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More Frequent Surveillance Following Lung Cancer Resection is Not Associated with Improved Survival: A Nationally Representative Cohort Study

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INTRODUCTION

There are 13.7 million Americans currently living with a history of cancer. With continued improvements in cancer treatment and increasing life expectancy, this number is expected to reach nearly 18 million within the next decade.[1] The care of these cancer patients, including surveillance during the post-treatment survivorship phase, is an increasingly important major health care concern and expenditure.[2] As the fourth leading diagnosis among cancer survivors, non-small cell lung cancer (NSCLC) is a chronic problem that affects 450,000 Americans and is expected to grow 20% by 2022.[3]

Clinicians follow patients after NSCLC resection to: detect loco-regional or distant recurrence; detect a second primary lung cancer; monitor for treatment toxicities of adjuvant therapy; and manage patient anxiety and fear of recurrence.[4] Although imaging is a common component of surveillance, clinical practice guidelines for surveillance imaging are inconsistent. The American College of Chest Physicians, The International Association for the Study of Lung Cancer, and the National Comprehensive Cancer Network (NCCN) each

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recommend different surveillance intensities and imaging modalities ranging from 3-month to annual surveillance with chest-x-ray (CXR) or computed tomography (CT). [5–7] Importantly, the NCCN describes their recommendation as category 2A, indicating there is consensus that the intervention is appropriate but based on lower-level evidence. This issue extends beyond surveillance to the larger topic of cancer screening. While some screening studies have compared different screening tests for their accuracy, little is known about the optimal intervals at which to screen patients for a variety of cancers.[6]

Because there is a paucity of high quality data on NSCLC surveillance, practice guidelines are based on small retrospective analyses and expert opinion.[5,7] This results in wide variation in practice including both underuse and overuse of surveillance services.[5] This study utilizes a unique dataset of patients who received surgery for NSCLC and is the result of a Commission on Cancer (CoC) special study that augmented data from the National Cancer Database (NCDB). Our primary objective is to determine the association between surveillance intensity (3-month, 6-month, annual) with overall survival. A secondary outcome is the association between surveillance intensity and survival following recurrence.

METHODS

Data Source and Patient Population

The CoC assembled a unique database through a special study mechanism as part of a quality improvement effort to better document comorbidity and cancer recurrence within the NCDB. The NCDB is a joint program of the American College of Surgeons and the American Cancer Society that captures approximately 70% of newly diagnosed cancer cases in the US from more than 1,500 CoC-accredited hospitals.[8,9]

Up to 10 eligible patients were randomly selected from each CoC-accredited facility for further data abstraction. Eligibility criteria included: surgery for stage I-III NSCLC (1/2006–12/2007), available medical records, and complete resection with negative margins. Patients with unknown recurrence status were excluded without replacement. To ensure a minimum of 5 years available follow-up, patients were followed through 12/2012 or until first diagnosis of recurrence, new primary cancer, or death.

Registry staff abstracted complete information on perioperative comorbidity, post-operative imaging and its indication, first lung cancer recurrence, and diagnosis of new primary cancer. Because patients may have received care at multiple facilities, registry staff also obtained records from outside the facility where initial data entry occurred. Weekly webinars educated registrars and standardized the abstraction process. The newly abstracted data were merged with corresponding NCDB records, deidentified, and transferred to our study team. Because data were deidentified, this study was exempted from IRB review. These efforts provide a unique dataset that allows evaluation of NSCLC surveillance practices for detection and treatment of recurrence within a representative nationwide cohort.

Surveillance Intensity Groupings

We used imaging history and surveillance indication data to place patients surveilled with CT-scans into 3 surveillance intensity groups: 3-month, 6-month, and annual, which

correspond to the major guideline recommendations.[5–7] Although patients can be prescribed specific follow-up intervals, real-world adherence is irregular. In addition, multiple providers (e.g. surgeon, oncologist, and primary care) may follow a patient, and may change surveillance after negative imaging following new patient reported symptoms or suspicious but inconclusive findings. Therefore, we believe that the time to first post-operative CT-surveillance imaging best captured surveillance intensity relative to current recommendations. Because most patients receive an initial post-operative follow-up approximately 30 days after surgery, patients whose first surveillance scan occurred >2.5 and <5 months post-surgery were placed in the 3-month surveillance group; if the first scan occurred ≥5 and <9 months they were placed in the 6-month surveillance group; and if the first scan occurred ≥9 and <14 months they were placed in the annual surveillance group. Registrars also recorded their confidence in obtaining the available imaging records (0–100%).

