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Clinical Impact of Frequent Surveillance Imaging in the First Year Following Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer

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Abstract

Purpose/Objective(s)—Uncertainty exists regarding the optimal surveillance imaging schedule following definitive chemoradiation (CRT) for locally advanced non-small cell lung cancer (LA-NSCLC) with regards to both frequency and modality. We sought to document the clinical impact of frequent (q 4 month) surveillance imaging.

Methods—The records of all patients treated with CRT for stage IIIA/IIIB NSCLC between August 1999 and April 2014 were reviewed. Patients were included if they underwent frequent (Q 4 month) chest computed tomography (CT) or positron emission tomography (PET/CT) for routine surveillance following CRT for at least one year or until progression or death. Radiographic findings and clinical interventions within the first year were identified.

Results—We identified 145 patients with LA-NSCLC treated with CRT, 63 with eligible imaging. Median age was 63.6 years (range, 41.0–86.9). Asymptomatic recurrence was radiographically detected in 38 (60.3%). Twenty-one (33.3%) initiated systemic therapy. Two (3.2%) underwent definitive-intent treatment for isolated disease, including lobectomy for a histologically-distinct primary NSCLC and stereotactic radiotherapy for an isolated recurrence, both of whom subsequently progressed. Eleven patients (17.5%) received no further therapy. Five patients (7.9%) underwent additional diagnostic procedures for false-positive findings.

Conclusions—Frequent surveillance within the first year following CRT for LA-NSCLC lung cancer detects asymptomatic recurrence in a high proportion of patients. However, definitive-intent interventions were infrequent. The predominant benefit of frequent surveillance appears to be expedient initiation of palliative systemic therapy. Evidence-based algorithms for surveillance are needed, and should account for expected patient tolerance of and willingness to undergo additional cancer-directed therapies.

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Keywords

Lung Cancer; Surveillance Imaging; Chemoradiation

Introduction

Approximately 25–30% of non-small cell lung cancer (NSCLC) patients present with locally advanced stage IIIA/IIIB disease (LA-NSCLC) [1]. Outcomes are generally poor in this population, with high rates of both local and distant failure and an overall survival of 19–36% at 5 years following definitive-intent therapy [2]. The majority of LA-NSCLC patients are managed non-surgically, with concurrent chemoradiation (CRT) the standard-of-care for inoperable cases.

Despite high rates of relapse, the optimal schedule and modality for post-treatment surveillance following concurrent chemoradiation remains poorly defined. Current National Comprehensive Cancer Network (NCCN) guidelines suggest follow-up with computed tomography (CT) of the chest every 6–12 months for the first 2 years, followed by annual low-dose non-contrast CT for those without evidence of clinical or radiographic disease [3]. Similar guidelines from the American Academy of Chest Physicians (AACP) recommend either chest x-ray or CT in combination with a history and physical exam every 6 months for 2 years following curative intent surgery for NSCLC, although the guidelines' authors acknowledge the limited data supporting this recommendation [4]. No current guidelines specifically address potential differences between post-operative and post-radiotherapy patients, and the implications for surveillance. Evidence to guide surveillance strategies following CRT for LA-NSCLC is lacking, and nuances specific to the post-radiation setting complicate follow-up approaches. Post-radiation scarring may obscure or mimic tumor recurrence on CT [5], and isolated locoregional failures are relatively rare [6], hence salvage options are frequently non-curative in intent.

The aim of this current study is to evaluate in a single institution cohort the ability of frequent, defined as q 4 month, post-treatment volumetric imaging to detect asymptomatic recurrence in patients with LA-NSCLC treated with definitive chemoradiation, and to identify curative-intent and non-curative intent interventions resulting from frequent surveillance within the first year after treatment.

Materials and Methods

Patients and Treatment

Following Institutional Review Board approval, the records of all patients with LA-NSCLC treated with concurrent CRT for LA-NSCLC between January 1995 and June 2014 at the University of California Davis were reviewed. All patients underwent comprehensive staging prior to treatment including CT of the chest with contrast (unless medically contraindicated), positron emission tomography (PET)/CT starting in 2000, CT or magnetic resonance imaging (MRI) of the brain, and physical examination. Patients were staged according to the American Joint Committee on Cancer 7th Edition [7].

Surveillance Imaging

Patients eligible for this study were those followed with frequent surveillance imaging, defined as chest computed tomography (CT) or positron emission tomography (PET/CT) performed with a frequency of at least every 4 months for a minimum of 1 year or until disease progression or death if within the first year. Imaging was classified as surveillance if performed for routine disease assessment rather than in response to specific clinical symptoms. Both CT and PET/CT were included as surveillance scans, if performed for general response assessment or re-staging, rather than in response to specific clinical symptoms. Only the first year following CRT was analyzed, as many patients moved to a less intensive schedule in the second year. Surveillance imaging schedule was determined at physician discretion. Multidisciplinary imaging review was frequently employed for cases with borderline findings.

