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SURVEILLANCE IMAGING FOLLOWING CURATIVE-INTENT SURGERY FOR NON-SMALL CELL LUNG CARCINOMA: A SYSTEMATIC REVIEW

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SURVEILLANCE IMAGING FOLLOWING CURATIVE-INTENT SURGERY FOR NON-SMALL CELL LUNG CARCINOMA: A SYSTEMATIC REVIEW

by

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Treatise

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Dedication

This treatise—and all I accomplish in this life—is dedicated to my husband, Chris, my son, Ethan, and my sweet baby yet to be born, for their unfailing love, support, and encouragement. You give me a million reasons every day to try to be better than I was the day before. Go Team Edwards!

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Dr. Edwards is a recipient of the Herzog Foundation Educational Enrichment Award, which provided financial support for her graduate studies.

SURVEILLANCE IMAGING FOLLOWING CURATIVE-INTENT SURGERY FOR NON-SMALL CELL LUNG CARCINOMA: A SYSTEMATIC REVIEW

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Following curative surgery for non-small cell lung carcinoma (NSCLC), patients remain at risk for recurrence of lung cancer or for development of second primary lung cancer (SPLC). While periodic surveillance may detect early stage recurrence or SPLC, the effectiveness of surveillance has not been established. Additionally, current practice guidelines conflict in terms of the optimal frequency of surveillance and modalities to employ. The purpose of this study is to evaluate whether the use of surveillance following curative surgery for NSCLC is effective in diagnosing recurrence or SPLC in asymptomatic patients, in comparison to usual care. Electronic databases (MEDLINE, EMBASE, CINAHL, and Cochrane Library) were searched for pertinent studies published between 1990 and 2010. Major search concepts included non-small cell lung carcinoma, surveillance, curative resection, recurrence, second primary lung cancer, computed tomography, and chest x-ray. Baseline data and results from individual studies were pooled. Odds ratios and confidence intervals were computed for each of the following endpoints: detection of recurrence by surveillance, asymptomatic presentation at recurrence, and site of recurrence. Eighteen cohort and case-control studies were included in this analysis. No randomized controlled trials were identified. A total of 1019 recurrences and second primary lung cancers were detected among 2716 patients. 53.1% of cases were detected by surveillance protocol (OR 1.28, 95% CI 0.97-1.69). 34.9% of patients were asymptomatic at time of detection (OR 0.42, 95% CI 0.33-0.53). Distant recurrence occurred much more frequently than local recurrence (OR 2.69, 95% CI 2.17-3.35). Only 172 patients were offered a second curative-intent surgery (16.9%). Current literature does not argue for or against routine surveillance imaging after curative surgery for NSCLC. We await the results of randomized, controlled trials to provide more conclusive evidence.

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Chapter 1: Introduction

Lung cancer is the leading cause of cancer death among men and women in the U.S. Non-small cell lung cancer (NSCLC) comprises about 80% of primary lung cancers. An estimated 219,440 of NSCLC cases were diagnosed in the U.S. in 2009.[1] Curative-intent surgery offers the best chance for survival in these patients. However, only 15% of patients have localized disease amenable to complete surgical resection at time of diagnosis.[2]

Following curative surgery, patients remain at risk for recurrence of lung cancer or for development of second primary lung cancer (SPLC).[3] Approximately 30%, 65%, and 80%, of patients undergoing resection for Tumor-Node-Metastasis (TNM) stage I, II, and III cancers, respectively, will have recurrence within 5 years. [4-6] Few of these recurrences are amenable to a subsequent curative resection. Second primary cancers will develop in approximately 2-3% of these patients each year, a risk that is relatively constant in the first 5 years after primary resection. [5,7] The widely accepted criteria for second primary lung cancers were established by Martini and Melamed. They contend that the first and second cancers must either be of different histological type; conversely, if the histology is the same, there must be a disease-free interval of at least 3 years between the first and second cancers. Additionally, the second primary should have arisen from a cancer *in situ*, the tumors should have occurred in different lobes without common lymph node involvement, and no extrapulmonary metastasis should be present at time of diagnosis of the second tumor.[8]

Surveillance regimens following curative treatment for NSCLC generally consist of some combination of office visits, chest roentgenography (x-ray), computed tomography (CT) of the

chest, serum tumor markers, sputum cytology, bone scans, and magnetic resonance imaging (MRI) of the chest and/or head. No single modality is simultaneously sensitive, specific, safe, convenient, and cost-effective. Additionally, each modality is useful for detecting specific types of lesions. Thus, combining strategies is preferred so as to optimize the chance of detecting recurrence or SPLC, with the goal of facilitating potentially curative treatment or early palliation.

To date, there are no published prospective, randomized trials evaluating surveillance in asymptomatic patients following curative resection for NSCLC. Likewise, there are no consensus guidelines for modes or frequency of surveillance. The American Society of Clinical Oncology recommends post-treatment surveillance with history and physical exam alone. In contrast, the American College of Chest Physicians (ACCP), and American College of Radiologists recommend the use of chest x-ray and the National Comprehensive Cancer Network (NCCN) recommends use of computed tomography for surveillance.[9.10] None of these recommendations are based on level 1 evidence.

