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Predictors of Imaging Surveillance for Surgically Treated, Early-Stage Lung Cancer

Leah M Backhus, MD^{1,2}, Farhood Farjah, MD, MPH², Steven B Zeliadt, PhD^{3,4}, Thomas K Varghese, MD, MS², Aaron Cheng, MD², Larry Kessler, ScD⁴, David H Au, MD⁵, and David R Flum, MD, MPH⁶

¹VA Puget Sound Health Care System, Surgery Service, Seattle, WA

²Department of Surgery, Division of Cardiothoracic Surgery, University of Washington

³VA Puget Sound Health Care System, Health Services Research & Development Service, Seattle, WA

⁴Department of Health Services, School of Public Health, University of Washington

⁵Department of Medicine, Division of Pulmonary and Critical Care, University of Washington

⁶Department of Surgery, University of Washington

Abstract

Background—Current guidelines recommend routine imaging surveillance for non-small cell lung cancer (NSCLC) patients following treatment. Little is known about surveillance patterns for surgically resected, early-stage lung cancer patients in the community-at-large. We sought to characterize surveillance patterns in a national cohort.

Methods—We conducted a retrospective study using Surveillance, Epidemiology, and End-Results (SEER)-Medicare database (1995-2010). Patients with stage I/II NSCLC treated with surgical resection were included. Our primary outcome was receipt of imaging between 4 and 8 months following surgery. Covariates included demographics and comorbidities.

Results—Chest radiography (CXR) was the most frequent initial modality (60%) followed by chest computerized tomography (CT) (25%). Positron emission tomography (PET) was least frequent as initial imaging modality (3%). A total of 13% of patients received no imaging within the initial surveillance period. Adherence to National Comprehensive Cancer Network (NCCN) guidelines for imaging by overall prevalence was 47% for receipt of CT, however rates of CT imaging increased over time from 28% to 61% ($p < 0.01$). Reduced rates of CT imaging were associated with stage I disease and surgery as the sole treatment modality.

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Correspondence: Leah M. Backhus, MD, Division of Cardiothoracic Surgery, Department of Surgery, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, lbackhus@u.washington.edu.

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Conclusions—Imaging following definitive surgery for NSCLC predominantly utilizes CXR rather than CT. Most of this imaging is likely for surveillance and in that context, CXR has inferior detection rates for recurrence and detection of new cancers. Adherence to guideline recommended CT surveillance following surgery is poor, but the reason multifactorial. Efforts to improve adherence to imaging surveillance must be coupled with greater evidence demonstrating improved long-term outcomes.

Introduction

There were an estimated 412,230 people living with lung cancer in the US in 2012.¹ This number of cancer survivors is expected to increase with adoption of the US Preventative Services Task Force recommendation for screening high-risk patients for early detection of lung cancer.² Seventy percent of patients with lung cancer detected via computerized tomography (CT) screening programs are identified at an early stage.³ Surgical resection remains the cornerstone for definitive treatment of early stage non-small cell lung cancer (NSCLC) given superior outcomes compared to non-surgical therapies. Yet, despite surgical advances, many patients will experience recurrence and remain at risk for second primary lung cancers in need of further treatment. Recognizing this risk, several national guidelines have been developed to standardize protocols for appropriate imaging surveillance following treatment.

Current guidelines are based almost exclusively on consensus opinion or selective single-center trials. Most guidelines recommend routine imaging using either CT or chest radiography (CXR) with more frequent surveillance in the first two years. The lack of evidence of efficacy is compounded by the lack of knowledge of real-world application of these guidelines. We sought to characterize the imaging surveillance patterns of resected NSCLC patients in a national cohort to determine adherence to national standards.