Analysis

In order to identify eligible patients, the interval between completion of CRT, the first scan, and each subsequent scan was calculated for all patients. Subsequent management steps, including additional diagnostic procedures and both definitive and palliative intent cancer-directed therapies that resulted were documented for each patient. Recurrences detected between surveillance scans (ie detected because of clinical symptoms) were also documented. Overall survival for the population was calculated with the Kaplan-Meier method.

Results

Patients

Of the 145 patients reviewed, 63 (43.4%) met the eligibility criteria for frequent surveillance imaging in the first year after treatment, including 33 men and 30 women. Among eligible patients, the median age was 63.3 years (range, 41.0–86.9 years). Forty-two (66.7%) presented with stage IIIA disease and 21 (33.3%) with stage IIIB disease. Table 1 summarizes the clinical and treatment characteristics of the patient cohort. All patients received concurrent chemotherapy with thoracic radiation, predominantly, weekly low dose paclitaxel and carboplatin (n=28 patients), or concurrent bolus cisplatin and etoposide given in 21 day cycles (n=25). Two patients also received induction chemotherapy. Radiation was prescribed to a median dose of 61 Gy (range: 38–67 Gy) in 1.8–2.0 Gy fractions. Only two patients received a dose of <59 Gy, one of whom truncated treatment after 38 Gy due to a non-cancer related medical emergency resulting in a lengthy hospital stay, and one of whom was treated to 54 Gy due to unacceptably high lung doses with plans delivering higher doses to the target. Treatment technique was three dimensional conformal RT for 43 (68.3%) and intensity modulated radiotherapy for 20 (31.7%).

Surveillance Imaging

During the first year post-CRT, the patient cohort of 64 patients underwent a total of 233 surveillance scans: 115 CT of the chest (49.4%), 77 CT of the chest/abdomen/pelvis (33.0%), and 41 PET/CT (17.6%). The mean number of scans per patient was 3.6.

Asymptomatic recurrence was detected by surveillance imaging during the first year post-CRT in 38 patients (60.3%), 8 (21.1%) by PET/CT and 30 (78.9%) by CT.

Subsequent Therapies

Following recurrence, two patients (3.2%) underwent definitive-intent cancer-directed therapy: one patient underwent lobectomy for a histologically distinct early stage NSCLC in the contralateral lung detected by PET/CT 6 months following completion of CRT. This patient later developed progressive metastatic disease and died 35 months after initial completion of CRT. A second patient was found to have a new lesion on the same lobe by chest CT 4.6 months following completion of CRT, clinically indeterminate for a new primary versus a metastasis. The patient underwent stereotactic body radiation therapy but eventually developed metastatic disease and began hospice care 22 months following original completion of CRT. The two and three-year Kaplan-Meier estimates of overall survival for the entire cohort were 45.2% and 38.6%, respectively.

Twenty-one patients (33.3%) had an asymptomatic recurrence that prompted initiation of systemic chemotherapy for disease progression. One patient (1.6%) had a finding that warranted urgent local therapy to prevent impending spinal cord compression. In total, 24 patients (38.1%) with an asymptomatic recurrence had their treatment course altered by early post-treatment imaging. Eleven other patients (17.5%) with an asymptomatic recurrence did not receive additional cancer-directed therapy because they either were not candidates for additional treatment or declined further interventions. Figure 1 summarizes the surveillance imaging outcomes.

Twenty-five patients (39.7%) did not have an asymptomatic recurrence detected. For 7 of these patients (11.1%), a recurrence was detected between surveillance scans from clinical symptoms leading to additional workup. Five patients (7.9%) had a false positive finding on surveillance imaging leading to additional diagnostic procedures, including bronchoscopy (n=2) nasopharyngolaryngoscopy (n=1), 1 fine needle aspirate (n=1), and thoracentesis (n=1). These false positive findings occurred at a median of 2.5 months post-CRT (range: 0.9–10.5 months).

