Original Article

Differences in optimal timing of post-surgical surveillance for limited stage lung cancer patients and associations with outcomes

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Background: Guidelines for post-operative surveillance for non-small cell lung cancer (NSCLC) are variable. Historically, providers have used a one-size fits all approach, such that surveillance guidelines incorporated few important prognostic indicators for recurrence and survival. The goal of this study was to determine optimal timing for detection of recurrence by CT scan and the association between surveillance CT and overall survival.

Methods: This was a retrospective, single institution series of patients undergoing surgical resection [2008–2012] with stage I or II disease (AJCC 7th edition) with at least 6 months of follow-up.

Results: Recurrence occurred in 27.2% of patients at a median of 29.5 months following surgery. Recurrences peaked at 2–3 years following surgery for the entire cohort. For those detected on CT scan surveillance, stage I the peak timing for recurrence was at 25–36 months (year 3) whereas stage II peak timing was at 19–24 months (year 2) following resection. Timing of recurrences detected by any means differed significantly based on cancer stage with 81% (n=27) of recurrences occurring more than 24 months following surgery for stage I patients compared to 41% (n=17) of stage II patients (P<0.01). Overall, higher rates of surveillance CT scans were associated with a reduced risk of death [HR 0.14 (95% CI, 0.06–0.36) P<0.01].

Conclusions: The timing of recurrence differs significantly based on stage such that few stage I patients have recurrences within 2 years following surgical resection. Additionally, rates of recurrence detected by surveillance CT scans performed less than 24 months following surgery is significantly lower for stage I patients compared to stage 2 which would favor delaying routine surveillance in this select group. Optimal timing of CT surveillance based on peak recurrence rates has the potential to eliminate unnecessary testing and expense for healthcare systems.

Keywords: Non-small cell lung cancer (NSCLC); surveillance; outcomes; CT scan

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Introduction

Lung cancer is the second most common cancer in both men and women, with estimates of over 230,000 new cases expected in 2018 (American Cancer Society). Of the cases of lung cancer in the US, 85% are non-small cell lung cancer (NSCLC). The standard of care for early stage lung cancer is surgery, however, the guidelines for post-operative surveillance is variable. Historically, surgeons have been using a one-size fits all approach, such that there is little incorporation of important prognostic indicators for recurrence and survival reflected in the current surveillance guidelines.

Rice *et al.* reported that for all patients who have undergone resection for NSCLC the risk for a second primary lung cancer is 1–4% per patient-year (1). Therefore follow-up of these patients is important, but also begs the question on the best way to follow them. In 2013 Mollberg and Ferguson published a review on the topic of post-resection surveillance and called for a more patient centered algorithm for surveillance after resection (2).

Most recent National Comprehensive Cancer Network (NCCN) guidelines have recommended scans to be performed every 6 months for 2 to 3 years then annually thereafter. This is a more intense surveillance regimen than that suggested by the recent findings of the Intergroupe Francophone de Cancerologie Thoracique (IFCT-0302) Trial which was a randomized controlled study comparing an intensive surveillance CT regimen to follow-up with routine clinic visits and chest X-ray alone (3). There was no difference in overall survival comparing regimens and the authors suggested that CT scans done every 6 months are not useful at all for early stage patients within the first 2 years following surgery.

Our study examined patient follow-up CT scans, the timing in which the scans occurred, and when documented recurrences where detected in order to help determine optimal timing for detection of recurrence by CT scan. We also sought to determine whether there was an association between timing of CT surveillance and overall survival.

Methods

The Institutional Review Board of Stanford University approved this study. The study design was a retrospective review of patients who underwent surgical resection for lung cancer at Stanford Hospital between the years 2008–2012. Data was pulled from our institutional Society of Thoracic Surgeons (STS) Thoracic Surgery Database. A total of 272 patients were identified. Chart review from our own electronic medical record was used for data collection. We excluded patients stage III and above (n=39), those who had histology other than adenocarcinoma and squamous (n=38), and patients with less than six months of follow-up from the time of surgery (n=33). The final study population consisted of 162 patients (*Figure 1*). All patients were staged according to the AJCC 7th edition lung cancer staging.