Material and Methods

Study Population

The Institutional Review Board of the University of Washington approved this study. Data was obtained from the national SEER registry database with Medicare linkage for patients with NSCLC diagnosed during 1996-2009. A total of 438,872 patients were identified. We excluded patients younger than age 65 years (n=58,744) or diagnosed at autopsy or by death certificate (n=12,119). We restricted the cohort to stage I and II patients (exclude n=280,476) who underwent lung resection within 6 months of diagnosis (exclude n=23,565). Patients with prior malignancy or other malignancy diagnosed within 12 months after lung cancer diagnosis were also excluded (n=5,235). Patients had to have continuous Medicare eligibility for 12 months or more after date of diagnosis (exclude n=40,327). The final study population consisted of 18,406 patients. (Appendix A)

Primary Outcome

Our primary outcome was receipt of CT during the initial surveillance period. Secondary outcomes were receipt of CXR, positron emission tomography (PET), or any of the three modalities within the defined surveillance period. National Comprehensive Cancer Network

(NCCN) guidelines for lung cancer management recommend imaging surveillance with chest CT between 4-6 months following definitive therapy. Accordingly, the initial surveillance period was defined as 4-6 months following date of surgery; however the interval was increased to 4-8 months to allow for a more liberal estimate of adherence. The latter served as the basis for all analyses. Given the fact that some patients may have received more than one imaging study during the surveillance period, we examined imaging both by rates of initial imaging modality exclusive to other modalities as well as prevalence of each imaging type inclusive of all modalities.

Analysis

Unadjusted analyses for rates of imaging were compared using chi-square test and Mantel-Haenszel chi-square test for trends over time. Kaplan-Meier estimates were used to examine the cumulative proportion of patients receiving imaging for each modality. Two multivariate logistic regression models were fitted to the data. One model assessed factors associated with receipt of CT as first imaging and the other model assessed factors associated with no imaging during the initial surveillance period. All analyses were performed in SAS, v9.3 (SAS Institute Inc, Cary, NC).

Results

The study population was 46% male and 89% white race. One half of patients had no comorbid conditions. Most patients were pathologic stage I (86%) and underwent surgery as their sole treatment (84%). The most frequent initial imaging modality performed during initial surveillance was CXR (60%), followed by CT (25%), and PET (3%). (Table 1) The prevalence of each imaging modality performed inclusive of one another is shown in Table 2. The proportion of patients receiving no imaging surveillance during the first 4-8 months following resection was 13%. On univariate analysis, increased rates of CT imaging were associated with younger age, ($p<0.01$), married status ($p<0.01$), low poverty level ($p<0.01$), stage II disease ($p<0.01$), and multimodality treatment ($p<0.01$). An inverse relationship was seen for receipt of no imaging which was associated with unmarried status ($p<0.01$), non-white race ($p<0.01$), fewer comorbid conditions ($p<0.01$) stage I disease ($p<0.01$), and surgery alone as primary therapy ($p<0.01$).

Examination of imaging trends over time demonstrated an increase from 10% to 36% ($p<0.01$) for CT comparing the earliest (1996-2000) to latest study periods (2006-2009) while CXR decreased from 75% to 47% ($p<0.01$). (Table 3) Receipt of no imaging declined from 15% to 13% ($p<0.01$). Time to event analysis estimated 75% of all patients would receive a CT by 538 days following surgery compared to 217 days for CXR. (Figure 1)

On multivariate analysis, receipt of CT as the first imaging modality was associated with older age (75-79 years, OR 1.08 [95% CI 1.00-1.18], Stage II disease (OR 1.32 [95% CI 1.15-1.41]) and multimodality therapy compared to surgery alone. (Table 4) Lower odds of CT during the surveillance period were associated with high poverty (middle, OR 0.75 [95% CI 0.70-0.80], high, OR 0.72 [95% CI 0.66-0.79]) compared to low, anatomic resection compared to wedge resection (lobectomy OR 0.81 [95% CI 0.76-0.87], bilobectomy OR 0.64 [95% CI 0.53-0.77], pneumonectomy OR 0.71 [95% CI 0.58-0.87] and more

comorbidities. Lack of any imaging during the surveillance period was associated with surgery as the sole treatment rendered.