While periodic surveillance may benefit NSCLC survivors by detecting early stage recurrence or SPLC, its bears the potential harm inherent in disease screening. It has not been established if post-surgical surveillance affects cancer or overall mortality. Any perceived benefit of detection may be attributable to lead-time bias. Additionally, the stress and anxiety associated with false positive results, as well as the risk for adverse outcomes related to treatment of benign nodules are not insignificant. Furthermore, the cost of surveillance scans and associated treatments must be considered.

The purpose of this systematic review is to evaluate whether the use of surveillance following curative surgery for non-small cell lung cancer is effective in diagnosing recurrent

NSCLC or SPLC in asymptomatic patients, in comparison to usual care. This study aims to compare patterns of surveillance testing after curative surgical resection for non-small cell lung cancer, including modalities employed, frequency of investigation, and provider characteristics. Effects of surveillance testing on disease-free survival and overall survival, as well as cost-effectiveness of various strategies are also examined.

Chapter 2: Methods

The PRISMA guidelines for systematic reviews were used for this study (Appendix A).[11,12] Electronic databases (MEDLINE, EMBASE, CINAHL, and Cochrane Library) were searched for pertinent studies published between 1990-2010. Other sources of data included meeting abstracts, completed studies, and references cited in the studies identified. Major search concepts included non-small cell lung cancer, surveillance, curative resection, recurrence, second primary lung cancer, computed tomography, and chest x-ray. These concepts and their synonyms were exploded to include all subheadings of Medical Subject Headings (MeSH). No other search filters were used. Non-English results were included in the screening.

Cohort and case-control studies with before- and after- controls were examined. Surveillance modalities of interest included chest x-ray, physical exam, computed tomography, and positron emission tomography. The types of outcome measures studied included detection of recurrent non-small cell lung cancer, detection of second primary lung cancer, site of recurrence or second primary, rates of asymptomatic presentation, rates of detection by modality, and rate of second curative-intent resection following recurrence or diagnosis second primary lung cancer.

All pertinent studies were retrieved and independently screened. Articles that did not meet the study criteria were excluded, with reasons recorded. Data from each study were recorded in the Data Extraction Form (Appendix B). The Cochrane Collaboration's tool for assessing risk of bias was used to evaluate each study.

Baseline data and results from the individual studies were pooled. Due to the heterogeneity of the studies, a formal meta-analysis could not be performed. However, odds ratios were computed for each of the following endpoints: detection of recurrence by surveillance, asymptomatic presentation at recurrence, and site of recurrence. Confidence intervals were computed for each odds ratio. All quantitative statistical analyses were performed using the software SAS, version 9.2 (Cary, North Carolina).

A flow diagram of the search strategy is shown in Figure 1. The initial database search generated 64 records. An additional 5 records were identified during review of meeting abstracts, unpublished studies, and cited references. After duplicates were removed, 61 unique records were screened. 31 records were excluded because they did not meet the study criteria. The remaining 30 full-text articles were retrieved and assessed for eligibility. Four case studies, 2 editorials, and 2 review articles were excluded. In addition, 2 studies that employed surveys to examine physician preferences on surveillance strategies were excluded. One article based on computer-based economic modeling and one clinical trial design was also excluded. The 18 remaining original studies were included the qualitative analysis. Characteristics, including study date, design, sample size, demographics, primary tumor characteristics, and rate of recurrence for each study is shown in Table 1.

