and mortality. Accordingly, the 2017 Fleischner guidelines recommend no routine surveillance for nodules less than 6 millimeters in size and less aggressive surveillance of high-risk patients with 7 to 8 millimeter pulmonary nodules. Prospective studies are needed to validate the impact of these updated guidelines on patient outcomes. Second, while the 2017 Fleischner guidelines are likely to significantly reduce the burden of recommended surveillance CT scans for patients and clinicians, adherence to new guidelines is still likely to be poor in usual care settings unless effective tracking and notification systems are established.(21, 22) These systems will be increasingly important to monitor guideline concordance as the United States Preventive Services Task Force recommendation for lung cancer screening(23) and the newer Fleischner guidelines, which allow clinicians' greater freedom and discretion in determining the need for surveillance, are integrated into clinical practice. Achieving high levels of adherence will also require understanding challenges that clinicians face when managing abnormal results(24–26) and improving communication of subcritical results requiring follow-up during transitions of care.(10, 27) Third, the uncertainties regarding the impact of adherence to Fleischner guidelines on significant patient outcomes emphasize the importance of shared decision-making between patient and clinician regarding the risks and benefits of nodule evaluation.(28, 29) Educational strategies to increase clinician knowledge and improve communication skills may support shared-decision making conversations and improve adherence.(30–32) Finally, our study demonstrates the importance of measuring guideline adherence and its impact on patient outcomes in real-world settings to validate practice guidelines, consistent with research mandates for pulmonary nodules from the American Thoracic Society.(33) This type of observational research is relevant across a spectrum of common findings with guideline-recommended surveillance and variable clinical significance such as adrenal

incidentalomas and abnormal cervical cancer screening results and has the potential to change the intensity of guideline recommendations for surveillance.(34, 35)

Our study has limitations. First, the low proportion of incident lung cancer diagnoses limits our ability to detect differences in all-cause and lung cancer related mortality between follow-up groups. Second, findings in a safety-net population may not be generalizable to other populations given the patient diversity and high prevalence of comorbid homelessness, substance abuse and psychiatric illness. Third, we cannot account for any follow-up testing that was done at outside facilities, which could alter our estimates of follow-up completeness. Fourth, we could not fully ascertain diagnoses of lung cancer in patients with incomplete surveillance. Finally, inadequate documentation of clinical reasons for not pursuing follow-up such as multiple comorbidities may have led to residual confounding in our observational study.

In conclusion, adherence to guideline-recommended surveillance of incidental pulmonary nodules was incomplete or completely lacking in most patients but was not associated with mortality in a safety-net population. Further study is needed to identify strategies to improve adherence to and to demonstrate empirical evidence for the effectiveness of pulmonary nodule guidelines.

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List of abbreviations:

CT	computed tomography
NLP	natural language processing
PET	positron-emission tomography
SFHN	San Francisco Health Network
SD	standard deviation