Comment

Guidelines for follow up of early stage lung cancer patients are widely reported, but the evidence underlying these guidelines is not strong. Agencies advocating for surveillance include NCCN⁴, American College of Radiology (ACR)⁵, American College of Chest Physicians⁶, American Society of Clinical Oncology⁷ and the European Society of Medical Oncology⁸. All recommend more frequent imaging in the first 2 years consistent with peak risk of recurrence.⁹⁻¹¹ However, they differ in recommended modality and intervals for follow-up. Both NCCN and ACR recommend CT as the preferred modality.

Imaging surveillance for lung cancer patients is supported by reported rates of recurrence between 4-41%.¹²⁻¹⁵ Recurrence detection is even higher within standardized imaging surveillance programs.^{14,16-18} Many patients with surveillance detected recurrent cancer will be eligible for secondary therapy with curative intent.^{10,12,16,17,19-22} Data regarding the impact of surveillance on improved survival have been mixed however. At least one study has demonstrated improved 3-year survival following treatment of surveillance-detected recurrence of 31% compared to 13% for those detected by symptoms.²³ Many have reported 5-year survival rates comparable to those undergoing surgical resection of initial lung cancers.^{10,12,21,24-27} Still others report no difference in overall survival for surveillance programs.^{17,28}

There is also limited data examining real-world practice of imaging surveillance in a large population. The largest claims based study of guideline recommended follow-up care studied 100 lung cancer patients and found that most underwent surveillance with CXR (74%) and only 37% had surveillance CT which is consistent our finding of less than 50% of patients receiving guideline recommended imaging.²⁹ We found low rates of surveillance associated with high poverty which raises the issue of access to care as a major determinant of health status and ongoing care.^{30,31} We also found that CT surveillance increased over time, potentially due to increase in imaging overall for reasons independent of cancer. Changes in the guidelines themselves over time may also have influenced this finding. In 1996, version 1 of the NCCN guidelines recommended surveillance with history and physical examination and CXR every 4 months for the first 2 years.³² Our earliest cohort (1996-2000) showed a 75% adherence rate for CXR. Following that, CXR use declined and CT use increased. Nonetheless, the rate of CT imaging only reached 36% by the latest study time period. Lack of imaging surveillance demonstrated only modest decline over time and still represented 12% of the population.

Two other findings that stand out were patients with stage I disease and those undergoing surgery as sole therapy are at increased risk for lack of imaging surveillance. This subset of patients stands to gain the most benefit from surveillance as they have the best overall survival and potential time-at-risk for recurrent disease. However, patients undergoing sublobar lung resections are also at higher risk for local recurrence, and had higher odds of receiving a CT than those undergoing more extensive surgical resection. Thus the patterns

observed demonstrate appropriate patient selection for some and inappropriate selection for others. Such heterogeneity in adherence is also found in post-treatment surveillance programs for other cancer types.³³⁻³⁸

We specifically targeted early stage lung cancer patients undergoing surgical resection for their favorable outcomes. Our findings of stage I patients or those receiving surgery alone associated with the lowest odds of surveillance might be explained by heterogeneity in their follow up. These patients are potentially less likely to be referred to medical oncology for adjuvant therapy and may bypass the usual home for cancer surveillance. The task of surveillance may default to the thoracic surgeon, pulmonologist, or primary care provider. Exactly which of these providers will take the lead for surveillance may be ill defined. Thus, while Stage I patients undergoing surgical resection may have the best long-term survival, they may also paradoxically have the worst chance for meaningful surveillance. Further barriers to surveillance may include lack of reimbursement incentives, poor communication between providers and specialists, heterogeneity in knowledge, and inconsistent dissemination of current practice guidelines. Surveillance strategies reported by thoracic surgeons vary widely with only 44% believing in survival benefit. This heterogeneity may not be specialty specific.^{39,40}

Our study has several limitations. We utilized administrative claims with inherent challenges, however claims data have demonstrated ability to characterize guideline adherence comparable to medical chart review for other types of cancer surveillance.⁴¹ We do not have data on indication for the studies being performed thus there is potential for misclassification bias. Additionally, patient selection may impact a provider's decision to request surveillance imaging. Optimal outcomes from surveillance programs are seen in patients with better performance status, female gender, and younger age.¹⁶ Careful patient selection may actually be the key to a successful surveillance program. A selective approach rather than universal surveillance might lead to improved outcomes and efficiency in healthcare expenditures.⁴² More prospective studies, including randomized trials of surveillance effectiveness in influencing lung cancer specific survival, are needed to determine this definitively.