Figure 1: Search Results

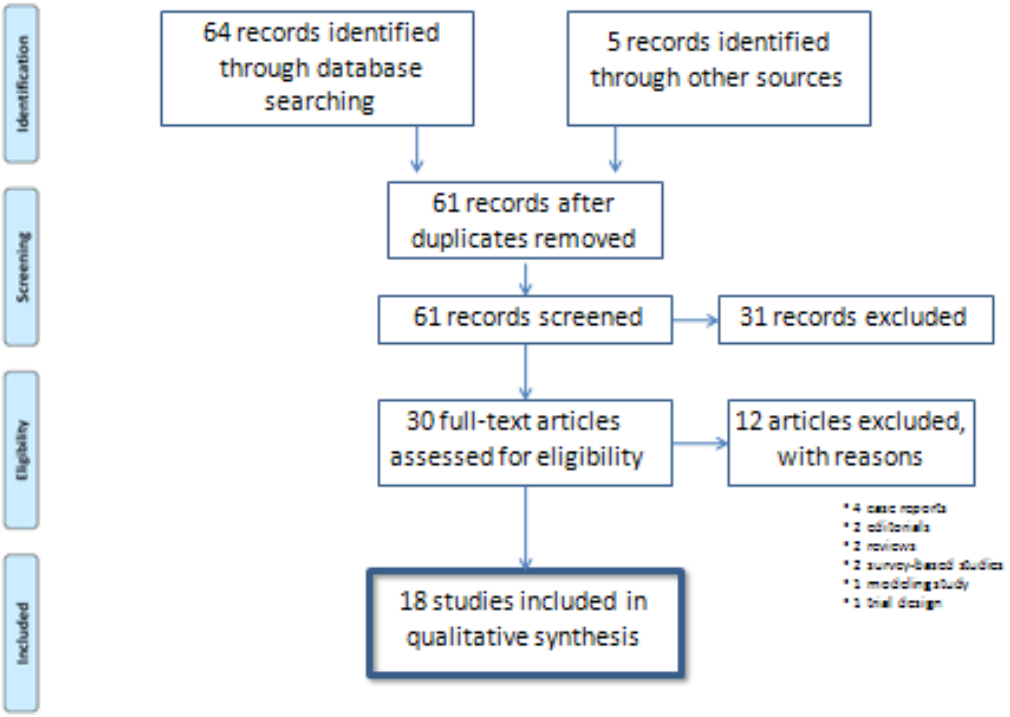

Table 1: Characteristics and Results of Included Studies

AUTHOR, YEAR	JOURNAL	LOCATION	STUDY DATES	DESIGN	NUMBER OF PATIENTS
Gorich et al, 1990[13]	Clinical Imaging	Germany	1986-1987	Prospective	17
Virgo et al, 1995[14]	Annals of Surgery	USA	1982-1992	Retrospective	182
Walsh et al, 1995[15]	Annals of Thoracic Surg	USA	1987-1991	Retrospective	358
Inoue et al, 1995[16]	J Nucl Med	USA	not given	Prospective	15
Bury et al, 1999[17]	Eur Respir J	Belgium	1994-1997	Prospective, consecutive series	44
Younes et al, 1999[18]	Chest	Brazil	1983-1993	Retrospective, case-control	130
Gilbert et al, 2000[19]	Ann Thorac Surg	Canada	1988-1997	Retrospective	245
Westeel et al, 2000[20]	Rev Mal Respir	France	1980-1993	Prospective, consecutive series	192
Weigel et al, 2000[21]	Ann Surg Oncol	USA	1997-1998	Prospective, consecutive series	25
Egermann et al, 2002[22]	Eur Respir J	Switzerland	1980-1997	Prospective, consecutive series	563
Lamont et al, 2002[23]	Archives of Surgery	USA	1996-2000	Retrospective	124
Chiu et al, 2003[24]	J Thorac and CV Surg	Taiwan	2000	Prospective, consecutive series	43
Hellwig et al, 2005[25]	Eur J Nucl Med and Mole Imag	Germany	1996-2004	Prospective, consecutive series	62
Korst et al, 2005[26]	J Thorac and CV Surg	USA	1994-2002	Retrospective	213
Aokage et al, 2006[27]	Lung Cancer	Japan	1992-2000	Retrospective, consecutive series	265
Benamore et al, 2007[28]	J Thorac Oncol	Canada	not given	Retrospective, two-cohort	75
Cho and Lee, 2009[29]	J Thorac and CV Surg	Korea	2003-2006	Retrospective	86
Nakamura et al, 2010[30]	Onkologie	Japan	1980-2008	Retrospective	1398