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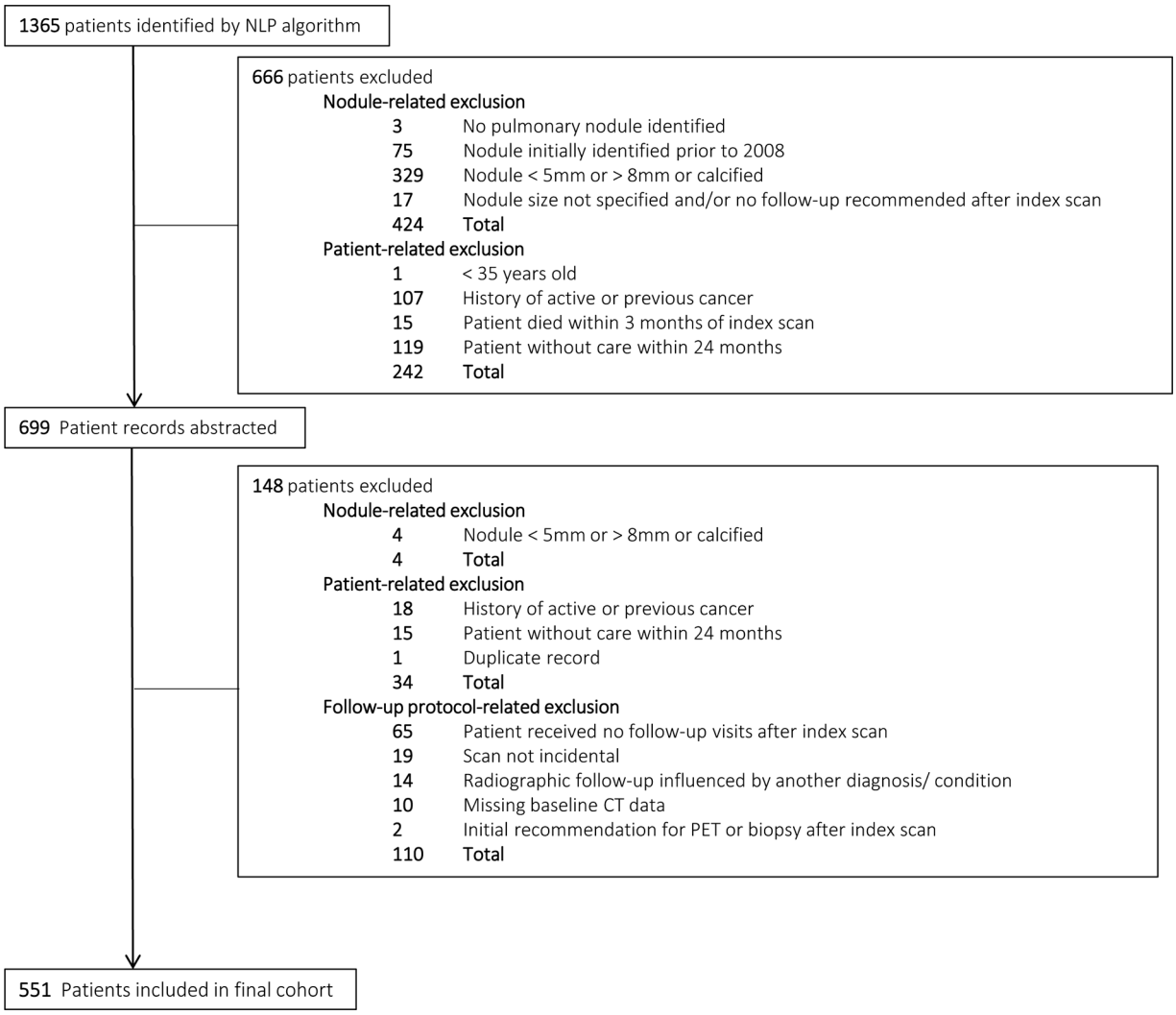

Figure 1. Patient identification and selection

NLP = natural language processing

Table 1.

Characteristics of patients and baseline incidental pulmonary nodules stratified by level of surveillance[a]

	Level of surveillance[b]				
Patient characteristic	**Complete N=156**	**Partial N=87**	**Late N=93**	**None N=215**	**P-value**
Demographics					
Age, y, mean (SD)	60 (9)	56 (11)	57 (9)	59 (13)	0.02
Male, %	51	60	62	61	0.17
Race and ethnicity, %					0.63
White, non-Hispanic	27	30	25	27	
Black, non-Hispanic	20	25	29	24	
Hispanic	6	1	2	5	
Asian	33	30	24	31	
Other[c]	14	14	20	14	
History of homelessness, %	21	22	34	30	0.13
Smoking history, %					0.16
Never smoker	38	31	25	36	
Former smoker	26	29	20	25	
Current smoker	36	40	55	39	
History of substance abuse, %	33	39	50	42	0.09
History of psychiatric illness, %					0.22
None	69	58	62	70	
Anxiety or depression	24	35	28	20	
Schizophrenia	7	8	10	10	
Nodule Characteristic					
Nodule size, millimeters, %					0.16
5–6	72	63	79	72	
7–8	28	37	22	28	
Upper lobe location, %	39	39	37	41	0.93
Ground glass, %	5	5	2	2	0.56
Multiple nodules, %	69	66	63	52	0.005
Reason for initial chest CT, %					<0.001
Pulmonary embolism evaluation	7	15	14	10	
Trauma	1	2	7	15	
Concern for infection	7	14	15	12	
Weight loss	6	1	1	1	
Chest pain	5	6	8	9	
General shortness of breath	6	8	9	10	
Nodule seen on other imaging	47	33	20	23	

Patient characteristic	Level of surveillance[b] Complete N=156	Partial N=87	Late N=93	None N=215	P-value
Chronic obstructive pulmonary disease	5	6	3	2	
Concern for aortic aneurysm or dissection	3	4	9	5	
Other	13	12	15	12	

CT, computed tomography; SD, standard deviation.