Discussion

Guidelines outlining the optimal surveillance strategy following definitive therapy for NSCLC are limited, and evidence supporting these guidelines is largely derived from single-institution retrospective analyses, despite lung cancer's prevalence and lethality [8]. Current NCCN and AACP guidelines suggest CT imaging every 6–12 months, while acknowledging the limited data supporting these recommendations [4]. Several patterns-of-care studies suggest that more frequent imaging is often performed after definitive CRT for NSCLC. In a study of 38 European cancer centers, almost all centers followed the same pretreatment evaluation procedure for treating LA-NSCLC patients with curative intent. However, there was marked variation in post-treatment evaluation in initiation, frequency, and type of scan used [9]. A number of cooperative group trials within the United States specify post-treatment CT imaging on an every 3 month basis [10–12].

Several studies have evaluated specific surveillance approaches following surgical resection of NSCLC. Westeel *et al* prospectively evaluated a post-lobectomy strategy including bronchoscopy and CT chest every 6 months with chest x-ray every 3 months. Among 192 eligible patients, 136 (71%) recurred. Thirty-six recurrences were detected through surveillance, and 5 patients with isolated locoregional recurrence were candidates for definitive-intent salvage. Three-year OS was improved among asymptomatic as compared to symptomatic recurrences (31% vs 13%; $p<0.001$) [13]. Similarly, Gourcerol *et al* analyzed a retrospective cohort of 162 surgically-treated patients followed with chest x-ray every 3 months and CT, bronchoscopy, abdominal ultrasound, CT head, and bone scan every 6 months for three years [14]. Curative intent salvage therapy was offered more frequently to patients with asymptomatic recurrences (41% vs 10%), and OS from time of recurrence was higher among asymptomatic patients (15.5 vs 7.2 months, $p=0.001$). In both studies, OS was measured from time of recurrence, leaving open the possibility of lead-time bias. Backhas *et al* analyzed the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, evaluating imaging studies performed during a designated surveillance window of 4–8 months following surgical resection of lung cancer. They identified no difference in overall or lung cancer-specific survival in patients who underwent an imaging study during the specified window and those who did not [15]. A systematic review analyzing the survival benefit of CT following surgery for lung cancer identified 5 relevant papers, 3 of which identified a survival benefit to surveillance CT and 2 of which did not. The authors conclude that “Owing to the limited and contradictory evidence, there is a need for a randomized controlled trial to assess the survival outcomes of patients followed up with a CT screening protocol vs a symptom-based follow-up” [16].

Far less data specifically address surveillance for LA-NSCLC treated with definitive CRT. Van Loon *et al* prospectively evaluated the use of a single PET/CT at 3 months following RT or CRT for lung cancer in 100 patients. Similar to our results, they identified a high percentage of asymptomatic recurrences (24%), but only 3% of patients had a recurrence amenable to curative-intent therapy [17]. In a subsequent paper, the authors performed a cost effectiveness analysis that suggested PET/CT surveillance did meet generally accepted thresholds for quality adjusted life years [18]. Benamore *et al* retrospectively compared patients from a single institution treated on clinical trials ($n=40$), who underwent a more intensive surveillance regimen averaging 2.9 scans per year, to patients treated off trial ($n=35$) who were followed with a less intensive surveillance regimen averaging 2 scans per year. More frequent scanning resulted in increased detection of asymptomatic recurrences with an associated increase in curative intent salvage therapy, but did not improve survival as compared to the group with less intensive surveillance [19].

In the present study, 60% of our frequent surveillance cohort had an asymptomatic recurrence detected in the first year. Although only 3% of our patients underwent definitive-intent treatment for recurrence, 33% of our patient cohort initiated systemic chemotherapy for an asymptomatic recurrence and one patient underwent urgent palliative radiation that may have averted a spinal cord compression. The survival impact of early initiation of systemic therapy for incurable, recurrent disease remains unclear; however, recent data addressing newly diagnosed stage IV patients does suggest expedient initiation of chemotherapy may impact survival. Gomez *et al* evaluated SEER/ Medicare and Texas

Cancer Registry/Medicare linked data for 11,810 patients stage IV NSCLC to evaluate the impact of treatment delays on survival. For patients who survived for at least 1 year, expedient treatment was associated with improved survival. [20]. Early detection of recurrence might allow for initiation of systemic therapy while patients have a good performance status. The early initiation of palliative care for metastatic NSCLC has also been shown to improve survival and quality of life in a prospective, randomized clinical trial. Temel *et al*, found that patients with metastatic NSCLC randomized to early palliative care integrated with standard oncologic care had better quality of life, fewer depressive symptoms, decreased hospital stay, and improved overall survival (11.6 vs. 8.9 months) despite receiving less aggressive care than patients randomized to standard therapy only who received later or no palliative care [21]. These studies highlight the possible benefits of early initiation of both systemic and palliative treatment, but do not clearly demonstrate whether these benefits might extend to asymptomatic recurrences based on imaging findings.