Our primary outcome was recurrence and secondary outcome was receipt of CT scan reviewed at Stanford during the surveillance period. We reviewed all imaging and progress notes for the primary clinical endpoints. Adhering to NCCN guidelines for lung cancer management, recommended chest CT surveillance was defined as receipt of CT scan at 180–210 days (month 6) following date of surgical resection. Chest CT every six months for first-two years following surgery and once a year thereafter were used as the standard follow-up guidelines. Each CT scan was further coded by the indication for the study and study findings. If a lesion was documented in the patient's chart as recurrence by either the treating oncologist or thoracic surgeon, then it was deemed a recurrence in our data set. CT-detected recurrence was defined either as a new radiographic finding on CT scan in conjunction with biopsy confirmation or documentation by the patient's medical oncologist as definite recurrence. Clinical recurrence was defined as any documented recurrence whether or not it was detected by CT scan or other means. Other recurrences were either detected by imaging being performed for symptoms, non-lung cancer related reasons such as trauma, or recurrences noted clinically by the cancer center registrar for which there was no accompanying surveillance imaging test.

Statistics

Continuous data were compared as mean and standard deviation, median and inter quartile range (IQR), and categorical variables as frequency and percentage. Tests of Normality of the continuous data was performed using Kolmogorov-Smirnov test. Patient demographics were compared using independent-sample *t*-test and ANOVA test for continuous variables and Pearson's Chi-square test for categorical variables. Time to event analyses was performed using Kaplan-Meier method and the differences were tested using log-rank test. Independent predictors of risk of recurrences and death risk were estimated using cox

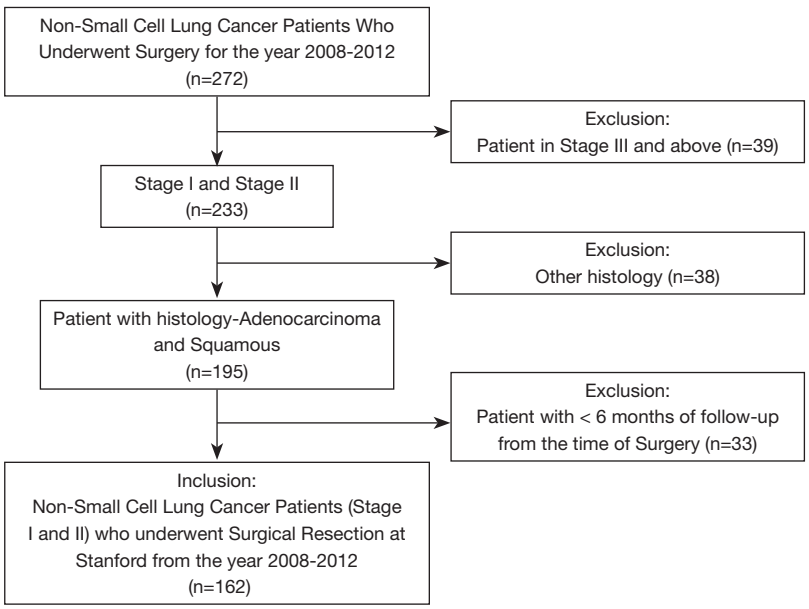


Figure 1 Study population—inclusion/exclusion criteria.

proportional hazard model. A probability (P) value of <0.05 was considered to be statistically significant. Statistical analyses were completed using SAS® Enterprise Guide (EG) 7.1 (SAS Institute, Cary, NC, USA) and IBM SPSS Statistics 24.

Results

The cohort consisted of 80% stage I and 20% stage II patients with median follow-up 57 months (IQR 24.75) (*Table 1*). Adherence to guideline recommended surveillance ranged from 61–76.3% (*Figure 2*) with the indication for the majority all CT scans done being for surveillance purposes (87–98%) (*Figure 3*). Recurrence occurred in 27.2% of patients at a median of 29.5 months following surgery. On univariate analysis, only stage was associated with recurrence such that 20.8% of stage I patients had documented recurrence *vs.* 53.1% of the stage II patients (P<0.01) (*Table 2*). Higher stage was found to be a significant risk for recurrence even after adjusting for comorbidities and other tumor characteristics [HR 4.31 (95% CI, 2.17–8.58) P<0.01] (*Table 3*).

