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Clinical Research in Pulmonology

Research Article

Surveillance Following Lung Cancer Resection

Tu-Quynh H. Edwards[1], Yong-Fang Kuo[1,2] and Gulshan Sharma[1]*

[1]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, USA
[2]Office of Biostatistics, University of Texas Medical Branch, USA

Corresponding author
Gulshan Sharma, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Texas Medical Branch Galveston, 301 University Blvd, Galveston, Texas 77555-0561, USA, Tel: (409)-772-2436; Fax: (409)-772-9532; E-mail: gusharma@utmb.edu

Submitted: 18 June 2013

Accepted: 31 July 2013

Published: 02 August 2013

Keywords
- Lung cancer
- Surveillance
- Non-small cell lung cancer
- Outcomes
- CT chest

Abstract

Background: Following curative surgery for non-small cell lung carcinoma (NSCLC), patients remain at risk for recurrence or for development of second primary lung cancer (SPLC). While regular surveillance imaging may detect early stage recurrence or SPLC, its effectiveness has not been established, and current practice guidelines conflict in terms of optimal frequency and modalities of surveillance. The purpose of this study is to evaluate the effectiveness of surveillance following curative surgery for NSCLC in comparison with usual care.

Methods: 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, and second primary lung cancer. Baseline data and results were pooled. Outcomes examined included rate of detection of recurrence, presence of symptoms at recurrence, and site of recurrence.

Results: 18 studies were included in this analysis. No randomized controlled trials were identified. A total of 699 recurrences and 88 second primary lung cancers were detected among 2716 patients. Of these, 53.1% of cases were detected by surveillance protocol. The majority of patients were symptomatic at detection (65.1%). Distant recurrence was more frequent than local recurrence (67% vs. 33%). Only 109 patients (13.9%) were offered a repeat surgery, primarily for SPLC.

ABBREVIATIONS

ACCP: American College of Chest Physicians; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CT: Computed Tomography; MeSH: Medical Subject Headings; MRI: Magnetic Resonance Imaging; NCCN: National Comprehensive Cancer Network; NSCLC: Non-Small Cell Lung Carcinoma; PET: Positron Emission Tomography; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized Controlled Trial; SPLC: Second Primary Lung Cancer; TNM: Tumor-Node-Metastasis; US: United States

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 NSCLC cases were diagnosed in the U.S. in 2009 [1]. Curative-intent surgeries offer 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 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 lung cancers will develop in approximately 2-3% of these patients each year, a risk that remains relatively constant in the first 5 years after primary resection [5,6-8].

Surveillance regimens following curative treatment for NSCLC generally consist of some combination of physical examination, laboratory studies, and imaging. No single modality is simultaneously sensitive, specific, safe, convenient, and cost-effective. Thus, combining strategies is preferred so as to optimize detection of recurrence or SPLC, with the goal of facilitating potentially curative treatment or early palliation.

To date, no published prospective, randomized trials have evaluated surveillance in asymptomatic patients following curative resection for NSCLC. Likewise, no consensus among national guidelines exists 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 (CT) 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, it bears the potential harm inherent in disease screening. It has not been established if post-surgical surveillance affects cancer-related or overall mortality. Any perceived benefit may be attributable to lead-time bias. Additionally, the risk of adverse outcomes related to treatment of benign nodules is not insignificant. Furthermore, the cost of surveillance studies and associated treatments must be considered.

The purpose of this systematic review is to evaluate whether the use of surveillance following curative surgery for NSCLC is effective in diagnosing recurrent NSCLC or SPLC in asymptomatic patients, in comparison to usual care defined as symptom triggered workup for reoccurrence. This study aims to compare patterns of surveillance testing after curative surgical resection for NSCLC, and to examine the relationship between surveillance imaging and disease-free survival, overall survival, and cost.

METHODS

The PRISMA guidelines for systematic reviews were used for this study [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 were identified. Major search concepts included non-small cell lung cancer, surveillance, curative resection, recurrence, second primary lung cancer, CT, and chest X-Ray. These concepts and their synonyms were exploded to include all Medical Subject Headings (MeSH) Subheadings. No other search filters were used. Non-English results were included in the screening.

Cohort and case-control studies were examined. Surveillance modalities of interest included chest x-ray, physical exam, CT, and positron emission tomography (PET). The types of outcome measures studied included detection of recurrent NSCLC, detection of second primary lung cancer, site of recurrence or second primary, rates of asymptomatic presentation, and rates of second curative-intent resection.

All pertinent studies were retrieved and independently screened. Data from each study were extracted by the primary investigator. The Cochrane Collaboration's tool for assessing risk of bias was used to evaluate each study. Although this tool was designed to aid assessment of randomized controlled trials, many aspects of the tool remained applicable. 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. Baseline data and results from the individual studies were pooled. Due to study heterogeneity, a formal meta-analysis could not be performed.

