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Imaging Surveillance and Survival for Surgically Resected NSCLC

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Abstract

Introduction—The importance of imaging surveillance following treatment for lung cancer is not well characterized. We examined the association between initial guideline recommended imaging surveillance and survival among early stage resected NSCLC patients.

Methods—A retrospective study was conducted using SEER-Medicare data (1995–2010). Surgically resected patients, with Stage I and II NSCLC, were categorized by imaging received during the initial surveillance period (4–8 months) following surgery. Primary outcome was overall survival. Secondary treatment interventions were examined as intermediary outcomes.

Results—The majority (88%) of patients had at least one outpatient clinic visit, and 24% received an initial CT during the first surveillance period. Five-year survival by initial surveillance imaging was 61% for CT, 58% for CXR, and 60% for no imaging. Following adjustment, initial CT was not associated with improved overall survival (HR 1.04; 95% CI 0.96,1.14). On subgroup analysis, restricted to patients with demonstrated initial post-operative follow-up, CT was

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associated with a lower overall risk of death for Stage I patients (HR 0.85; 95% CI 0.74–0.98), but not for Stage II (HR 1.01; 95% CI 0.71–1.42). There was no significant difference in rates of secondary interventions predicted by type of initial imaging surveillance.

Conclusions—Initial surveillance CT is not associated with improved overall or lung cancer specific survival among early stage NSCLC patients undergoing surgical resection. Stage I patients with early follow-up may represent a subpopulation that benefits from initial surveillance although this may be influenced by healthy patient selection bias.

Keywords

Imaging Surveillance; Lung Cancer Survival; Cancer Follow Up; Guidelines

1 Introduction

Despite advances in treatment and early detection, patients undergoing definitive treatment for non-small cell lung cancer (NSCLC) remain at risk for recurrence or second primary lung cancers (SPLC). The risk is estimated at 2%–3% per patient year for recurrence and 1%–4% per patient year for SPLC. (1–5) As such, many international guidelines have advocated for routine surveillance for treated patients.(6–9) Although there are some inconsistencies, most guidelines recommend more frequent imaging within the first two years and favor surveillance with computerized tomography (CT) over chest radiography (CXR). The National Comprehensive Cancer Network (NCCN) guidelines are some of the most widely referenced guidelines and currently recommend surveillance CT at 6–12 month intervals.(8)

Our prior work examining rates of recommended imaging surveillance found marked heterogeneity with relatively poor rates of adherence overall. Using the NCCN guidelines in place between 1995–2010, we found that only 24% of patients received CT as their initial examination in the first surveillance period.(10) One potential explanation for the low observed adherence rate is the relative lack of high quality studies substantiating the benefit of surveillance towards improving lung cancer outcomes. Several small studies have suggested that intense surveillance is associated with increased secondary treatment interventions leading to improved survival. These studies serve as the basis for the consensus opinion of the NCCN. In this study, we sought to determine if receipt of initial surveillance imaging is associated with improved survival among a large national cohort of early stage NSCLC patients undergoing surgical resection.

2 Materials and Methods

2.1 Data Source

We used data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program from all registries representing a non-random sample of 28% of the US population. SEER data was linked to Medicare claims for outpatient clinic visit, imaging, and procedures following surgical treatment for all NSCLC patients between 1995–2009 with follow-up through 2010.

2.2 Study Cohort

A total of 438,872 patients were identified with NSCLC. We limited the analysis to patients with Stage I or II disease based on the American Joint Committee on Cancer 6th Edition having undergone surgical resection (excluded n=280,476), who were aged >65 years, eligible for Medicare Part A and B, with at least 12 months of continuous enrollment (excluded n=46,201). (11) We excluded patients who were diagnosed at time of death or died within 6 months of surgery (n=12,119), had a diagnosis of other malignancy within 12 months prior to or following NSCLC diagnosis (n=5,235), and those who received induction chemotherapy or radiation therapy (n=23,565). This resulted in our main analytic cohort of 18,406 patients.