The timing of recurrences also differed significantly based on stage such that the majority, 81% (n=27) of recurrences

Table 1 Baseline demographics and disease characteristics of the non-small cell lung cancer patients treated with primary surgery [2008–2012]

Patient characteristics	N=162 (%)
Gender	
Male	67 (41.4)
Female	95 (58.6)
Age (median/IQR)	70/11
Race	
Caucasian	101 (62.3)
Asian	37 (22.8)
Other	24 (14.8)
Smoking status	
Never smoked	54 (33.3)
Smoked	108 (66.7)
Cumulative Charlson comorbidities	
0	95 (58.6)
1	38 (23.5)
≥2	29 (17.9)

Table 1 (*continued*)

Table 1 (*continued*)

Patient characteristics	N=162 (%)
Stage/prognostics group	
Stage I	130 (80.2)
Stage II	32 (19.8)
Resection type	
Lobar	122 (75.3)
Sublobar	39 (24.1)
Pneumonectomy	1 (0.6)
Grade differentiation	
Well	50 (30.9)
Moderate	75 (46.3)
Poor	31 (19.1)
Cannot be assessed	6 (3.7)
Pleural invasion	28 (17.3)
Lymphovascular invasion	8 (4.9)
Mutation status	
EGFR positive (n=101)	32 (31.7)
KRAS positive (n=86)	19 (22.1)
ALK positive (n=72)	6 (8.3)
Triple negative (n=65)	29 (44.6)
Adjuvant therapy	
Adjuvant chemotherapy	22 (13.6)
Adjuvant radiation	4 (2.5)
Recurrence (yes)	44 (27.2)
Median time to recurrence months/IQR	29.5/26
Median follow-up months/IQR	56.5/24.75
Vital status	
Dead	29 (17.9)

presenting more than 24 months following surgery for stage I patients compared to 41% (n=17) of recurrences in stage II patients (P<0.01). The rate of suspicious findings on CT scans remained relatively stable over time ranging from 30–35% (*Figure 4*). However, the rate of CT scans with confirmed recurrence was variable, peaking at 2–3 years following surgery for the entire cohort (*Figure 5*). Also for the entire cohort, the time at which CT recurrences were detected varied with 36% (n=7) identified less than 24 months after surgery while the majority of all recurrences, 63% (n=12) were detected more than 24 months after surgery. When examined by stage, however stage I recurrences peaked at 25–36 months (*Figure 6*) compared to stage II patients with an earlier recurrence peak at 19–24 months (*Figure 7*) (P<0.01). When looking at overall recurrences, stage was a significant predictor of for time to recurrence. For stage I patients 75.9% recurred after 2 years, whereas stage II patients recurred earlier with 66.7% of their recurrences happening before two years (P<0.01) (*Table 4*). Recurrences occurred in 7 squamous cell patients, 35 adenocarcinoma patients, and 2 patients with adenosquamous histology (*Table 4*). Overall, higher rates of surveillance CT were associated with a reduced risk of death [HR 0.14 (95% CI, 0.06–0.36) P<0.01].

Discussion

We know that not all cancers are biologically equal, yet surveillance strategies remain the same for all patients. Clinical and pathologic stage remain some of the strongest predictors of outcomes in lung cancer and even in the earliest stage patients, recurrence is problematic. Rubins and colleagues, reported post-resection recurrence rates for Stage I tumors to be anywhere from 20–39% (4). More recently Pepek and colleagues at Duke University reported their five-year rates of locoregional recurrence to be 16%, 26%, 43%, 35%, and 40% for stages IA, IB, IIB, and IIIA disease respectively (5). Furthermore, the risk of recurrence is cumulative increasing over time and is compounded by the risk of developing metachronous tumors estimated at 1–2% per year (6).