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. Because they did not meet the study criteria, 31 records were excluded. The remaining 30 full-text articles were assessed for eligibility. Four case studies, 2 editorials, 2 review articles, and 2 survey-based studies were excluded. One article employing computer-based economic modeling and 1 clinical trial design was also excluded. The 18 remaining original studies were included in the qualitative analysis. Characteristics, including study date, design, sample size, demographics, primary tumor characteristics, primary treatment, and rate of recurrence are shown in Table 1.

RESULTS

Baseline characteristics

Baseline characteristics of the study population are summarized in Table 2. Not all data were available for every patient. In total, 4119 patients were involved in these 18 studies. The median age of the study population was 63.3 years, and most male. Information on primary tumor histology was available for 3669 patients. The primary NSCLCs included 46.8% adenocarcinoma and 40% squamous cell carcinoma. Post-resection stage information was available for 3776 patients. The 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 (71.8%), followed by pneumonectomy (22.3%), and wedge resection (5.5%). Approximatly one quarter of the patients underwent adjuvant chemotherapy following their primary surgery.

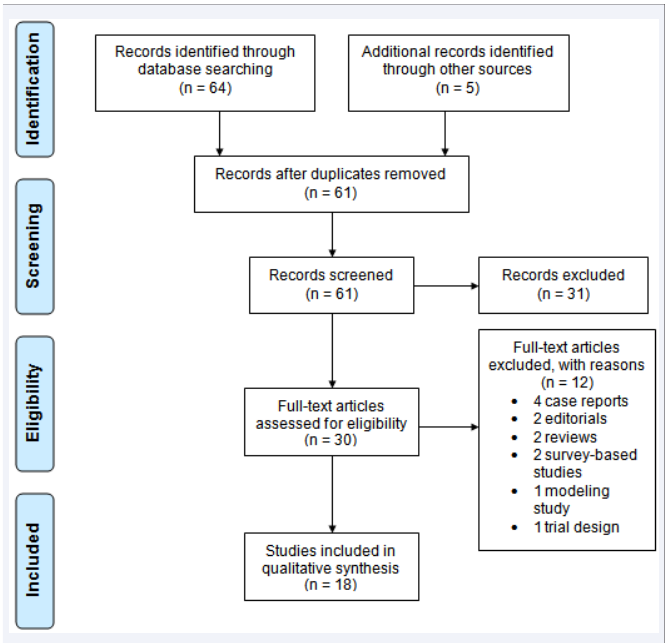

Figure 1 Search results of studies included in the analyses.

Table 1: Characteristics and results of included studies of surveillance following resection of non- small cell lung cancer.

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 [13]	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 [14]	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)

Egermann et al., 2002 [22]	64 (28-85)	Male 441 (78.3) Female 122 (21.7)	Adeno 146 (25.9) SCC 314 (55.8) LCC 57 (10.1) BAC 33 (5.9) Undiff 13 (2.3)	1A 112 (19.9) 1B 192 (34.1) 2 173 (30.7) 3 86 (15.3)	Lobectomy 361 (64.2) Pneumonectomy 201 (35.8)	239/563 (42.5)
Lamont et al., 2002 [23]	66 (39-85)	Male 65 (52.4) Female 59 (47.6)	Not described	1 64 (51.6) 2 20 (16.1) 3 40 (32.3)	Wedge resection 25 (20.2) Lobectomy 88 (71) Bilobectomy 4 (3.2) Pneumonectomy 17 (13.7)	28/124 (22.6)
Chiu et al., 2003 [24]	71 (43-82)	Male 39 (90.7) Female 4 (9.3)	Adeno 26 (60.5) SCC 10 (23.3) AS 3 (7) LCC 4 (9.3)	1A 6 (14) 1B 20 (46.5) 2B 4 (9.3) 3A 9 (20.9) 3B 2 (4.7) 4 1 (2.3) Unk 1 (2.3)	Wedge resection 6 (14) Lobectomy 34 (79) Bilobectomy 2 (4.7) Pneumonectomy 1 (2.3)	14/43 (32.6)
Hellwig et al., 2005 [25]	62 (38-81)	Male 51 (82.3) Female 11 (17.7)	Adeno 24 (38.7) SCC 33 (53.2) LCC 1 (1.6) BAC 5 (8.1) Undiff 3 (4.8) Other 1 (1.6)	Not described	Surgery not described Adjuvant therapy 14 (22.6)	55/62 (88.7)
Korst et al., 2005 [26]	67 (range not described)	Male 101 (47.4) Female 112 (52.6)	Adeno 141 (66.2) SCC 41 (19.2) AS 2 (0.5) LCC 4 (1.9) BAC 11 (5.2) Undiff 14 (6.6)	1 2 (1) 1A 92 (43.2) 1B 56 (26.3) 2A 6 (2.7) 2B 18 (8.5) 3A 17 (8) 3B 9 (4.2) 4 10 (4.7) Unk 3 (1.4)	Segmentectomy 9 (4.2) Wedge resection 2 (1) Lobectomy 169 (79.3) Bilobectomy 12 (5.6) Sleeve lobectomy 2 (1) Pneumonectomy 15 (7) Completion pneumonectomy 1 (0.5)	25/213 (11.7)
Aokage et al., 2006 [27]	64 (31-84)	Male 152 (57.4) Female 113 (42.6)	Adeno 198 (75.7) SCC 39 (14.7) Other 28 (10.6)	1A 130 (49.1) 1B 65 (24.5) 2A 11 (4.2) 2B 30 (11.3) 3A 29 (10.9)	Limited resection 1 (0.4) Lobectomy 254 (95.8) Pneumonectomy 10 (3.8) Adjuvant therapy 4 (1.6)	59/265 (22.3)
Benamore et al., 2007 [28]	60 (range not described)	Male 45 (60) Female 30 (40)	Adeno 33 (44) SCC 2 8 (37.3) LCC 6 (8) AS 2 (2.7) Undiff 6 (8)	2B 13 (17.3) 3A 54 (72) 3B 8 (10.7)	Surgery not described Adjuvant therapy 46 (61.3)	45/75 (60)
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