Analytic Methods

The primary objective was to assess the association between surveillance intensity and post-operative overall survival. Patients' survival was then compared across follow-up groups using Cox proportional hazards survival models controlling for age, sex, comorbidities, histology, pathological stage, and surgical procedure.

The impetus for increased surveillance intensity is the hope that earlier detection can lead to improved post-recurrence outcomes. Therefore, we also evaluated the association between surveillance intensity and survival following recurrence in the subset of patients who recurred. We assessed this relationship between survival and the time between recurrence diagnosis and the most recent preceding surveillance using a Cox proportional hazards regression with time since the most recent surveillance CT scan as a covariate. Times were trimmed to a maximum of 14 months, with an additional greater than 14-month indicator variable used to model patients receiving less than annual surveillance. We controlled for the patient and disease characteristics included in the post-resection survival model as well as symptomatic detection and loco-regional vs. distant site of recurrence.

All regression models used weighted and clustered survey analysis procedures, accounting for random patient sampling within CoC facilities, making results representative of the NCDB population. Proportional hazards models were stratified by pathologic stage.

There is a selection bias when grouping patients into the 3-month/6-month/annual surveillance categories. For surveillance intensity to be apparent, a patient scheduled for 6-month surveillance must remain cancer free through their first scheduled appointment, roughly 7 months post-surgery (assuming the first screening occurs 6 months after a 30 day post-operative assessment). However, another patient whose physician recommended 3-month surveillance must only stay healthy for roughly 4 months. To reduce this bias, when comparing the 3-month, 6-month, and annual surveillance groups, we restricted the study population to only those patients who remained disease free through 14 months post-surgery. When comparing the 3- and 6-month cohorts, we restricted to only those patients who remained disease free through 9 months post-surgery. Both analyses are included to

maximize the power of the comparison between the 3- and 6-month cohorts, while also incorporating a comparison with the annual surveillance cohort.

As an alternate approach to controlling for this selection bias, we considered multiple imputation to impute surveillance times when patients recurred, developed a new primary cancer, or were lost to follow-up before surveillance was observed. For this approach, surveillance times were imputed based on patient stage, time to recurrence/new primary cancer/loss to follow-up, and the empirical distribution of surveillance times for patients who stayed healthy through 14 months.

Missing Data

NCDB data were remarkably complete. Four percent of patients were missing chemotherapy and/or radiation treatment information. Registrars were also unable to document comorbidities for 4% of patients. These were handled by including separate “not documented” indicator variables in the regression models. One patient with unknown sex was removed.

All data cleaning and statistical analyses were performed in R (version 3.4.3) using the survival (v. 2.41–3) and survey(v. 3.32–1) packages.

RESULTS

The special study captured data for 9,668 patients. 28 of these patients were coded as having macroscopic residual tumor, and therefore did not meet inclusion criteria. 27 patients who had cancer recurrence coded after death were also excluded. Among the remaining 9,613 patients, over the 5-year follow-up period, 12% developed loco-regional recurrence, 21% developed distant recurrence, and 11% developed new primary cancers. The median time to recurrence was 15.7 months and median post-recurrence survival ranged between 3.0 and 19.9 months depending on whether the recurrence was distant or loco-regional and on whether the patient received active treatment or only supportive care.[10] Overall 5-year post-surgery survival was 64% for stage I patients, 46% for stage II patients, and 36% for stage III patients, although these estimates are somewhat upwards biased because selected patients were alive and cancer free 90 days post-surgery.

Of the 9,613 patients, 5,150 were not followed with CT (Figure 1). Because CT has been shown to be superior to CXR for lung cancer screening and is increasingly being used as the imaging method of choice in post-surgical surveillance,[11] our study focuses on the remaining 4,463 patients from 1,066 hospitals. 1,614 of these patients were placed in the 3-month surveillance group, 1,999 in the 6-month group, and 850 in the annual group (Figure 2).