We recognized that some patients may have never received initial post-operative follow up when a surveillance plan may have been initiated thus limiting their opportunity for surveillance. In order to address this confounding by selection bias, we performed a sensitivity analysis on a subgroup of patients who had demonstrated initial post-operative follow up. This smaller subgroup was defined as patients who had at least one clinic visit and 1–2 CXRs within the first three months following surgery corresponding to early post-surgical clinical follow up (excluded n=10,537). Patients who underwent pneumonectomy (n=489) were also excluded in an effort to reduce the effect of selection bias against patients for whom additional treatment options may have been viewed as impractical. The resulting 7,380 patients defined our cohort for the subgroup analyses.

2.3 Analysis

Patients entered the cohort at the time of surgical resection. Exposure variables of interest were initial imaging type and outpatient clinic visit during the first surveillance period, defined as 4–8 months following surgery. This timeframe was selected to provide a more conservative definition based upon NCCN guidelines in place during the observation period (1995–2009), which recommended CT at 4–6 month intervals for the first two years. Patients were categorized by type of imaging received as the first image performed in the initial 4–8 months following surgical resection such that image types were mutually exclusive of one another. This was done in an attempt to account for those patients who received an initial test which may have led to subsequent tests identified during the same observation period. The main outcome of interest was overall and lung-cancer specific survival. Since one potential means by which surveillance may lead to improved survival is by early detection of recurrences and second primary lung cancers that are amenable to additional treatment, we also examined receipt of secondary interventions as intermediary outcomes. Secondary interventions were defined as: bronchoscopy, chemotherapy, radiation therapy, and repeat surgical resection performed at any time more than 8 months following treatment. Patients alive at the end of 2009 were censored. For lung cancer specific survival, deaths not due to lung cancer were also treated as censored. Additional covariates in the regression models included: demographics, socioeconomic status (as defined by the 2000 census tract poverty percentage category), cancer stage, sex, Charlson Comorbidity score (12) and year of surgery.

Categorical data were compared using the chi-squared test. Unadjusted differences between surveillance imaging groups were compared using the log-rank test. Estimates and visualizations of unadjusted survival curves by imaging type were made using Kaplan-Meier curves. Covariate-adjusted associations for outcomes were assessed using Cox proportional hazards models.(13) All analyses were performed using R version 2.14.(14) Results are reported with summary statistic [and 95% confidence intervals (CI)] with p value <0.05 considered significant.

3. Results

The majority of patients (88%) were seen in an outpatient clinic visit between 4–8 months following surgical resection. (Table 1) A total of 24% of patients received a CT as their initial imaging. Five-year survival was 58.8% for the main cohort. Survival was lowest among patients receiving CXR (57.9% [95% CI 56.9%, 59.0%]) or PET/CT (53.0% [95% CI 47.5%, 59.2%]) as their initial imaging. (Table 2) Initial CT was not associated with a significant difference in 5-year survival (61.4% [95% CI 59.5%, 63.4%]) compared to no imaging (60.4% [95% CI 58.1%, 62.9%]) (p=0.110). Following adjustment for covariates, CT was not associated with a reduced risk of death (HR 1.04 [95% CI 0.96, 1.14]) whereas clinic visit was associated with a 16% reduced risk of death (HR 0.84 [95% CI 0.79, 0.89]). (Table 3)

Sensitivity analysis examining the subgroup of patients with demonstrated post-operative follow-up (defined above) showed that CT was associated with a 15% reduced risk of death for Stage I patients (HR 0.85 [95% CI 0.74–0.98]) compared to no imaging, however there was no difference in lung cancer specific survival (HR 1.03 [95% CI 0.85–1.26]). CT was not associated with a significant difference in either overall (HR 1.01 [95% CI 0.71–1.42]) or lung cancer specific survival (HR 0.98 [95% CI 0.65–1.47]) for Stage II patients. (Table 4)