Other studies suggest extrapolation of these data to the recurrent setting may not be appropriate. For at least one other cancer type with limited curative salvage options, aggressive surveillance was shown in a randomized trial to provide no survival benefit. Investigators from the European Organization for the Research and Treatment of Cancer performed a large randomized trial in 1442 ovarian cancer patients, evaluating the use of routine 3 month CA-125. Surveillance not only did not improve OS, but also increased the use of chemotherapy decreased patient quality of life [22]. Despite these findings, CA-125 and CT imaging are still widely employed in the follow-up of ovarian cancer [23]. These data strongly suggest prospective randomized trials are warranted in other cancers such as NSCLC with limited salvage options.

Recent developments in the treatment of NSCLC may impact the benefit of frequent surveillance imaging. The aggressive management of oligometastases using SBRT or surgical resection for limited metastatic sites has demonstrated long-term survival in a subset of patients, particularly those with solitary brain or adrenal lesions [24, 25]. Subsets of patients with tyrosine kinase driven lung cancers such as those harboring mutations in endothelial growth factor receptor (EGFR) or translocations of the anaplastic lymphoma kinase (ALK) have systemic salvage options that may lead to years, rather than months, additional survival. Immunotherapy agents, including the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors have also shown promise in some metastatic NSCLC patients, particularly those whose tumors overexpress PD-L1, with dramatic and durable responses in a subset of patients [26, 27]. These patients might benefit from the detection of asymptomatic recurrences more than patients with more limited treatment options.

The potential issue of false positive results leading to additional procedures with their own attendant risks is also salient. In our population, 8% of patients underwent an additional procedure such as bronchoscopy, endoscopic exam, FNA, or thoracentesis as a result of an imaging finding, although none lead to complications. Also notably, 17.5% of our total cohort had an asymptomatic recurrence detected but were either not candidates for or declined any additional cancer-directed therapy. This relatively high percentage suggests increased patient involvement in decision-making including early discussions about patients'

willingness to undergo further therapy and overall goals of care is important. Furthermore, the impact of follow-up imaging (or lack thereof) on patient-reported quality-of-life is almost entirely unstudied in the lung cancer population.

Significant limitations of the present study include the relatively modest sample size and the retrospective single institution design. As a retrospective study on patients treated by multiple physicians over an extended period, there was heterogeneity in the specific interval between scans and the imaging modality used. We included both CT and PET/CT, although the majority of imaging performed was CT. Despite these limitations, our results build on the scant existing data on surveillance following CRT for locally advanced NSCLC, and suggest that frequent radiographic surveillance detects a high number of asymptomatic recurrences, but rarely results in a curative-intent intervention.

Conclusion

Frequent volumetric imaging within the first year following chemoradiation for LA-NSCLC leads to detection of asymptomatic recurrence in a majority of our study population. However, curative-intent interventions took place in only 3% of patients. The primary benefit of frequent surveillance appears to be the expedient initiation of palliative systemic therapy. Larger, prospective studies should be undertaken to clarify the survival impact of surveillance imaging and its effect on patient-reported quality of life.

Acknowledgments

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Clinical Practice Points

- The optimal surveillance strategy following CRT for LA-NSCLC is poorly defined, with very limited available data
- We review a single institution cohort of LA-NSCLC who underwent frequent surveillance, defined as CT or PET/CT at least every 4 months the first year after CRT
- An asymptomatic recurrence was detected in over half, but a curative intent therapy was attempted in only 3%. 17.5% underwent no additional therapy.
- The predominant benefit to frequent surveillance appears to be expedient initiation systemic therapy. Prospective studies are warranted to better define the role of surveillance imaging for LA-NSCLC

Figure 1.

Table 1

Patient Characteristics

Age (median)	63.3 (range 41.0–86.9)
Gender	
Male	33 (52.4%)
Female	30 (47.6%)
Stage	
IIIA	42 (66.7%)
IIIB	21 (33.3%)
Histology	
Adenocarcinoma	27 (42.9)
Squamous Cell Carcinoma	16 (25.4)
Mixed or other	20 (31.7)
Radiation Dose (median)	61 Gy (range: 38–67 Gy)
Planning Technique	
3DCRT	43 (68.3%)
IMRT	20 (31.7%)
Concurrent Chemotherapy Regimen	
Carboplatin/Paclitaxel	28 (44.4%)
Cisplatin/Etoposide	25 (39.7%)
Other	10 (15.9%)

Abbreviations: 3DCRT: Three dimensional conformal radiation therapy; IMRT: Intensity modulated radiation therapy