Patient demographics are shown in Table 1, overall and split by surveillance group. Comorbidities affecting >5% of the cohort were included. Patients are similar across the 3 groups by age, sex, race, comorbidities, histology, and surgical procedure. Higher stage patients tend to receive more frequent surveillance ($p < 0.001$). The 3-month and 6-month surveillance groups were most common (36% and 45%), while annual surveillance was less

frequent (19%). Registrar confidence in imaging availability was high across all 3 groups (median 100, IQR: 90–100 in each group).

There were 3,552 patients alive and cancer free 14 months post-surgery. 11.0% of these patients developed a new primary cancer and 23.8% experienced a recurrence over the remainder of the follow up period; these rates were consistent across surveillance groups (p = 0.49). In this cohort, using Cox regression, more frequent surveillance was not associated with longer survival; the hazard ratio (HR) for 6-month follow-up relative to 3-month was 1.16 (95% CI: 0.99–1.36) while the HR for annual surveillance was 1.06 (CI: 0.86–1.31) (Table 2). While building the model, we performed standard regression diagnostics and observed that pathologic stage violated the proportional hazards assumption. Stage was therefore included as a stratification factor, which allows the model to control for stage, but without estimating a corresponding hazard ratio. Hence, stage does not appear in Tables 2 or 3.

In a parallel regression comparing the 3,165 patients in the 3-month and 6-month surveillance groups who were alive and cancer free 9 months post-surgery, more frequent surveillance also showed no survival benefit; the HR for 6-month relative to 3-month was 1.12 (CI: 0.98–1.29; p-value 0.09) (Table 3). In this cohort, 10.6% of patients developed a new primary cancer, while 28.9% experienced a recurrence; these rates were consistent between the 3- and 6-month groups (p=0.80).

The regression using all data and imputed surveillance times for patients who recurred, developed new primary cancers, or were lost to follow-up in the first 14 months post-surgery also showed no difference between surveillance groups (p-value 0.45). The HR for 6-month surveillance relative to 3-month was 1.08 (CI: 0.95–1.22) while the HR for annual surveillance relative to 3-month was 1.10 (CI: 0.93, 1.32).

Table 4 shows the association between time since last surveillance and survival following recurrence among the 1,056 patients with documented recurrence diagnosis dates. More recent pre-recurrence imaging was not associated with post-recurrence survival (HR: 1.02/month since imaging; CI: 0.99–1.04), and patients who had gone more than 14 months without imaging were at no greater risk of death (HR: 1.01; CI: 0.62–1.65), (overall p-value: 0.43). Symptomatic recurrence was associated with worse survival (HR: 1.49; CI: 1.20–1.85; p-value: < 0.01). Other factors associated with decreased survival include: distant recurrence (vs. loco-regional), age, male sex, histology, and certain comorbidities.

DISCUSSION

Post-treatment surveillance was identified as a high priority topic by the Institute of Medicine, which included cancer surveillance among their top 25 priorities for comparative effectiveness research.[2] Our study, including 4,463 patients surveilled with CT, and with 5-year follow-up on all patients, demonstrates that more frequent surveillance was not associated with improved overall survival or post-recurrence survival.

While there are several studies comparing types of post-operative surveillance,[12–14] there is only one recent systematic review and meta-analysis comparing surveillance intensity and

survival for patients with lung cancer.[7] The analysis included eight small retrospective studies and one small prospective trial with a combined total of 1,669 patients. Surveillance programs were heterogeneous and survival was not statistically associated with surveillance intensity. Importantly, the authors cautioned that better evidence was needed to confirm these findings. The current study used a much larger unique data set that explicitly captured the indication for each post-operative chest imaging study. With these data on imaging indications, our study differentiates between routine surveillance, imaging for new symptoms, and imaging unrelated to cancer.