Of the main cohort, 32% received a secondary intervention following surgical resection of which radiation therapy was the most common (22%). (Table 5) Rates of repeat surgical resection did not differ significantly by type of initial imaging received (CXR 4.7%, PET 5.1%, CT 4.9%, None 3.8%, p=0.182). On multivariable analyses, higher rates of secondary interventions were associated with all surveillance imaging (CXR HR 1.32 [95% CI 1.21, 1.45], CT HR 1.49 [95% CI 1.35, 1.65], PET HR 2.14 [95% CI 1.83, 2.49]) compared to no imaging at all but no difference between imaging types. (Table 6)

4 Discussion

We found no survival benefit associated with receipt of CT during the initial surveillance period compared to those receiving no imaging. Other studies have reported mixed results on the association between intensive follow-up and improved survival. In a meta-analysis examining the effect of intense surveillance on survival among NSCLC patients, investigators identified only 9 studies meeting rigorous inclusion criteria, but found a non-significant trend for intensive follow-up associated with improved survival (HR: 0.83).(15) Another meta-analysis identified only 4 studies meeting inclusion criteria with marked

methodological compromises such that no firm conclusions could be determined.(16) In our subgroup analysis, we did find an overall survival benefit associated with early CT for Stage I disease but only for this select group. This finding was not influenced by an underlying decrease in lung cancer specific survival, as indeed, we found no difference in the latter for either Stage I or II patients. This could be explained by a healthy selection bias such that patients with improved health maintenance may experience better health outcomes overall. In keeping with this, we found that an initial outpatient clinic visit was also associated with improved survival. Additional explanation may stem from the fact that Stage I patients with performance status sufficient for lung resection could represent a more robust group of patients with favorable lung cancer specific survival, but with sufficient comorbidity that they are more likely to die from competing mortalities. This may be analogous to the unexpected observation in the National Lung Screening Trial whereby patients undergoing CT screening experienced improved overall survival in addition to lung cancer specific survival.(17) We observed an increased risk of death associated with PET scan, which is not surprising since this likely reflects the association between early PET and higher rates of chemotherapy and radiation. Accordingly, PET could be a marker of more aggressive tumor biology and early recurrence.

One of the main goals of post-treatment surveillance for NSCLC is to improve survival by early detection of recurrences and second primary lung cancer (SPLC). Secondary interventions and treatment are the presumed intermediaries for surveillance to impact outcomes. Routine surveillance programs have proven effective at detecting SPLC and the majority of recurrent lung cancers in several published series. In these programs, detection rates range from 21%–72%(18–25) for recurrence and 1%–7% for SPLC (21, 26–28). Rates of curative treatment for recurrences and SPLC range widely from 4%–85%. Many of these studies reflect single institution experiences in small series. Our study examined a large cohort of patients treated in a variety of clinical settings and found no difference in the rate of secondary interventions based on initial surveillance imaging. Thus the argument that early surveillance leads to more therapeutic interventions as a means of influencing survival is potentially weakened. The lack of association could be explained by the fact that our study cohort was restricted to early stage patients who might be more likely to present with SPLC rather than recurrent disease well beyond the 4–8 month exposure period studied.

Our study has several limitations. There are challenges with interpreting the literature surrounding surveillance. Many surveillance interventions report findings in terms of both recurrence and SPLC. The timing of recurrence differs from that of SPLC and the latter is more often amenable to curative intent treatment.(28–32) We were unable to distinguish between recurrence and SPLC using our dataset thus our ability to interpret the results may be influenced by this. Poor outcomes in patients presenting with recurrent disease may potentially obscure an observation of benefit for those presenting with SPLC which has a much more favorable prognosis. Furthermore, given the longer time to detection of SPLC (median 45 months)(21, 26, 28) the exposure period (4–8 months following treatment) may be too early in the post-treatment course to influence long-term outcomes. Finally, our study is unable to establish causality between early surveillance and long-term outcomes based on administrative data that lack information regarding the clinical indication for the imaging studies being performed nor does it provide information regarding use of private insurance.