AUTHOR, YEAR	MEDIAN AGE (RANGE)	GENDER DISTRIBUTION (%)	HISTOLOGY (%)	STAGE POST-RESECTION (%)	PRIMARY TREATMENT (%)	RATE OF RECURRENCE (%)
Gorich et al, 1990[12]	59 (41-79)	Male 15 (88.2) Female 2 (11.8)	Adeno 6 (35.3) SCC 10 (58.8) Other 1 (5.9)	1A 2 (11.7) 1B 3 (17.6) 2B 4 (23.5) 3A 7 (41.2)	Lobectomy 13 (76.6) Bilobectomy 2 (11.7) Pneumonectomy 2 (11.7)	16/17 (94.1)
Virgo et al, 1995[16]	Not described	Not described	Not described	Not described	Not described	42/182 (23.1)
Walsh et al, 1995[15]	63 (41-88)	Male 222 (62) Female 136 (48)	Adeno 175 (48.9) SCC 120 (33.5) LCC 15 (4.2) BAC 26 (7.3) Undiff 22 (6.1)	1A 85 (23.7) 1B 105 (29.3) 2A 16 (4.5) 2B 31 (8.7) 3A 111 (31) 3B 10 (2.8)	Wedge resection 68 (19) Lobectomy 229 (64) Pneumonectomy 61 (17)	135/358 (37.7)
Inoue et al, 1995[16]	62 (37-80)	Male 8 (53.3) Female 7 (46.7)	Adeno 6 (40) SCC 7 (46.7) BAC 1 (6.7) Undiff 1 (6.7	Not described	Not described	8/15 (53.3)
Bury et al, 1999[17]	Not described	Male 78 (61.9) Female 48 (38.1)	Not described	1 20 (45.5) 2 20 (45.5) 3 4 (9)	Surgery not described Adjuvant therapy 12 (27.3)	13/44 (29.5)
Younes et al, 1999[18]	60 (range not described)	Male 111 (85.4) Female 19 (14.6)	Adeno 41 (31.5) SCC 80 (61.5) LCC 9 (7)	1 38 (29.2) 2 30 (23) 3A 57 (43.8) 3B 5 (3.8)	Lobectomy 80 (61.5) Bilobectomy 15 (11.5) Pneumonectomy 35 (27) Adjuvant therapy 52 (40)	32/130 (24.6)
Gilbert et al, 2000[19]	64 (34-83)	Male 144 (58.8) Female 101 (41.2)	Adeno 124 (50.6) SCC 86 (35.1) LCC 27 (11) BAC 8 (3.3)	1A 88 (35.9) 1B 110 (44.9) 2A 17 (6.9) 2B 30 (12.3)	Wedge resection 18 (7.3) Lobectomy 167 (68.2) Bilobectomy 20 (8.2) Pneumonectomy 40 (16.3)	111/245 (45.3)
Westeel et al, 2000[20]	60 (33-81)	Male 177 (92.2) Female 15 (7.8)	Adeno 43 (22) SCC 146 (76) LCC 4 (2)	1 86 (44.8) 2 36 (18.8) 3A 57 (29.7) 3B 9 (4.7) 4 4 (2.1)	Limited resection 3 (1.5) Lobectomy 71 (37) Bilobectomy 6 (3.1) Pneumonectomy 113 (58.9) Adjuvant therapy 68 (35.4)	136/192 (70.8)
Weigel et al, 2000[21]	62 (38-80)	Male 17 (68) Female 8 (32)	Not described	3A 5 (20) Unk 20 (80)	Not described	3/25 (12)

Adeno = adenocarcinoma; SCC = Squamous cell carcinoma; AS = Adenosquamous cell carcinoma; LCC = Large cell carcinoma; BAC = Bronchoalveolar cell carcinoma; Undiff = Undifferentiated; Unk = Unknown

			Undiff 6 (8)					
Cho and Lee, 2009[29]	61.2 (35-76)	Male 64 (74.4) Female 22 (25.6)	Adeno 31 (36) SCC 49 (57) BAC 4 (4.7) Other 2 (2.3)	1A 20 (23.3) 1B 36 (41.9) 2A 3 (3.5) 2B 12 (13.9) 3A 15 (17.4)	Lobectomy 83 (96.5) Pneumonectomy 3 (3.5) Adjuvant therapy 19 (22.1)		27/86 (31.4)	
Nakamura et al, 2010[30]	67 (25-95)	Male 1014 (72.5) Female 384 (27.5)	Adeno 722 (51.6) SCC 504 (36.1) Undiff 172 (12.3)	1 713 (51) 2 240 (17.2) 3 445 (31.8)	Surgery not described Adjuvant therapy 303 (21.7)		Not described	

Adeno = adenocarcinoma; SCC = Squamous cell carcinoma; AS = Adenosquamous cell carcinoma; LCC = Large cell carcinoma; BAC = Bronchoalveolar cell carcinoma; Undiff = Undifferentiated; Unk = Unknown

Chapter 3: Results

BASELINE CHARACTERISTICS

Baseline characteristics of the study population, including age, gender, primary tumor histology, primary tumor stage, and primary surgical procedure are summarized in Table 2. Not all data were available for every patient. In total, there were 4119 patients involved in these 18 studies. The median age of the study population was 63.3 yrs, and there was a predominance of male subjects. Information on primary tumor histology was available for 3669 patients. The primary non-small cell lung cancers included 46.8% adenocarcinoma and 40% squamous cell carcinoma. Post-resection stage information was available for 3776 patients. There stage distribution included 54.2% stage I, 18.9 % stage II, 25.9% stage III tumors, and 0.4% stage IV tumors. Information on primary surgical treatment was available for 2243 patients. The most common surgical procedures were lobectomy, followed by pneumonectomy, and wedge resection. Approximate one quarter of the patients underwent adjuvant chemotherapy following their primary surgery.

Table 2: Patient Demographics, Tumor Characteristics, and Primary Treatment (N=4119). Not all information was available for every patient. Sample sizes for subheadings are provided. † $p<0.05$

CHARACTERISTICS	NUMBER (%)
Total patients	4119
Median age, yr	63.3
Gender†	
Male	2744 (66.7)
Female	1193 (33.3)