Following surgery for curative intent, lung cancer patients are generally followed post-operatively with surveillance scans which are dictated by NCCN guidelines. Historically, these guidelines have been uniform, applying the same surveillance strategy to all post-operative patients. The newest iteration of the NCCN guidelines are tailored according to pathologic stage and type of treatment received (7). In this version, the panel now recommends more frequent (i.e., more "intense") surveillance with CT every 3–6 months for patients with late cancer stage (stage III or IV) or treated with radiation therapy compared to those with early cancer stage (stages I and II) or treated with chemotherapy. The new guidelines have reasonable clinical basis given higher rates of recurrence associated with late stage disease. Nonetheless, there has been no new high-level evidence to support the change. Historically, limited

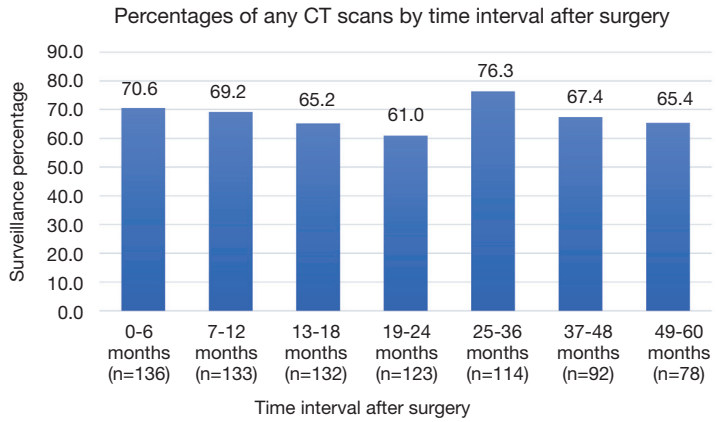
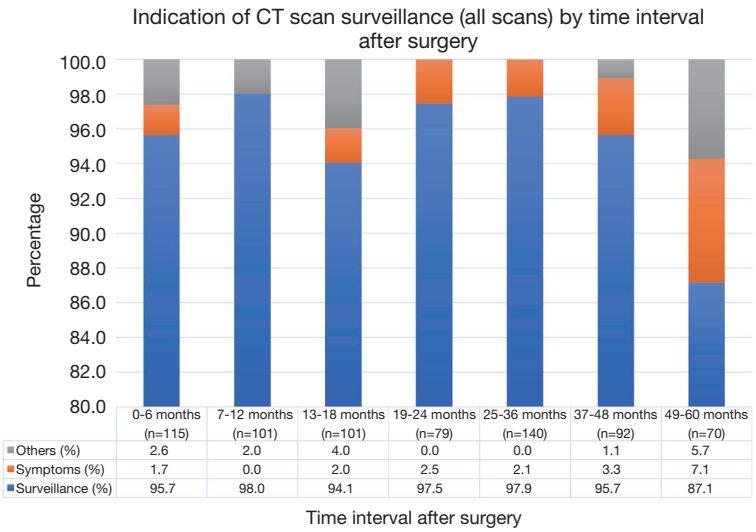


Figure 2 Adherence to guideline recommended surveillance by time interval [2008–2012].



	0-6 months (n=115)	7-12 months (n=101)	13-18 months (n=101)	19-24 months (n=79)	25-36 months (n=140)	37-48 months (n=92)	49-60 months (n=70)
Others (%)	2.6	2.0	4.0	0.0	0.0	1.1	5.7
Symptoms (%)	1.7	0.0	2.0	2.5	2.1	3.3	7.1
Surveillance (%)	95.7	98.0	94.1	97.5	97.9	95.7	87.1

Figure 3 CT scans indications for all the scans by time interval after surgery.

single institution or single time point studies have been used to support certain surveillance strategies and outcomes. A retrospective study of 1,294 lung cancer patients undergoing surveillance CT imaging found 60% of recurrences in asymptomatic patients with a false-positive rate of 25% (8). Another study found that 78% of recurrences detected during surveillance were in asymptomatic patients (9). Both authors concluded that recurrent disease is rarely missed by post treatment surveillance CT and recommended its routine use.

The recommendations for more intense surveillance for late stage patients are in contrast to the recent findings of the IFCT which recommend less frequent surveillance for late stage patients based on their findings of a lack of survival benefit in this group. The IFCT data did suggest that more intense surveillance could be beneficial for certain subgroup populations, namely: males, patients with early stage disease, and those having undergone surgery as sole treatment. More recently, a large national study conducted by McMurry and colleagues among 4,463 stage I–III patients examined surveillance CT scans and also found that more frequent surveillance was not associated with longer risk-adjusted overall survival nor with post-recurrence survival (10).