5 Conclusion

Despite its limitations, our data suggest that Stage I patients may represent a subset of for which routine imaging surveillance may provide survival benefit. Future investigation should couple these population-based observations with evolving techniques such as the use of biomarkers to develop personalized risk prediction models that may in fact be more cost effective with little lost in terms of potential impact on long-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
a: Stage I Subgroup Kaplan-Meier Overall Survival
b: Stage II Subgroup Kaplan-Meier Overall Survival

Table 1

Cohort Description and Follow Up at 4–8 Months Post-Resection

	All	Clinic visit	CT
N (%)	18406 (100.0)	16195 (88.0)	4421 (24.0)
Age			
65–69	4902 (26.6)	4217 (86.2)	1268 (25.9)
70–74	5568 (30.3)	4916 (88.3)	1333 (23.9)
75–79	4735 (25.7)	4212 (89.0)	1087 (23.0)
89+	3201 (17.4)	2850 (89.0)	733 (22.9)
Sex			
Male	8435 (45.8)	7296 (86.5)	2001 (23.7)
Female	9971 (54.2)	8899 (89.3)	2420 (24.3)
Marital Status			
Married at Diagnosis	10602 (57.6)	9351 (88.3)	2636 (24.9)
Others	7804 (42.4)	6844 (87.8)	1785 (22.9)
Poverty Level			
>=75%tile	3570 (19.4)	2996 (83.9)	690 (19.3)
25–75%tile	9004 (48.9)	7946 (88.3)	2082 (23.1)
<=25%tile	5745 (31.2)	5176 (90.2)	1634 (28.4)
Race			
White	16404 (89.1)	14570 (88.9)	3955 (24.1)
Black	964 (5.2)	779 (81.0)	230 (23.9)
Other	1021 (5.5)	832 (81.6)	230 (22.5)
Unknown	17 (0.1)	14 (82.4)	6 (35.3)
Comorbidity			
No conditions	9199 (50.0)	8139 (88.5)	2190 (23.8)
1	5555 (30.2)	4934 (88.8)	1350 (24.3)
2–3	2983 (16.2)	2592 (86.9)	728 (24.4)
4+	568 (3.1)	473 (83.3)	132 (23.2)
Stage			
I	15863 (86.2)	13957 (88.0)	3722 (23.5)
II	2543 (13.8)	2238 (88.1)	699 (27.5)
Initial Treatment			
Surgery	15510 (84.3)	13611 (87.8)	3465 (22.3)

	All	Clinic visit	CT
Surgery + Radiation	705 (3.8)	608 (86.2)	157 (22.3)
Surgery + Chemo	1907 (10.4)	1733 (90.9)	713 (37.4)
Surgery + Rad + Chemo	284 (1.5)	243 (85.6)	86 (30.3)
Surgical Treatment			
Wedge resection	4851 (26.4)	4248 (87.7)	1324 (27.3)
Segmentectomy	839 (4.6)	745 (88.9)	224 (26.7)
Lobectomy	11569 (62.9)	10226 (88.4)	2634 (22.8)
Bilobectomy	590 (3.2)	505 (85.6)	108 (18.3)
Pneumonectomy	489 (2.7)	413 (84.5)	120 (24.5)
Mediastinoscopy			
No	15129 (82.2)	13323 (88.1)	3540 (23.4)
Yes	3277 (17.8)	2872 (87.7)	881 (26.9)
Histology			
Adenocarcinoma	10346 (56.2)	9195 (88.9)	2621 (25.3)
Squamous	5527 (30.0)	4794 (86.8)	1197 (21.7)
Large Cell	690 (3.7)	605 (87.7)	142 (20.6)
NSCLC Undiff	707 (3.8)	626 (88.5)	197 (27.9)
Other	1136 (6.2)	975 (86.0)	264 (23.2)