Histology (n=3669)	
Adenocarcinoma	1716 (46.8)
Squamous Cell	1467 (40)
Adenosquamous	7 (0.2)
Large Cell	127 (3.5)
Bronchoalveolar Cell	88 (2.4)
Undifferentiated	232 (6.2)
Other	32 (0.9)
Stage Post-Resection (n=3776)	
1	2045 (54.2)
2	714 (18.9)
3	979 (25.9)
4	15 (0.4)
Unknown	23 (0.6)
Primary Treatment (n=2243)	
Segmentectomy	9 (0.4)
Wedge Resection	123 (5.5)
Lobectomy	1549 (69)
Bilobectomy	61 (2.7)
Sleeve Lobectomy	2 (0.1)
Pneumonectomy	498 (22.2)
Completion Pneumonectomy	1 (0.1)
Adjuvant therapy	546 (24.3)

SURVEILLANCE PROTOCOLS

Reported surveillance protocols are summarized in Table 3. Although no two protocols were identical, there were notable trends. The most commonly employed modalities were physical exam, chest x-ray, and CT of the chest. Many protocols included physical exam and chest x-ray at every visit, with more advanced radiological modalities being used at less frequent intervals (e.g. every other visit) or as confirmatory studies. There was a trend toward more frequent monitoring in the first two years after surgery, with a tapering of surveillance frequency thereafter. The majority of surveillance was performed by thoracic surgeons.

Table 3: Surveillance Protocols. q = every; w = week; m = month; y = year; PE = physical exam; CXR = Chest x-ray; CT = computed tomography; PET = positron emission tomography; US = ultrasound; CEA = carcinoembryonic antigen; MRI = magnetic resonance imaging; LDCT = low-dose computed tomography; N/R = not reported

Author/Year	Follow-up Interval	Surveillance Protocol	Provider	Median Follow-up (mos)
Gorich et al, 1990[13]	Some f/u between 2-6m	CXR/CT, then PET for any suspicious CT finding	N/R	30
Virgo et al, 1995[14]	Variable	Intensive = 4+visits, 1+CT, 4+blood tests, 4+CXRs,bronch, or sputum cytology in 12m; Nonintensive = none of the above	Thoracic surgeon	40
Walsh et al, 1995[15]	Variable	Per physician discretion	Thoracic surgeon and Oncologist	76
Inoue et al, 1995[16]	One time	FDG-PET in conjunction with CT or MRI; "positive" scans confirmed by other methods	N/R	N/R
Bury et al, 1999[17]	q3m x 4y	PE q3m; CT and PET q6m	Pulmonologist	N/R
Younes et al, 1999[18]	1,3w; 2,4,6m; then q3m up to 24m	PE qvisit; CXR at first 4 visits then q other visit; CT q6m; LFTs qy	Thoracic surgeon	N/R
Gilbert et al, 2000[19]	q3-4 m x 2y; then q6m x 3y; then qy	PE, CXR, CT, bone scan, abdominal US, or biopsy	Thoracic surgeon or Pulmonologist	41
Westeel et al, 2000[20]	q3m x 3y; then q6m x 4y; then qy	PE/CXR q3m and CT/bronchoscopy q6m x3y; then PE/CXR q6m and CT scan qy x 4y; then CXR qy	Thoracic surgeon and Pulmonologist	131
Weigel et al, 2000[21]	One time	Fluorescence bronchoscopy	Thoracic surgeon	N/R
Egermann et al, 2002[22]	q3m x 2y; then q6m x 3y; then qy x 5y	PE, CXR qvisit	Family doctor	48
Lamont et al, 2002[23]	CT qy; CXR q4m x 2y; then q6m x 3y	PE/CXR q4m x 2y; then PE/CXR q6m; CT qy	Thoracic surgeon	N/R
Chiu et al, 2003[24]	q3m x 2y; then q6m x 3 y	PE, sputum cytology, serum CEA, CXR, LDCT	N/R	15.5
Hellwig et al, 2005[25]	Variable	PET ordered for any suspicious CT lesion greater than 1.3cm found during routine surveillance	Thoracic surgeon or Pulmonologist	N/R

Korst et al, 2005[26]	q3m x 1y; then q6m x 1y; then qy	PE qvisit; CXR at 3, 9, 18m; CT at 6, 12m, then qy	Thoracic surgeon	79
Aokage et al, 2006[27]	q3m x 1y; then q6m x 4y	PE/CXR/serum CEA qvisit, abdominal US qy	Thoracic surgeon	72
Benamore et al, 2007[28]	q3m x 2-3y; then q6m up to 5y	PE/CXR/bloodwork qvisit, CT or MRI only for suspicion of relapse	N/R	36
Cho and Lee, 2009[29]	q3m x 2y	PE/CXR/tumor marker q3mos, CT q 6mos; PET at 1 year post-op or for suspicion	Thoracic surgeon or Pulmonologist	31
Nakamura et al, 2010[30]	Surgeon - 1m then q3-4m x 3y; Pulmonologist - q3-4m	Thoracic surgeon - PE/CXR qvisit; Pulmonologist - PE/CXR q3m and CT q6m	Thoracic surgeon or Pulmonologist	79