Surveillance protocols

Reported surveillance protocols are summarized in Table 3. Although no 2 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 2 years after surgery, with surveillance tapering thereafter. The majority of follow-up post resection was performed by thoracic surgeons.

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. A total of 699 recurrences (25.7%) and 88 SPLCs (3.2%) were detected among 2716 patients. Information on 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 (p=0.2195). Presence or absence of symptoms was available for 625 patients with recurrence or SPLC. Among those 625 patients, 407 (65.1%) were symptomatic at the time of detection and 218 (34.9%)

Table 2: Patient Demographics, Tumor Characteristics, and Primary Treatment (N=4119).

Characteristic	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)

Not all information was available for every patient. Sample sizes for subheadings are provided. † $p<0.05$

were asymptomatic ($p<0.001$). Site of recurrence was available for 699 cases. Of those, 231 (33%) were local, 399 (57.1%) were distant, and 69 (9.9%) were both ($p<0.001$). Notably, of the 787 recurrences and SPLCs, only 109 (13.9%) were offered a second surgery. The majority of these surgeries (77%) were for SPLC.

Disease-free interval

Younes and colleagues found no difference in disease-free interval between patients monitored via a surveillance protocol and those given usual care [18]. In a series of 239 patients with recurrent NSCLC or SPLC, Egermann and colleagues found no correlation between disease-free interval and duration of survival after the second curative surgery [22]. In contrast, Walsh and colleagues determined that a disease-free interval 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, and overall survival were conflicting. In a retrospective analysis of 182 patients, Virgo and colleagues found that patients intensively followed after primary resection survived an average of 192 days longer than those without intensive follow-up [14]. Walsh and colleagues found that mode of presentation and site of recurrence did not significantly affect survival in a series of 358 patients. Egermann and colleagues 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 and colleagues examined the cost associated with surveillance and second curative-intent treatment for a series of 563 patients [22]. A total of 239 cases of recurrence and SPLC were detected, with over 70% of the cases occurring in the first year after primary surgery. Only 23 patients were eligible for a second curative resection. Of these, 21 cases 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 approximately 56,000 US dollars. Based on these cost estimates, the authors recommended a strategy consisting solely of chest X-ray every 6 months for the first 5 years after primary surgery.

Using Medicare fee schedules, Korst et al. compared the cost of surveillance CT 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 for the hypothetical usual care group.

Prognostic indicators

Nakamura and colleagues conducted the largest retrospective review to date, with a population of 1,398 patients treated between 1980-2008 [30]. Using univariate and multivariate analyses, 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 score of 0-1 were all positive prognostic factors for survival. Similarly, Westeel and colleagues identified asymptomatic recurrence, female sex, performance status of 2 or less, and age 61 years or younger as favorable prognostic indicators [20]. In contrast, Gilbert and colleagues 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, advanced tumor stage at time of recurrence or SPLC, and presence of symptoms at detection of recurrence.

DISCUSSION

No current practice guidelines exist for surveillance following curative-intent surgery for NSCLC based on high-grade evidence. As a result, wide variation exists in both the type and frequency of surveillance investigations employed. Nonetheless, trends in results were noted both within studies and with the pooled data. Rates of recurrence and detection of SPLC are high. Evidence from these studies suggests that surveillance protocols do not

Table 3: Surveillance Protocols followed in patients who underwent resection for non small cell lung cancer.