Table 2

Unadjusted Overall Survival

	Survival (95% CI)	
	3 year	5 year
All	75.4% (74.7%, 76.1%)	58.8% (57.9%, 59.6%)
None	78.4% (76.5%, 80.2%)	60.4% (58.1%, 62.9%)
CXR	74.6% (73.7%, 75.5%)	57.9% (56.9%, 59.0%)
PET	70.6% (66.4%, 75.0%)	53.0% (47.5%, 59.2%)
CT	76.7% (75.2%, 78.2%)	61.4% (59.5%, 63.4%)

Table 3

Cox Proportional Hazards Model for Death: Full Cohort

	Univariable	p-value	Multivariable	p-value
<u>Imaging</u>				
None	Ref		Ref	
CXR	1.09 (1.02, 1.17)	0.015	1.08 (1.01, 1.16)	0.032
PET/CT	1.30 (1.11, 1.52)	0.001	1.40 (1.20, 1.65)	<0.001
CT	1.00 (0.92, 1.09)	0.948	1.04 (0.96, 1.14)	0.344
Clinic Visit (4–8mo)	0.81 (0.76, 0.87)	<0.001	0.84 (0.79, 0.89)	<0.001
Cancer Stage II	1.74 (1.64, 1.85)	<0.001	1.80 (1.69, 1.91)	<0.001
Female sex	0.75 (0.72, 0.78)	<0.001	0.78 (0.75, 0.82)	<0.001
<u>Comorbidity</u>				
No Conditions	Ref		Ref	
1	1.32 (1.25, 1.39)	<0.001	1.31 (1.24, 1.38)	<0.001
2–3	1.65 (1.55, 1.76)	<0.001	1.64 (1.53, 1.74)	<0.001
4+	2.32 (2.04, 2.63)	<0.001	2.32 (2.04, 2.63)	<0.001
<u>Age</u>				
65–69	Ref		Ref	
70–74	1.25 (1.17, 1.33)	<0.001	1.22 (1.14, 1.29)	<0.001
75–79	1.42 (1.33, 1.51)	<0.001	1.41 (1.33, 1.51)	<0.001
80+	1.81 (1.69, 1.94)	<0.001	1.88 (1.75, 2.01)	<0.001
<u>Race</u>				
White	Ref		Ref	
Black	0.94 (0.85, 1.04)	0.224	0.89 (0.80, 0.99)	0.030
Other	0.91 (0.83, 1.01)	0.070	0.85 (0.77, 0.94)	0.002
Unknown	0.95 (0.43, 2.11)	0.898	0.64 (0.29, 1.42)	0.270
<u>Poverty</u>				
>=75%tile	Ref		Ref	
25–75%tile	0.92 (0.86, 0.97)	0.003	0.92 (0.86, 0.98)	0.006
<=25%tile	0.84 (0.78, 0.89)	<0.001	0.85 (0.79, 0.91)	<0.001
<u>Surgery Year</u>				

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	Univariable	p-value	Multivariable	p-value
1996–2001	Ref		Ref	
2001–2004	0.88 (0.83, 0.92)	<0.001	0.85 (0.80, 0.89)	<0.001
2004–2007	0.86 (0.80, 0.92)	<0.001	0.80 (0.74, 0.85)	<0.001
2007–2009	0.73 (0.65, 0.83)	<0.001	0.66 (0.59, 0.75)	<0.001

Table 4

Cox Proportional Hazards Model for Death: Subgroup Analysis

	None	CXR	CT	PET
Overall *				
Stage I	Reference	0.94 (0.84, 1.05)	0.85 (0.74, 0.98)	1.01 (0.75, 1.34)
Stage II	Reference	1.16 (0.85, 1.59)	1.01 (0.71, 1.42)	1.01 (0.71, 1.42)
Lung Cancer-Specific *				
Stage I	Reference	1.09 (0.92, 1.28)	1.03 (0.85, 1.26)	1.44 (1.01, 2.04)
Stage II	Reference	1.11 (0.77, 1.62)	1.38 (0.80, 2.36)	0.98 (0.65, 1.47)