To our knowledge, ours is the first large study examining recurrence as it relates to timing of surveillance in an attempt to move towards a more tailored approach to care for lung cancer patients. We found the rate of recurrence

Table 2 Associations of baseline characteristics with the recurrence for NSCLC patients treated with primary surgery

Patient characteristics	Recurrence (no =118), n (%)	Recurrence (yes =44), n (%)	P value
Gender			0.32
Male	46 (39.0)	21 (47.7)	
Female	72 (61.0)	23 (52.3)	
Age (median/IQR)	69/15	70/11	0.99
Race			0.08
Caucasian	76 (64.4)	25 (56.8)	
Asian	22 (18.6)	15 (34.1)	
Others	20 (16.9)	4 (9.1)	
Smoking status			0.62
Never smoked	38 (32.2)	16 (36.4)	
Smoked	80 (67.8)	28 (63.6)	
Cumulative Charlson comorbidities			0.28
0	73 (61.9)	22 (50.0)	
1	27 (22.9)	11 (25.0)	
≥2	18 (15.3)	11 (25.0)	
Stage/prognostics group			<0.01*
Stage I	103 (87.3)	27 (61.4)	
Stage II	15 (12.7)	17 (38.6)	
Resection type			0.16
Lobar	87 (73.7)	35 (79.5)	
Sublobar	31 (26.3)	8 (18.2)	
Grade differentiation			0.13
Well	41 (34.7)	9 (20.5)	
Moderate	48 (40.7)	27 (61.4)	
Poor	24 (20.3)	7 (15.9)	
Cannot be assessed	5 (4.2)	1 (2.3)	
Pleural invasion	17 (14.4)	11 (25.0)	0.11
Lymphovascular invasion	5 (4.2)	3 (6.8)	0.50
Mutation status			
EGFR positive (n=101)	19 (28.4)	13 (38.2)	0.31
KRAS positive (n=86)	11 (19.6)	8 (26.7)	0.45
ALK positive (n=72)	2 (4.5)	4 (14.3)	0.20
Triple negative (n=65)	22 (53.7)	7 (29.2)	0.06
Adjuvant therapy			
Adjuvant chemotherapy	13 (11.0)	9 (20.5)	0.12
Adjuvant radiation	2 (1.7)	2 (4.5)	0.30
Median follow-up months (IQR)	59	56.50	0.61

*, P≤0.05. NSCLC, non-small cell lung cancer.

Table 3 Cox PH model for recurrence for NSCLC patients with primary surgery [2008–2012]

Important predictors	Risk for recurrences			Recurrence-EGFR tested			Recurrence-KRAS tested		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Race									
Asian *vs.* Caucasian	1.75	0.90–3.41	0.10	1.87	0.85–4.14	0.12	3.11	1.26–7.66	0.01*
Others *vs.* Caucasian	0.54	0.18–1.65	0.28	0.12	0.02–1.02	0.05*	0.50	0.06–3.98	0.51
Cumulative Charlson comorbidities score									
1 *vs.* 0	1.78	0.82–3.87	0.15	2.63	1.04–6.61	0.04*	3.20	1.16–8.84	0.03*
≥2 *vs.* 0	2.08	0.96–4.48	0.06	2.10	0.86–5.14	0.11	1.95	0.71–5.41	0.20
Stage									
II vs I	4.31	2.17–8.58	<0.01*	3.75	1.67–8.40	<0.01*	5.04	2.11–12.1	<0.01*
Chemo adjuvant therapy status									
Yes *vs.* no	1.30	0.59–2.87	0.52	2.82	1.06–7.49	0.04*	2.29	0.83–6.36	0.11
EGFR mutation status									
Yes *vs.* no				1.00	0.43–2.32	0.99			
KRAS mutation status									
Yes *vs.* no							1.59	0.62–4.08	0.33

*, P≤0.05. NSCLC, non-small cell lung cancer.