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Appendix A: Study cohort and exclusion criteria

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Figure 1. Kaplan-Meier estimates for Imaging over time

Table 1
First Imaging Surveillance 4-8 months following surgical resection

Number of subjects		First Surveillance Imaging in Patients with Early Stage Lung Cancer 4-8 Months Following Surgical Resection		P value	
Number of subjects	N (%)	CXR	CT	PE/CT	None of Three Imaging
Total N (%)	18,406	10,964 (59.6)	4,531 (24.6)	482 (2.6)	2,429 (13.2)
Age (years)					
65~69	4,902 (26.6)	57.4	26.7	2.6	13.2
70~74	5,568 (30.3)	59.6	24.5	2.9	13.0
75~79	4,735 (25.7)	61.4	23.4	2.5	12.7
80+	3,201 (17.4)	60.0	23.3	2.3	14.3
Gender					
Male	8,435 (45.8)	60.3	24.3	2.7	12.7
Female	9,971 (54.2)	58.9	24.9	2.6	13.6
Marital Status					
Married	10,602 (57.6)	59.8	25.5	2.6	12.1
Others	7,804 (42.4)	59.3	23.4	2.6	14.7
Poverty Level					
High	3,570 (19.5)	62.8	20.3	2.9	14.1
Middle	9,004 (49.2)	60.3	23.7	2.6	13.5
Low	5,745 (31.4)	56.4	28.9	2.6	12.1
Education Level					
Low	3,555 (19.4)	61.5	21.6	2.8	14.1
Middle	9,193 (50.2)	60.6	23.8	2.5	13.1
High	5,571 (30.4)	56.5	28.1	2.7	12.7
Race					
White	1,6402 (89.1)	59.9	24.7	2.6	12.8
Black	962 (5.2)	56.3	24.5	2.3	16.9
Other/unknown	1,038 (5.7)	57.8	23.9	2.7	15.6
Charlson Comorbidity					
No conditions	9,199 (50.3)	59.4	24.4	2.5	13.7

Number of subjects		First Surveillance Imaging in Patients with Early Stage Lung Cancer 4-8 Months Following Surgical Resection				P value
Number of subjects	N (%)	CXR	CT	PE/CT	None of Three Imaging	
1 Condition	5,555 (30.3)	60.1	25.0	2.5	12.4	
2-3 Conditions	2,983 (16.3)	59.6	24.8	3.1	12.5	
4 Conditions	568 (3.1)	63.9	23.6	3.0	8.8	
Stage						< .0001
I	15,863 (86.2)	60.1	23.9	2.3	13.7	
II	2,543 (13.8)	56.6	28.9	4.4	10.2	
Initial Treatment						< .0001
Surgery alone	15,510 (84.3)	60.7	22.8	2.1	14.4	
Surgery and XRT	705(3.8)	66.2	22.3	3.0	8.5	
Surgery and Chemo	1,907 (10.4)	47.9	39.3	6.2	6.5	
Surgery and XRT and Chemo	284 (1.5)	58.1	32.0	6.7	3.2	
Surgical Resection						< .0001
Wedge	4,851 (26.4)	55.4	28.0	2.7	13.9	
Segmentectomy	839 (4.6)	55.5	27.5	3.9	13.0	
Lobectomy	11,569 (62.9)	61.0	23.3	2.6	13.1	
Bilobectomy	590 (3.2)	68.5	18.6	1.9	11.0	
Pneumonectomy	494 (2.7)	62.5	24.7	1.4	11.4	
Mediastinoscopy Performed						0.0002
Yes	3,277 (17.8)	60.0	24.0	2.6	13.4	
No	15,129 (82.2)	57.7	27.5	2.6	12.1	
Histology						< .0001
Adenocarcinoma	10,346 (56.2)	57.8	26.2	2.7	13.3	
Squamous	5,527 (30.0)	62.8	21.9	2.3	13.0	
Large Cell	690 (3.8)	64.9	21.3	3.3	10.4	
NSCLC Undiff	707 (3.8)	56.4	28.0	2.7	12.9	
Others	1,136 (6.2)	58.7	23.7	2.6	15.1	