Author, year	Follow-up Interval	Surveillance Protocol	Provider	Median Follow-up (mos)
Gorich et al., 1990 [13]	Some f/u between 2-6m	/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 ; "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 q visit; 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, , 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/ q3m and CT/bronchoscopy q6m x3y; then PE/ q6m and CT scan qy x 4y; then 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; q4m x 2y; then q6m x 3y	PE/ q4m x 2y; then PE/ q6m; CT qy	Thoracic surgeon	N/R
Chiu et al., 2003 [24]	q3m x 2y; then q6m x 3 y	PE, sputum cytology, serum , , 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; 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//serum qvisit, abdominal US qy	Thoracic surgeon	72
Benamore et al., 2007 [28]	q3m x 2-3y; then q6m up to 5y	PE//bloodwork qvisit, CT or only for suspicion of relapse	N/R	36
Cho and Lee, 2009 [29]	q3m x 2y	PE//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/ q3m and CT q6m	Thoracic surgeon or Pulmonologist	79

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 = Carcino Embryonic Antigen; MRI = Magnetic Resonance Imaging; LDCT = Low-Dose Computed Tomography; N/R = Not Reported

appear significantly better at detecting these recurrences than usual care. This is supported by the finding that many patients are already symptomatic at 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" actually represent progression of micrometastases undetected at time of primary staging and treatment.

Only 1 study found a survival difference between patients under surveillance and those 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 NSCLC, the cumulative cost of surveillance care represents a sizable expenditure.

Nonetheless, some nuances of the physician-patient relationship 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 to improve patient satisfaction, for medicolegal purposes, or simply to assess the outcomes of the care they are providing.

Novel treatment 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 improve survival, with increased benefit over radiation

Table 4: Recurrent Non-small Cell Lung Cancer and Second Primary Lung Cancer.

Result (number of eligible cases)	**Number (%)**
Recurrent NSCLC (n=2716)	699 (25.7)
Second primary lung cancer (n=2716)	88 (3.2)
Status of recurrence or SPLC (number of eligible cases)	**Number (%)**
Found by protocol (n=392)	208 (53.1)
Found by usual care (n=392)	184 (46.9)
Asymptomatic (n=625)	218 (34.9)
Symptomatic (n=625)	407 (65.1) †
Site of recurrence (n=699)*	
Local recurrence	231 (33)
Distant recurrence	399 (57.1) †
Local and distant	69 (9.9) †

Not all information was available for each patient. "Number of eligible cases" represents total number of data points available for each outcome of interest, with corresponding percentages for each subgroup. †p<0.001 for differences from 50%.

alone [33]. In addition, growing interest in genotyping and personalized medicine has led to the identification of genetic variants 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 5 of the studies examined in this review involved the use of PET scans, and only 2 incorporated PET scans at regular intervals. PET scans have traditionally been utilized for secondary investigation of suspicious lesions, but as their availability has grown, so has their routine 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 CT 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 efficacious and cost-effective in detecting recurrence following curative-intent surgery for primary NSCLC. However, 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 screened annually with low-dose CT [35]. Although this study was focused on screening prior to diagnosis of a primary lung carcinoma, it calls into question again the potential benefit of surveillance following treatment for lung cancer. With routine screening, most patients will be diagnosed at an early stage potentially amenable to curative surgery increasing the number of patients in the surveillance pool. 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 in the context of patient-centered care, and to strive towards advances in the treatment of NSCLC.

CONFLICTS OF INTEREST

Tu-Quynh H. Edwards, MD, MS has no conflicts of interest to disclose.

Yong-Fang Kuo, PhD has no conflicts of interest to disclose.

Gulshan Sharma, MD, MPH has no conflicts of interest to disclose.

FINANCIAL/NONFINANCIAL DISCLOSURES

The authors have reported no potential conflicts of interest exist with any organizations whose services may be discussed in this article.

ACKNOWLEDGEMENTS

The authors thank Sarah Toombs Smith PhD for help in preparation of the manuscript.

SOURCE OF FUNDING STATEMENT

Dr. Edwards was a student in the UTMB Clinical Science Graduate Program, which is supported in part by a Clinical and Translational Science Award (UL1RR029876) from the National Center for Research Resources, National Institutes of Health, at the time this research was conducted.

Dr. Edwards is a junior co-investigator member of the Comparative Effectiveness Research on Cancer in Texas (CERCIT) consortium, which is funded by the Cancer Prevention and Research Institute of Texas (CPRIT) [Grant RP101207]. Dr. Sharma is supported by K08-AG31583 mentored career development award from the NIA.

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Cite this article

Edwards TQH, Kuo YF, Sharma G (2013) Surveillance Following Lung Cancer Resection. Clin Res Pulmonol 1: 1001.