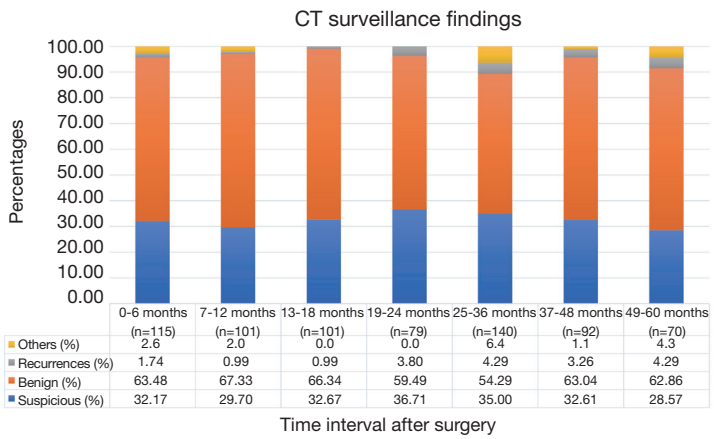


Figure 4 CT surveillance findings.

to be 27.5% of all early staged lung cancer patients at a median of 29.5 months following surgery which is on par with reported rates of recurrence in the literature. Martini and colleagues looked at stage I lung cancer patients and found the overall incidence of recurrence for resected lung cancer to be 27%, with 60% of those recurrences occurring within two years of the initial operation (11). Varlotto and colleagues reported local recurrence rates for patients with potentially curative resection for stage I NSCLC at 2, 3, and 5 years to be 14%, 21%, and 29% respectively (12). Similar to other published reports, we found stage to be the strongest predictor of recurrence in this select cohort. Thus, if stage is indeed the strongest predictor, our findings that the timing of recurrence differed significantly according to stage make sense and that stage should be considered when defining surveillance strategies aimed at reducing

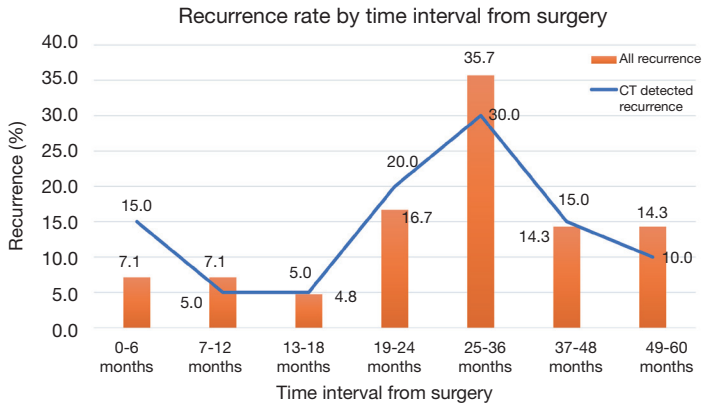


Figure 5 Recurrence by surveillance by time interval after surgery for non-small cell lung cancer patients treated with primary surgery [2008–2012].

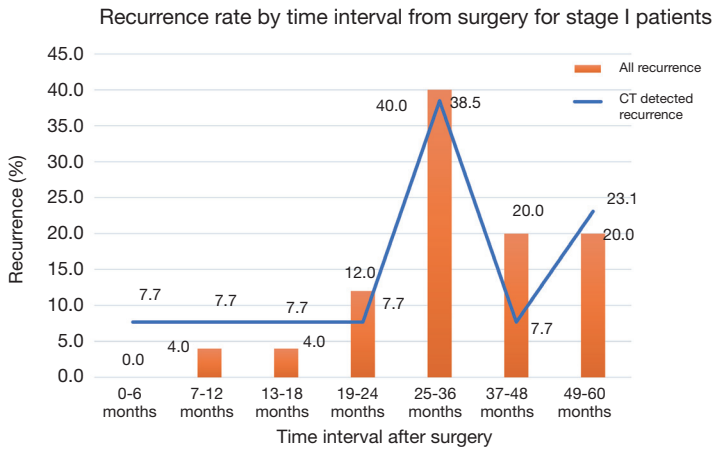


Figure 6 Recurrence rate by time interval after surgery for non-small cell lung cancer stage I patients treated with primary surgery [2008–2012].