Surveillance recommendations need to be considered in the context of potential harms and benefits to patients and their caregivers. Follow-up imaging and office visits increase cost and can lead to patient anxiety.[15] While it seems intuitive that earlier detection of asymptomatic recurrence could improve outcomes, patients with recurrent NSCLC do very poorly. This cohort had 5-year post-recurrence survival between 2.0% and 11.6% depending on whether the recurrence was distant or loco-regional and whether the patient received additional treatment.[10] Poor survival following recurrence helps explain why more intense surveillance following surgical resection was not associated with improvement in overall survival. However, after decades of limited progress for treating recurrence and metastatic disease, systemic therapy[16] and targeted agents[17] are demonstrating clinically significant survival benefits for small patient subgroups, which, in the future, may augment the benefits of early recurrence detection.

Another benefit of post-treatment surveillance is the identification of new primary lung cancers. Lung cancer survivors are the highest risk group for developing a second primary lung cancer (incidence of 2–4% per year).[5,18,19] The survival of this subgroup approaches 70% at 5 years, and guidelines recommend following these patients with at least annual CT scans.[5,20] Our patient cohort had a 10% incidence of developing a second primary cancer, and 48% of these were classified and treated as metachronous lung cancers.

This retrospective, observational study has several limitations. First, patients do not consistently adhere to surveillance recommendations. However, we believe our data are reflective of typical patient care. In a recent SEER-Medicare study, only 61% of patients received guideline-adherent surveillance during the initial 2 years after treatment.[21] Another limitation is that surveillance patterns are only apparent after patients have been followed for some time. While we believe our patient selection criteria, described in detail in the methods section, adequately controlled for the resulting biases, some patients were omitted from our analyses. In addition, the special study was performed in 2014–15 on patients who underwent surgical resection in 2006 and 2007. These years were selected because there is a lag in the NCDB data, they facilitated complete 5-year follow-up required for our primary aim, and then additional time is required to clean and analyze the data. Although these resections occurred ten years ago, there have been no systematic changes in lung cancer surveillance over the past decade. Finally, 1.1% of patients were lost to follow-up within 3 years and 5.8% were lost within 5 years. Unfortunately, no prospective trial has been funded to examine whether increased surveillance intensity improves survival. However, an ongoing French surveillance study is prospectively comparing the effectiveness of CXR vs. CT for NSCLC surveillance.[13]

Survival following surgical resection for NSCLC is dependent on a variety of patient and tumor related factors.[1,22] Historically, five-year survival for the earliest stage of lung cancer, stage IA, was only 70%. However, increased use of CT scanning has resulted in a decrease in the median tumor size of resected NSCLC and a shift toward earlier stage disease.[23,24] A longitudinal NSCLC screening study demonstrated that 10-year survival for stage I patients who underwent surgical resection was 92%.[25] The National Lung Screening Trial prospectively evaluated annual low dose screening CT scans and demonstrated a 20% reduction in mortality from lung cancer.[11] This enormous improvement in survival for NSCLC patients provides great promise for the future and is likely to increase the volume of lung cancer resections performed and the number of lung cancer survivors needing routine surveillance. [3] In the absence of similar prospective studies specifically focused on NSCLC surveillance following resection, we believe these results justify the use of CT scanning over CXR. Our data, combined with the results of the National Lung Screening Trial, suggest that at least annual surveillance is appropriate but that there is no benefit to more than biannual surveillance.

In conclusion, this study used a large cohort of patients who had surgical resection of their NSCLC and then underwent routine post-surgical surveillance. The study performed by the CoC allowed for accurate documentation of cancer recurrence, medical comorbidities, 5-year survival, and the indication and results of all surveillance imaging performed. Our results demonstrate that more frequent surveillance imaging was not associated with improved overall survival or post-recurrence survival.