[a]Group totals may not sum to 100% due to imputation and rounding. Data were missing from the complete 551 patient cohort and imputed for the following variables, reported as missing n (%): male 7 (1), race/ethnicity 13 (2), smoking history 113 (21), homelessness history 119 (22), substance abuse history 104 (19), ground glass nodule 7 (1).

[b]We defined surveillance as “complete” if all recommended testing was completed and timely, “partial” if the first follow-up CT scan was completed and timely but any subsequent recommended evaluation was not completed or not timely, “late” if the first follow-up scan was completed but was not timely regardless of subsequent evaluation, and “none” if patients had no follow-up evaluation. We defined scans as timely if they occurred within 2 or 3 months of the recommended follow-up time period depending on the specific time period.

[c]Other race and ethnicity consisted of patients whose race was reported as Native American or Alaskan Native.

Table 2.

Adjusted all-cause mortality rate ratios by level of adherence and patient and nodule characteristics[a]

Level of surveillance[b]	Adjusted mortality rate ratio (95% CI)
Complete	Reference
Partial	1.20 (0.64–2.25)
Late	1.24 (0.65–2.36)
None	1.47 (0.86–2.52)
Patient characteristic	
Age, per 10 years	1.37 (1.16–1.62)
Male	1.13 (0.71–1.81)
Race and ethnicity	
White, non-Hispanic	Reference
Black, non-Hispanic	1.23 (0.79–1.92)
Hispanic	1.71 (0.89–3.28)
Asian	0.48 (0.23–1.02)
Other[c]	0.54 (0.23–1.24)
History of homelessness	0.80 (0.48–1.34)
Smoking history	
Never smoker	Reference
Former smoker	1.57 (0.69–3.56)
Current smoker	1.58 (0.74–3.33)
History of substance abuse	1.33 (0.77–2.30)
History of psychiatric illness	
None	Reference
Anxiety or depression	1.38 (0.86–2.21)
Schizophrenia	1.50 (0.74–3.02)
Nodule Characteristic	
Nodule size, millimeters	
5–6	Reference
7–8	2.19 (1.51–3.20)
Upper lobe location	1.21 (0.82–1.80)
Ground glass	1.64 (0.65–4.16)
Multiple nodules	0.85 (0.57–1.28)

[a]Adjusted rate ratios were calculated using Poisson models adjusted for patient (age, sex, race/ethnicity, and history of smoking, substance abuse, and psychiatric illness) and nodule (size, upper lobe location, ground glass and multiple) characteristics.

[b]We defined surveillance as “complete” if all recommended testing was completed and timely, “partial” if the first follow-up CT scan was completed and timely but any subsequent recommended evaluation was not completed or not timely, “late” if the first follow-up scan was completed but was not timely regardless of subsequent evaluation, and “none” if patients had no follow-up evaluation. We defined scans as timely if they occurred within 2 or 3 months of the recommended follow-up time period depending on the specific time period.

[c]Other race and ethnicity consisted of patients whose race was reported as Native American or Alaskan Native.

Table 3.

Unadjusted and adjusted all-cause mortality rates by level of surveillance

	Mortality rate per 100 person-years (95% CI)		
Level of surveillance[a]	**Unadjusted**	**Adjusted**[†]	**Adjusted Difference**[†]
Complete	2.22 (1.23–3.21)	2.24 (1.24–3.25)	Reference
Partial	2.84 (1.56–4.11)	2.70 (1.50–3.89)	0.45 (−1.10–2.01)
Late	2.64 (1.39–3.90)	2.79 (1.52–4.06)	0.55 (−1.08–2.18)
None	3.50 (2.48–4.51)	3.30 (2.36–4.23)	1.05 (−0.35–2.45)

[a]We defined surveillance as “complete” if all recommended testing was completed and timely, “partial” if the first follow-up CT scan was completed and timely but any subsequent recommended evaluation was not completed or not timely, “late” if the first follow-up scan was completed but was not timely regardless of subsequent evaluation, and “none” if patients had no follow-up evaluation. We defined scans as timely if they occurred within 2 or 3 months of the recommended follow-up time period depending on the specific time period.

[†]Mortality rates were adjusted for patient (age, sex, race/ethnicity, and history of smoking, substance abuse, and psychiatric illness) and nodule (size, upper lobe location, ground glass and multiple) characteristics. Adjusted difference is the difference between mortality rates in comparison to the complete surveillance group.