* Adjusted for all covariates in full cohort regression model in Table 3

Table 5

Secondary Interventions by Initial Imaging and Clinic Visit

N (%)	All	Clinic Visit	*p-value	Imaging			None	*p-value
				CXR	PET	CT		
All		16195 (88.0)		11047 (60.0)	645 (3.5)	4421 (24.0)	2293 (12.5)	
Bronchoscopy	3430 (18.6)	2664 (87.5)	0.314	1946 (17.6)	97 (15.0)	703 (15.9)	299 (13.0)	<0.001
Resection	858 (4.7)	762 (88.8)	0.513	521 (4.7)	33 (5.1)	217 (4.9)	87 (3.8)	0.182
Chemotherapy	3244 (17.6)	2867 (88.4)	0.538	1994 (18.1)	154 (23.9)	791 (17.9)	305 (13.3)	<0.001
Radiation	4003 (21.7)	3515 (87.8)	0.622	2542 (23.0)	164 (25.4)	915 (20.7)	382 (16.7)	<0.001
None	12572 (68.3)	11058 (88.0)	1.000	7405 (67.0)	397 (61.6)	3042 (68.8)	1728 (75.4)	<0.001

Table 6

Cox Proportional Hazards Model for Secondary Interventions

	Univariable	p-value	Multivariable	p-value
<u>Imaging</u>				
None	Ref		Ref	
CXR	1.37 (1.25, 1.49)	<0.001	1.32 (1.21, 1.45)	<0.001
PET/CT	2.08 (1.79, 2.42)	<0.001	2.14 (1.83, 2.49)	<0.001
CT	1.44 (1.30, 1.59)	<0.001	1.49 (1.35, 1.65)	<0.001
Clinic Visit	0.98 (0.90, 1.06)	0.556	0.97 (0.89, 1.05)	0.434
Cancer Stage II	1.93 (1.81, 2.06)	<0.001	1.88 (1.76, 2.01)	<0.001
Female sex	0.76 (0.72, 0.80)	<0.001	0.79 (0.75, 0.83)	<0.001
<u>Comorbidity</u>				
No Conditions	Ref		Ref	
1	1.07 (1.00, 1.13)	0.034	1.08 (1.02, 1.15)	0.009
2-3	1.05 (0.98, 1.13)	0.190	1.10 (1.02, 1.19)	0.013
4+	0.90 (0.76, 1.08)	0.262	0.96 (0.80, 1.15)	0.658
<u>Age</u>				
65-69	Ref		Ref	
70-74	1.10 (1.03, 1.17)	0.007	1.09 (1.02, 1.17)	0.010
75-79	0.97 (0.90, 1.04)	0.380	0.99 (0.92, 1.06)	0.761
80+	0.77 (0.71, 0.84)	<0.001	0.81 (0.74, 0.88)	<0.001
<u>Race</u>				
White	Ref		Ref	
Black	1.10 (0.98, 1.24)	0.090	1.11 (0.99, 1.25)	0.074
Other	1.07 (0.96, 1.20)	0.204	1.04 (0.93, 1.17)	0.451
Unknown	0.19 (0.03, 1.37)	0.100	0.20 (0.03, 1.45)	0.111
<u>Poverty</u>				
>=75%tile	Ref		Ref	
25-75%tile	0.98 (0.91, 1.05)	0.499	1.02 (0.95, 1.09)	0.613
<=25%tile	1.02 (0.95, 1.10)	0.607	1.08 (1.00, 1.16)	0.060
<u>Surgery Year</u>				

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	Univariable	p-value	Multivariable	p-value
1996–2001	Ref		Ref	
2001–2004	0.87 (0.82, 0.93)	<0.001	0.85 (0.80, 0.91)	<0.001
2004–2007	0.82 (0.76, 0.88)	<0.001	0.76 (0.70, 0.81)	<0.001
2007–2009	0.68 (0.63, 0.74)	<0.001	0.63 (0.58, 0.68)	<0.001