DETECTION OF RECURRENT NSCLC OR SECOND PRIMARY LUNG CANCER

Patient data from the studies were pooled for analysis. Not all data of interest were available for each patient. Summary measures are shown in Table 4 and odds ratios are shown in Table 5. A total of 1019 recurrences and SPLCs (37.5%) were detected among 2716 patients. Information regarding mode of detection was available for 392 cases. Of those, 208 (53.1%) were detected by surveillance protocol and 184 (46.9%) were detected by usual care. There was no significant difference in detection by protocol (OR of detection by surveillance 1.28, 95% confidence interval 0.97-1.69). Among 625 patients with recurrence or SPLC, 407 (65.1%) were symptomatic at the time of detection and 218 (34.9%) were asymptomatic (OR of being asymptomatic 0.42, 95% confidence interval 0.33-0.53). Of 699 cases of recurrence or SPLC, 231 (33%) were local, 399 (57.1%) were distant, and 69 (9.9%) were both local and distant. Distant recurrence was much more likely than local recurrence (OR 2.69, 95% confidence interval 2.17-3.35). Notably, of the 1019 cases or recurrence or SPLC, only 172 (16.9%) were offered a second curative-intent surgery.

Table 4: Recurrent Non-small Cell Lung Cancer and Second Primary Lung Cancer
Not all information was available for each patient. "Number of eligible cases" represent total number of data points available for outcome of interest, with corresponding percentages reported.

Result (number of eligible cases)	**Number (%)**
Any recurrence or SPLC (n=2716)	1019 (37.5)
Status of recurrence or SPLC (number of eligible cases)	**Number (%)**
Found by protocol (n=392)	208 (53.1)
Found outside of protocol (n=392)	184 (46.9)
Asymptomatic (n=625)	218 (34.9)
Symptomatic (n=625)	407 (65.1)
Site (n=699)	
Local recurrence	231 (33)
Distant recurrence	399 (57.1)
Local and distant	69 (9.9)
Second Primary	65 (9.3%)

Table 5: Odds of Recurrence or SPLC, by Protocol, Symptoms, and Site

CONDITION	**ODDS RATIO (95% CI)**
Recurrence detected by surveillance protocol	1.28 (0.97-1.69)
Recurrence detected by usual care	1.00
Asymptomatic at recurrence	0.42 (0.33-0.53)
Symptomatic at recurrence	1.00
Distant recurrence	2.69 (2.17-3.35)
Local and distant recurrence	0.22 (0.17-0.30)
Local recurrence only	1.00

DISEASE-FREE INTERVAL

Disease-free interval refers to the amount of time between the completion of treatment for the primary cancer and the detection of a recurrence or SPLC. Younes et al found no difference in disease-free interval between a group of patients enrolled in a surveillance protocol and those who were given usual care.[18] In a series of 239 patients with recurrent NSCLC or SPLC, Egermann et al found no correlation between the disease-free interval and duration of survival after the second curative surgery.[22] In contrast, Walsh et al determined that a disease-free interval of greater than 12 months was the most important predictor of survival after recurrence.

SURVIVAL

Associations between surveillance protocols, mode of presentation (asymptomatic or symptomatic), site of recurrence, or second treatment, and overall survival among the various studies were conflicting. In a retrospective analysis of 182 patients, Virgo et al found that patients who were intensively followed after primary resection survived an average of 192 days longer than those without intensive follow-up.[14] Walsh et al found that mode of presentation and site of recurrence did not significantly affect survival in a series of 358 patients. Egermann et al found no significant difference in survival between patients who underwent a second curative-intent resection for recurrent NSCLC or SPLC and those who did not.[22]

COST-EFFECTIVENESS

Egermann et al examined the cost associated with the surveillance and second curative-intent treatment for a series of 563 patients.[22] In this population, a total of 239 cases of recurrence and SPLC were detected, with over 70% of the cases being detected in the first year after primary surgery. Only 23 patients were eligible for a second curative resection. Among this group, 21 of the tumors were identified as SPLC, and 15 were detected by surveillance. Taken together, the 23 patients gained a calculated benefit of 17 additional life-years. The associated cost per life-year gained was estimated at $56,000 US dollars. Based on these cost estimates, the authors recommended a surveillance strategy consisting solely of chest x-ray every 6 months for the first five years after primary surgery.

Using Medicare fee schedules, Korst et al compared the cost of surveillance computed tomography scans and associated care in a cohort of 213 patients with a hypothetically identical cohort not subjected to surveillance scans.[26] The authors estimated that the cost in the surveillance group would be 16.6% higher than the hypothetical usual care group.

PROGNOSTIC INDICATORS

Nakamura et al conducted the largest retrospective review to date, with a population of 1,398 patients treated between 1980-2008.[30] The group used univariate and multivariate analyses to identify patient factors associated with favorable prognosis. They concluded that age less than 65 years, female sex, early stage disease (TNM stage I or II), lack of adjuvant therapy, and a Charlson Index of 0-1 (indicating few comorbidities) were all positive prognostic factors for survival. Similarly, Westeel et al showed asymptomatic recurrence, female sex, performance

status of 2 or less, and age 61 years or younger to be favorable prognostic factors.[20] In contrast, Gilbert et al sought to identify factors that negatively impacted survival.[19] In their study of 245 patients with initial early stage NSCLC, negative prognostic factors included a disease-free interval of less than 12 months, advance tumor stage at time of recurrence or SPLC, and presence of symptoms at time of detection of recurrence.