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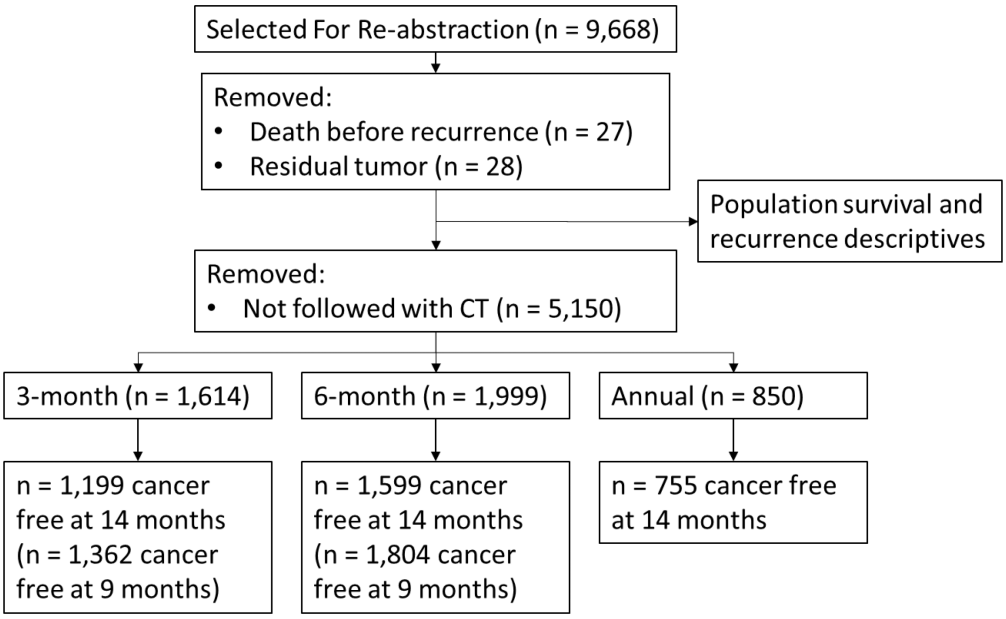

Figure 1:

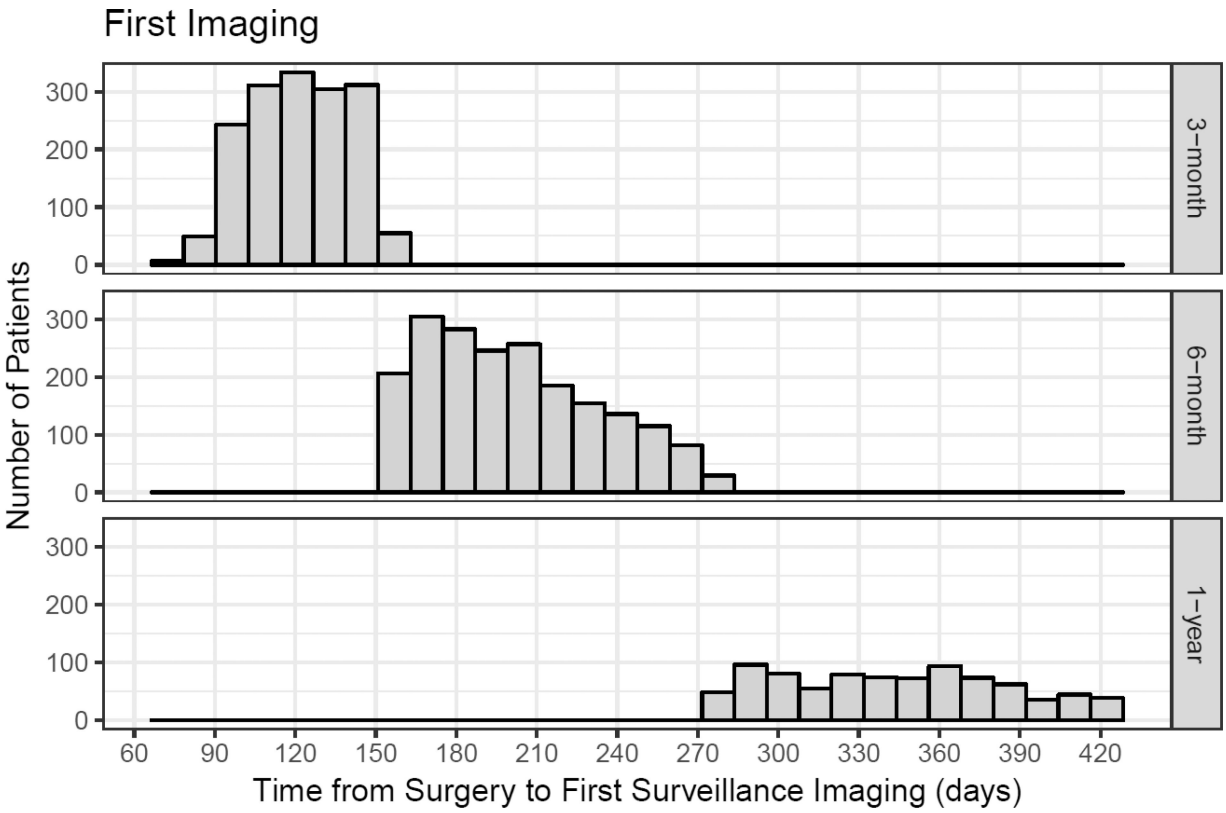

Figure 2:
Time from surgery to first surveillance imaging by surveillance intensity group.

Table 1:

Patient Demographics overall and for the 3 surveillance groupings, presented as n (%) for categorical variables and Median (IQR) for continuous variables.

	All patients	3-month	6-month	1-year	p-value
n	4,463	1,614	1,999	850	
Age (SD)	65.7 (9.9)	65.4 (9.8)	65.7 (10.0)	66.2 (9.7)	0.138
Sex (male)	2,147 (48.1%)	761 (47.2%)	971 (48.6%)	415 (48.8%)	0.636
Chronic obstructive pulmonary disease	1,788 (41.1%)	648 (41.1%)	771 (39.7%)	369 (44.2%)	0.081
Congestive heart failure	233 (5.4%)	90 (5.7%)	104 (5.4%)	39 (4.7%)	0.560
Coronary artery disease	927 (21.3%)	307 (19.5%)	425 (21.9%)	195 (23.4%)	0.061
Diabetes	682 (15.7%)	262 (16.6%)	301 (15.5%)	119 (14.3%)	0.302
Peripheral vascular disease	364 (8.4%)	125 (7.9%)	156 (8.0%)	83 (10.0%)	0.182
Psychiatric	363 (8.3%)	148 (9.4%)	149 (7.7%)	66 (7.9%)	0.162
Substance abuse	242 (5.6%)	86 (5.5%)	105 (5.4%)	51 (6.1%)	0.737
Biopsies	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,1)	0.248
Registrar confidence in imaging availability	100 (90,100)	100 (90,100)	100 (90,100)	100 (90,100)	0.373
Race					
White	3,973 (89.0%)	1,435 (88.9%)	1,776 (88.8%)	762 (89.6%)	0.961
Black	354 (7.9%)	131 (8.1%)	159 (8.0%)	64 (7.5%)	
Other	136 (3.0%)	48 (3.0%)	64 (3.2%)	24 (2.8%)	
Pathologic Stage					
I	2,889 (64.7%)	978 (60.6%)	1,300 (65.0%)	611 (71.9%)	< 0.001
II	875 (19.6%)	337 (20.9%)	398 (19.9%)	140 (16.5%)	
III	699 (15.7%)	299 (18.5%)	301 (15.1%)	99 (11.6%)	
Histology					
Adenocarcinoma	2,570 (57.6%)	932 (57.7%)	1,163 (58.2%)	475 (55.9%)	0.557
Squamous	1,329 (29.8%)	469 (29.1%)	588 (29.4%)	272 (32.0%)	
Other	564 (12.6%)	213 (13.2%)	248 (12.4%)	103 (12.1%)	
Surgical procedure					
Lobectomy	3,594 (80.5%)	1,306 (80.9%)	1,593 (79.7%)	695 (81.8%)	0.683
Pneumonectomy	271 (6.1%)	98 (6.1%)	127 (6.4%)	46 (5.4%)	
Segmentectomy	104 (2.3%)	38 (2.4%)	52 (2.6%)	14 (1.6%)	
Wedge resection	494 (11.1%)	172 (10.7%)	227 (11.4%)	95 (11.2%)	

Table 2:

Cox proportional hazards model for post-operative survival by surveillance intensity adjusted for patient and treatment characteristics.