Poverty: quartile of national poverty level by census tract; High: $\geq 75\%$, Middle: 25%-75%, Low: $\leq 25\%$

Education: quartile of national non-high school graduation rate by census tract; Low: $\geq 75\%$, Middle: 25%-75%, High: $\leq 25\%$

Table 2
Overall Imaging Surveillance 4-8 months following surgical resection

Number of subjects	N (%)	CXR	P-value	CT	P-value	PET/CT	P-value	None	P-value
Size N	Total 18,406	12,608 (68.5)		8,758 (47.6)		1,952 (10.6)		2,429 (13.2)	
Age			0.0078		< .0001		< .0001		0.1684
	65~69	4,902 (26.6)	66.8	49.7		11.9		13.2	
	70~74	5,568 (30.3)	68.8	48.1		11.6		13.0	
	75~79	4,735 (25.7)	70.0	46.8		9.3		12.7	
	80+	3,201 (17.4)	68.5	44.5		8.8		14.3	
Gender			0.0008		0.2805		0.1571		0.0593
	Male	8,435 (45.8)	69.8	48.0		11.0		12.7	
	Female	9,971 (54.2)	67.5	47.2		10.3		13.6	
Marital Status			0.0476		0.0013		0.2729		< .0001
	Married	10,602 (57.6)	69.1	48.6		10.8		12.1	
	Others	7,804 (42.4)	67.7	46.2		10.3		14.7	
Poverty Level			< .0001		< .0001		0.0947		0.0093
	High	3,570 (19.5)	71.8	44.9		11.6		14.1	
	Middle	9,004 (49.2)	69.2	45.7		10.5		13.5	
	Low	5,745 (31.4)	65.3	52.3		10.2		12.1	
Education Level			< .0001		0.0007		0.0076		0.1709
	High	5,571 (30.4)	65.3	49.7		10.4		12.7	
	Middle	9,193 (50.2)	69.8	46.8		10.3		13.1	
	Low	3,555 (19.4)	70.2	46.4		12.1		14.1	
Race			0.0567		0.0816		0.3269		0.0002
	White	1,6402 (89.1)	68.8	47.9		10.6		12.8	
	Black	962 (5.2)	66.1	45.4		9.4		16.9	
	Other/unknown	1,038 (5.7)	65.7	44.4		11.9		15.6	
Charlson Comorbidity			< .0001		< .0001		< .0001		0.0017
	No conditions	9,199 (50.3)	67.3	44.9		9.7		13.7	
	1 Condition	5,555 (30.3)	69.5	49.1		11.0		12.4	

Number of subjects	N (%)	CXR	P-value	CT	P-value	PET/CT	P-value	None	P-value
2-3 Conditions	2,983 (16.3)	70.4	51.9	12.4	12.5				
4 Conditions	568 (3.1)	74.8	56.9	13.6	8.8				
Stage			0.1404		< .0001		< .0001		< .0001
I	15,863 (86.2)	68.3	45.7	9.4	13.7				
II	2,543 (13.8)	69.8	59.6	18.0	10.2				
Initial Treatment			< .0001		< .0001		< .0001		< .0001
Surgery alone	15,510 (84.3)	68.6	43.5	8.4	14.4				
Surgery and XRT	705 (3.8)	77.3	58.0	13.8	8.5				
Surgery and Chemo	1,907 (10.4)	62.6	72.5	24.1	6.5				
Surgery and XRT and Chemo	284 (1.5)	78.8	77.1	30.6	3.2				
Surgical Resection			< .0001		< .0001		< .0001		0.3308
Wedge	4,851 (26.4)	64.9	50.8	11.9	13.9				
Segmentectomy	839 (4.6)	66.0	51.7	14.2	13.0				
Lobectomy	11,569 (62.9)	69.5	46.2	10.0	13.1				
Bilobectomy	590 (3.2)	78.0	41.2	8.6	11.0				
Pneumonectomy	494 (2.7)	71.8	49.3	9.2	11.4				
Others	63 (0.3)	73.0	46.0	6.4	11.1				
Mediastinoscopy			0.9100		< .0001		0.0003		0.0435
Yes	3,277 (17.8)	68.4	46.4	10.2	13.4				
No	15,129 (82.2)	68.5	53.1	12.4	12.1				
Histology			< .0001		0.0189		0.3296		0.0744
Adenocarcinoma	10,346 (56.2)	66.6	47.9	10.6	13.3				
Squamous	5,527 (30.0)	71.9	46.8	10.5	13.0				
Large Cell	690 (3.8)	74.1	47.1	10.7	10.4				
NSCLC Undiff	707 (3.8)	66.6	52.8	13.0	12.9				
Others	1,136 (6.2)	67.1	45.3	10.3	15.1				