QUALITY ASSESSMENT

The Cochrane collaboration's tool for assessing risk of bias was used in the evaluation of the included studies. Although this tool was designed for the assessment of randomized controlled trials, many aspects of the tool remained applicable to this systematic review. Individual studies were evaluated on the basis of generalizability, sample size, dropout rate, and statistical methodology. No studies were excluded on the basis of quality.

Chapter 4: Discussion

There are no current practice guidelines for surveillance following curative-intent surgery for NSCLC based on high-grade evidence. As a result, wide variation exists in both the types of surveillance investigations employed and the frequency of surveillance. Nonetheless, trends in results were noted among the individual studies and with the pooled data. Rates of recurrence and detection of SPLC are high. Evidence from these cohort and case-control studies suggest that surveillance protocols do not seem to be significantly better at detecting these recurrences than usual care. This is supported by the finding that the majority of patients are already symptomatic at time of presentation for work-up. Furthermore, recurrences are more likely to be distant. This may represent a failure of surveillance strategies that focus on lung alone, and do not take into account common sites of distant disease, such as bone. Alternatively, this may imply that many early "recurrences" may actually represent progression of micrometastases left undetected at time of primary staging and treatment.

Only one study found a survival difference between patients under surveillance and patients who received usual care. Several studies reported no significant difference in survival with active surveillance. These findings further argue against the utility of surveillance protocols. Any perceived benefit of active surveillance may be related to lead-time bias, without an associated survival advantage.

Additionally, the costs of surveillance tests and associated work-up are significantly higher than the cost of usual care. Even when a modest survival benefit of surveillance is

assumed, the costs per life-year gained remain high. Given the prevalence of non-small cell lung cancer, the cumulative cost of surveillance care represents a sizable expenditure.

Nonetheless, there are nuances of the physician-patient relationship that are not highlighted by these studies, which may influence the use of surveillance imaging. First, there is a gap between what a patient may want to know about disease progression or recurrence and what a physician is capable of treating or curing. Poor understanding of the prognosis associated with recurrence or SPLC may unduly increase the use of surveillance. Secondly, physicians may be motivated to apply surveillance strategies in order to improve patient satisfaction, for medicolegal purposes, or simply to assess the outcomes of the care that they are providing.

While little progress has been made in the treatment of Stage IV non-small cell lung cancer, which still carries a dismal 5-year survival rate, novel strategies have improved survival in earlier stage NSCLC.[31] Adjuvant therapy with cisplatin-based chemotherapy agents have been shown to improve cure rates.[32] Similarly, concurrent chemoradiation therapy has been shown to have improve survival, with increased benefit over radiation alone.[33] In addition, growing interest in genotyping and personalized medicine has lead to the identification of genetic variants that are associated with response to treatment and with survival.[34] Given these advances beyond the mainstay of surgical resection, the role of surveillance imaging may be evolving and could be significant.

It is important to note that only five of the studies examined in this review involved the use of positron emission tomography (PET) scans, and only two incorporated PET scans at regular intervals instead. PET scans have traditionally been utilized for secondary investigation of suspicious lesions, but as their availability has grown, so has their use. Since the majority of

recurrent lung cancers are extrapulmonary, PET scans have become an attractive and viable option for whole body imaging in post-treatment surveillance. Nonetheless, the effectiveness of PET scans as a surveillance tool in comparison to x-ray and computed tomography remains unclear. More studies using PET scans as a primary surveillance tool are needed to address this issue.

Taken alone, these studies argue against surveillance as an efficacious and cost-effective tool for detecting recurrence following curative-intent surgery for primary NSCLC. Nonetheless, this systematic review is limited by the strength of evidence currently available. The included studies were all cohort or case-control studies, mostly reflective of various institutions' anecdotal experience. Data for all study patients were incomplete, limiting the strength of the statistical analysis.

The recently published results of the large National lung Screening Trial suggest a mortality benefit in high-risk patients who were screened annually with low-dose computed tomography.[35] Although this study was focused on screening prior to the diagnosis of a primary lung carcinoma, it calls into question again the potential benefit of surveillance following treatment for lung cancer. Evidence from randomized, controlled trials (RCTs) would be most useful in determining best practice guidelines for this area. One large RCT, currently underway in France, is expected to conclude in 2014, with 10 years of data to be collected.[36] While we await these results, we must continue to weigh the risks and benefits of routine surveillance imaging in the context of patient-centered care, and continue to strive towards advances in the treatment of non-small cell lung carcinoma.