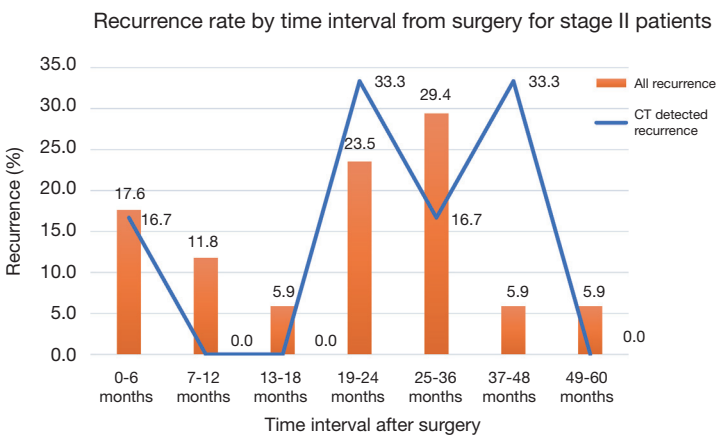


Figure 7 Recurrence rate by time interval after surgery for non-small cell lung cancer stage II patients treated with primary surgery [2008–2012].

Table 4 Association of stage, histopathologic type and recurrences

Characteristics	Staging, n (%)			Histopathologic type, n (%)			
	Stage I	Stage II	P	Squamous cell carcinoma	Adenocarcinoma	Adenosquamous carcinoma	P
CT detected recurrences (n=19)							
<24 months (n=7)	4 (57.1)	3 (42.9)	0.62	2 (28.6)	5 (71.4)	0 (0.0)	1.00
>24 months (n=12)	9 (75.0)	3 (25.0)		3 (25.0)	8 (66.7)	1 (8.3)	
All recurrences (n=44)							
<24 months (n=15)	5 (33.3)	10 (66.7)	≤0.01*	1 (6.7)	13 (86.7)	1 (6.7)	0.46
>24 months (n=29)	22 (75.9)	7 (24.1)		6 (20.7)	22 (75.9)	1 (3.4)	

*, P≤0.05.

unnecessary procedures and cost.

While the percentage of CT scans with suspicious findings was relatively stable over time in our study, the rate of CT scans with documented recurrence was variable. We found that the peak time for recurrence to be 2–3 years following surgery. When we broke down stage I and stage II, we found that stage I recurrences peaked slightly later at 25–36 months whereas stage II peaked slightly earlier at 19–24 months. Once again, this data shows that factoring stage into a surveillance strategy would be prudent.

There are limitations to our study. First, due to the time frame in which our study took place, we found that many of the early patients of a specific surgeon in the cohort were not followed up with CT scans but rather CXR in the early post-resection years. Also, due to the fact that we are a tertiary center with referrals from significant distances, we had a significant amount of people who did not receive follow-up with us and therefore were lost to follow up unless referred back to us for a recurrence, potentially confounding the findings. Our follow up is limited as well as we had to choose a starting point and end point to include patients. Although it is short, we chose the minimum follow up of 6 months in order to limit the main analyses to those patients for whom surveillance is appropriate. The maximal follow up is only limited by the fact that we were following NCCN guidelines for 5 years.

In conclusion, as we continue to work in an arena where we are able to get more and more information on each individual cancer, whether it be the stage, histological type, genetic mutational status, or any other variable, we should work to incorporate this information into a more patient specific surveillance regimen to optimize our use of CT scans and better serve our patients. Our data suggests that the timing of recurrence differs significantly based on stage such that few stage I patients have recurrences within 2 years following surgical resection, however these patients currently get scans every 6 months in the first two years. Although more investigation is warranted, our data may help support recommending less frequent scans in the early post-operative period. Optimal timing of CT surveillance based on peak recurrence rates has the potential to eliminate unnecessary testing and expense for healthcare systems.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm.2019.10.02). LB reports personal fees from Johnson and Johnson, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by an institutional review board at Stanford University. Protocol #39411. This study will not affect the future management of the patients. Informed consent was not obtained for this retrospective study as information was taken through chart review. The patient's personal data was secured using

REDCAP.

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