Table 3
Imaging by Study Period

	1996-2000	2001-2005	2006-2009	*p-value
Total (n=18,406)	4144 (22%)	7690 (42%)	6572 (36%)	
First Surveillance Imaging				
CXR %	75	62	47	<0.0001
CT %	10	23	36	
PET/CT %	0	2	5	
None %	15	13	12	
Prevalence of Surveillance Imaging				
CXR %	79	71	59	<0.0001
CT %	28	47	61	<0.0001
PET/CT %	2	9	18	<0.0001

Table 4

Predictors of Imaging

	Initial CT Chest @ 4-8 months			No Imaging @ 4-8 months		
	OR	95% CI		OR	95% CI	
Age						
65~69	REF					
70~74	1.06	0.98	1.15	0.98	0.87	1.10
75~79	1.08	1.00	1.18	1.04	0.92	1.18
80+	1.13	1.03	1.24	0.95	0.83	1.09
Gender						
Female	REF					
Male	0.97	0.91	1.03	1.03	0.94	1.13
Marital Status						
Not Married	REF					
Married	1.06	1.00	1.13	0.82	0.75	0.90
Poverty Level						
Low	REF					
Middle	0.76	0.70	0.81	1.13	1.01	1.27
High	0.71	0.63	0.79	1.11	0.93	1.31
Education Level						
Low	REF					
Middle	1.08	0.98	1.20	1.04	0.90	1.19
High	1.06	0.94	1.19	1.04	0.88	1.23
Race						
White vs Black	1.08	0.94	1.24	0.77	0.64	0.93
White vs Other/unknown	1.12	0.98	1.28	0.79	0.66	0.95
Black vs Other/unknown	1.04	0.87	1.25	1.03	0.81	1.32
Charlson Comorbidity Index						
No conditions	REF					
1 condition	0.83	0.77	0.89	1.13	1.02	1.25

Initial CT Chest @ 4-8 months		No Imaging @ 4-8 months				
	OR	95% CI	OR	95% CI		
2-3 Conditions	0.72	0.66	0.78	1.02	1.31	
	4 Conditions	0.55	0.46	0.65	1.82	1.35
Stage						
I	REF					
II	1.32	1.15	1.41	0.96	0.83	1.12
Treatment						
Surgery Alone	REF					
Surg+Rads	1.69	1.43	1.96	0.56	0.43	0.74
Surg+Chemo	3.23	2.86	3.57	0.43	0.36	0.53
Surg+Rads+Chemo	4.35	3.23	5.88	0.20	0.10	0.30
Surgical Resection						
Wedge	REF					
Segmentectomy	0.99	0.85	1.15	0.93	0.74	1.16
Lobectomy	0.81	0.76	0.87	0.93	0.85	1.03
Bilobectomy	0.64	0.53	0.77	0.78	0.59	1.02
Pneumonectomy	0.71	0.58	0.87	0.94	0.69	1.28
Mediastinoscopy						
No	REF					
Yes	0.80	0.73	0.86	1.06	0.94	1.19