Chapter 5: Conclusion

Non-small cell lung carcinoma comprises the majority of lung cancers, and is associated with high mortality. Rates of recurrence and of second primary lung cancer remain high even after curative-intent resection. Systematic review of current evidence suggests that routine surveillance imaging detects recurrence and SPLC at rates similar to usual care. Patients are more likely to be symptomatic at time of recurrence or SPLC, and are more likely to present with distant disease. However, the lack of level 1 evidence prohibits the development of best practice guidelines regarding the use of surveillance imaging following curative-intent surgery for non-small lung carcinoma. While we await the results of randomized, controlled trials addressing this issue, the results of this systematic review must be balanced with current advances in NSCLC treatment and individual patient goals.

Appendix A: PRISMA Checklist for Systematic Review

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Appendix B: Data Extraction Form

Study name:
Authors:
Date of publication:
Journal of publication:
Study Dates:
Location:
Number of centers involved in study:
Study Design:

Number of patients:
- Male:
- Female:

Median age:

Primary tumor stage:
- Ia:
- Ib:
- IIa:
- IIb:
- IIIa:
- IIIb:
- IV:
- Unknown:

Primary tumor histology:
- Adenocarcinoma:
- Squamous cell:
- Bronchoalveolar cell:
- Adenosquamous:
- Large cell:
- Undifferentiated:
- Other:

Primary treatment:
- Segmentectomy:
- Wedge resection:
- Lobectomy:
- Bilobectomy:
- Sleeve resection:
- Pneumonectomy:

Completion pneumonectomy:
Adjuvant chemotherapy:
Radiation therapy:

Surveillance protocol (type and frequency):
Clinical exam:
Sputum cytology:
Chest x-ray:
Computed tomography:
Bronchoscopy:
Positron emission tomography:
Bloodwork:
MRI:
Bone scan:

Surveillance provider:
Primary care provider
Chest physician
Thoracic surgeon

Median follow-up:

Incidence of recurrence:

Incidence of second primary lung cancer:

Recurrence/second primary lung cancer:
Identified by surveillance study:
Identified by usual care:

Asymptomatic at discovery:
Symptomatic at discovery:

Identified by chest x-ray:
Identified by computed tomography:
Identified by positron emission tomography:
Identified by other:

Local recurrence:
Distant recurrence:
Local and distant recurrence:

Stage of second tumor:
- Ia:
- Ib:
- IIa:
- IIb:
- IIIa:
- IIIb:
- IV:
- Unknown:

Histology of second tumor:
- Adenocarcinoma:
- Squamous cell:
- Bronchoalveolar cell:
- Adenosquamous:
- Large cell:
- Undifferentiated:
- Other:

Treatment offered:
- Second surgical resection:
- Chemotherapy:
- Radiation therapy:
- Palliative care:

Median disease-free survival:

Median survival without reoperation:

Median survival with reoperation:

Study quality assessment:
- Risk of bias in individual study:
- Data collection methods:
- Confounding:
- Rate of attrition:
- Strength of statistical analysis:
- Study limitations:
- Conflicts of interest:

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Vita

Dr. Edwards was born on November 6, 1977 in Fort Worth, Texas to parents Phi-Ho and Thanh-Mai Hoang. She attended Rice University in Houston, Texas as a National Merit Scholar and completed her Bachelor of Arts in Cell Biology and French Studies in 2000. During her time at Rice, she was president of the Vietnamese Students Association and Pi Delta Phi French Honor Society. She was also active in the multicultural group ADVANCE (Advocating DiVersity And the Need for Cultural Exchange), and was selected to Leadership Rice and the Schlumberger Initiative for Women.

Upon graduating, Dr. Edwards matriculated at the University of Texas Medical Branch (UTMB) School of Medicine. During medical school, she served as chair of the Honor Education Council, and was the recipient of the Hector P. Garcia Award for Cultural Competence and the Evelyn S. Cowles Endowed Scholarship. She was also the inaugural recipient of the John D. and Mary Ann Stobo Award in Oslerian Medicine, which recognizes one student in any of the four UTMB schools for exemplifying humanistic medicine and compassionate patient care.

Dr. Edwards then matched to a combined residency in Internal Medicine and Pediatrics at UTMB, during which she was recognized as Intern of the Year and awarded a Resident Teaching Award. Following residency, Dr. Edwards completed a combined fellowship in Pulmonary Disease and Critical Care Medicine. During her postgraduate training, Dr. Edwards served on multiple departmental and institutional committees, and pursued education and training in quality improvement. She completed the Clinical Safety and Effectiveness program at University of

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Dr. Edwards' research focuses on quality improvement and comparative effectiveness. Her interests include outcomes related to lung cancer, chronic obstructive pulmonary disease, and processes of care in the intensive care unit. She has presented her research at the international meetings of the American Thoracic Society and American College of Chest Physicians. She is currently serving as a Clinical Instructor in the Division of Pulmonary & Critical Care Medicine, Department of Internal Medicine, at the University of Texas Medical Branch. She hopes to establish a career that encompasses clinical practice, outcomes research, and quality improvement.

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