	HR (95% CI)	p-value
Surveillance group: 3-month	(reference)	0.135
6-month	1.16 (0.99, 1.36)	
1-year	1.06 (0.86, 1.31)	
Histology: Adenocarcinoma	(reference)	0.809
Squamous histology	1.03 (0.88, 1.19)	
Other histology	0.95 (0.75, 1.20)	
Surgery: Lobectomy	(reference)	0.122
Pneumonectomy	0.93 (0.65, 1.33)	
Segmentectomy	1.40 (0.93, 2.13)	
Wedge resection	1.20 (0.99, 1.44)	
Any chemotherapy	0.93 (0.78, 1.11)	0.697
Any radiation	1.29 (1.01, 1.65)	0.043
Age (per decade)	1.26 (1.15, 1.39)	0.000
Sex: Male	(reference)	0.026
Female	0.85 (0.74, 0.98)	
Chronic obstructive pulmonary disease	1.24 (1.05, 1.47)	0.012
Congestive heart failure	1.78 (1.35, 2.33)	0.000
Coronary artery disease	1.03 (0.88, 1.21)	0.715
Diabetes	1.15 (0.96, 1.38)	0.122
Peripheral vascular disease	1.31 (1.04, 1.64)	0.023
Psychiatric	1.25 (0.98, 1.60)	0.067
Substance abuse	1.47 (1.13, 1.91)	0.004

Table 3:

Post-surgery survival by surveillance intensity in patients alive and disease free 9 months post-surgery.

	HR (95% CI)	p-value
Surveillance group: 3-month	(reference)	0.091
6-month	1.12 (0.98, 1.29)	
Histology: Adenocarcinoma	(reference)	0.991
Squamous	0.99 (0.86, 1.14)	
Other histology	1.00 (0.80, 1.26)	
Surgery: Lobectomy	(reference)	0.010
Pneumonectomy	0.95 (0.70, 1.30)	
Segmentectomy	1.39 (0.86, 2.26)	
Wedge resection	1.34 (1.12, 1.60)	
Any chemotherapy	1.01 (0.86, 1.20)	0.976
Any radiation	1.39 (1.11, 1.72)	< 0.001
Age (per decade)	1.23 (1.12, 1.36)	< 0.001
Sex: Male	(reference)	0.011
Female	0.84 (0.73, 0.96)	
Chronic obstructive pulmonary disease	1.17 (1.00, 1.37)	0.054
Congestive heart failure	1.50 (1.14, 1.97)	0.003
Coronary artery disease	1.11 (0.94, 1.31)	0.215
Diabetes	1.07 (0.90, 1.29)	0.435
Peripheral vascular disease	1.37 (1.09, 1.72)	0.007
Psychiatric	1.20 (0.95, 1.51)	0.133
Substance abuse	1.32 (1.03, 1.70)	0.029

Table 4:

Proportional hazards model for post-recurrence survival based on time since most recent previous surveillance.

	HR (95% CI)	p-value
Time since last surveillance (per month)	1.02 (0.99, 1.04)	0.432
≥ 14 months since last surveillance	1.01 (0.62, 1.65)	
Recurrence: Distant	(reference)	0.020
Local	0.78 (0.64, 0.96)	
Detection: Asymptomatic		< 0.001
Symptomatic	1.49 (1.20, 1.85)	
Age (per decade)	1.17 (1.08, 1.27)	< 0.001
Sex: Male		0.001
Female	0.76 (0.64, 0.89)	
Histology: Adenocarcinoma		0.023
Squamous	1.29 (1.05, 1.60)	
Other histology	1.20 (0.96, 1.49)	
Surgery: Lobectomy		0.837
Pneumonectomy	0.85 (0.58, 1.23)	
Segmentectomy	1.01 (0.66, 1.55)	
Wedge resection	1.04 (0.80, 1.35)	
Chronic obstructive pulmonary disease	1.04 (0.85, 1.28)	0.684
Congestive heart failure	1.47 (1.13, 1.92)	0.004
Coronary artery disease	0.80 (0.64, 0.98)	0.034
Diabetes	1.17 (0.91, 1.51)	0.229
Peripheral vascular disease	1.49 (1.16, 1.91)	0.002
Psychiatric	0.99 (0.74, 1.33)	0.963
Substance abuse	1.36 (0.96, 1.94)	0.083