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Outcomes of patients with disease recurrence after treatment for locally advanced non-small cell lung cancer detected by routine follow-up CT scans versus a symptom driven evaluation

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ABSTRACT

Objectives: The majority of patients with locally advanced non-small cell lung cancer (LANSCLC) will recur after receiving multimodal treatment with curative intent. Current guidelines recommend routine follow-up with computerized tomography (CT) scans, though minimal data exist on the utility of this approach nor has an optimal follow-up strategy to detect recurrence been defined. This study examined whether survival varied if relapse was detected with scheduled follow-up CT versus symptoms, and whether the pattern of recurrence affected these outcomes.

Materials and methods: Single institution retrospective review of patients who had undergone definitive management of LANSCLC with chemoradiotherapy +/- surgical resection. Standard follow-up testing consisted of routine exam and chest CT beginning at every 3 months in the first year and decreasing to annually after the fifth year.

Results: 311 patients were assessed, of which 167 patients recurred and were evaluable. 104 progressions were detected by follow-up and 63 by symptoms. For the entire group, there was no difference in overall survival (OS) for those detected by scans vs. symptoms (7.6 vs. 6.1 months, $p = 0.797$). After excluding patients with oligometastatic (1–3) brain metastases (OBM), OS was superior in patients with scan detected relapse (7.5 vs. 3.4 months, $p = 0.013$).

Conclusions: Routine surveillance by CT chest detects more localized disease than symptom driven follow-up, though OS does not differ. This null result is largely driven by the favorable outcomes for patients with OBM who present symptomatically. A strategy of both chest and brain imaging could be considered and warrants further investigation.

1. Introduction

Lung cancer continues to be the leading cause of cancer-related death in the U.S. [1]. Approximately 75% of patients with locally advanced non-small cell lung cancer (LANSCLC, stage IIIa/b 7th edition AJCC) receiving definitive multimodal treatment that includes chemoradiotherapy with or without surgery will recur. Given the high rates of recurrence, most patients are followed with intensive surveillance strategies that typically involve CT imaging at set intervals post-treatment with the hope that early detection of recurrence or a new primary cancer may improve outcome. A basic principle is that follow up of any cancer should result in demonstrable benefit in the form of an improved outcome, most importantly improved survival for patients with recurrent cancer [2]. However, there are relatively little data describing the utility of such strategies. Nor has an optimal follow-up strategy to detect recurrence been determined. The purpose of this retrospective cohort study was to evaluate whether outcomes differed based on whether relapse was detected via routine interval imaging versus imaging due to symptom development.

2. Materials and methods

Three hundred and eleven patients with LANSCLC were definitively treated with chemotherapy plus radiotherapy, with or without surgery, between January 1, 2000 and February 28, 2015 at the University of Maryland Greenebaum Cancer Center (UMGCC). Of these 311 patients, 207 patients had documented relapse and of these patients, 167 had adequate records to be included in the study cohort. The institutional

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Table 1
Characteristics of study cohort.

Characteristic	Total (N = 167)	F/U (n = 104)	SX (n = 63)	P-value
Gender – n (%)				
Male	86 (51.5)	53 (51.0)	33 (52.4)	0.859
Female	81 (48.5)	51 (49.0)	30 (47.6)	
Race – n (%)				
White	92 (56.0)	56 (53.8)	36 (60.0)	0.444
African American	72 (44.0)	48 (46.2)	24 (40.0)	
Median Age at Diagnosis – year (min, max)	60 (30, 81)	61 (30, 81)	57 (36, 81)	0.288
Stage – n (%)				
IIIa	76 (45.5)	50 (48.1)	26 (41.3)	0.392
IIIb	91 (54.5)	54 (51.9)	37 (58.7)	
Tumor Histology n (%)				
Nonsquamous	65 (38.9)	44 (42.3)	21 (33.3)	0.139
Squamous	41 (24.6)	28 (26.9)	13 (20.6)	
NSCLC NOS	61 (36.5)	32 (30.8)	29 (46.0)	
Treatment				
Chemoradiotherapy alone	120 (73.6)	78 (75.7)	42 (70.0)	0.424
Chemoradiotherapy + surgery	43 (26.4)	25 (24.3)	18 (30.0)	
Recurrence Pattern – n (%)				
Localized recurrence	75 (44.9)	55 (52.9)	20 (31.7)	< 0.001
Multiple metastatic sites	54 (32.3)	32 (30.8)	22 (34.9)	
Single extra-cranial site	15 (9.0)	12 (11.5)	3 (4.8)	
OBM (< 3)	23 (13.8)	5 (4.8)	18 (28.6)	

F/U – Recurrence detected with routine follow-up CT chest scan.
SX – Recurrence detected with symptom development **OBM** – Oligometastatic brain metastases.

Table 2
Time to progression (months) from diagnosis of disease and overall survival (months) after recurrence by method of relapse detection and recurrence pattern.

	N	Total (n = 167)	Routine F/U (n = 104)	SX Directed (n = 63)	P-value
Median Time to Progression		**Median (min, max)**			
All sites (full sample)	167	10.7 (1.6, 163.5)	10.7 (2.4, 163.5)	10.7 (1.6, 81.1)	0.446
All sites (excluding OBM)	144	11.2 (1.6, 163.5)	11.5 (2.4, 163.5)	11.1 (1.6, 81.1)	0.721
By Recurrence Pattern					
Localized recurrence	75	12.1 (2.9, 163.5)	12.3 (2.9, 163.5)	11.1 (3.3, 81.1)	0.908
Multiple metastatic sites	54	10.1 (1.6, 68.4)	11.9 (3.0, 68.4)	8.1 (1.6, 26.8)	0.318
Single extra-cranial site	15	6.7 (2.4, 38.6)	5.4 (2.4, 38.6)	18.0 (10.7, 21.2)	0.172
OBM	23	7.7 (2.9, 27.0)	7.5 (3.4, 8.3)	8.0 (2.9, 27.0)	0.043
Median Overall Survival					
All sites (full sample)	167	7.3 (0.0, 169.3)	7.6 (0.1, 169.3)	6.1 (0.0, 138.1)	0.797
All sites (excluding OBM)	144	6.5 (0.0, 71.5)	7.5 (0.1, 71.5)	3.4 (0.0, 49.6)	0.013
By Recurrence Pattern					
Localized recurrence	75	8.5 (0.0, 71.5)	10.3 (0.2, 71.5)	4.7 (0.0, 49.6)	0.141
Multiple metastatic sites	54	3.7 (0.1, 46.4)	5.0 (0.1, 46.4)	2.9 (0.1, 22.8)	0.135
Single extra-cranial site	15	8.9 (1.0, 49.0)	7.5 (1.0, 49.0)	8.9 (5.9, 37.3)	0.854
OBM	23	12.9 (1.3, 169.3)	12.7 (2.7, 169.3)	12.9 (1.3, 138.1)	0.794

F/U – Recurrence detected with routine follow-up CT chest scan.
SX – Recurrence detected with symptom development.
OBM – Oligometastatic brain metastases.

standard follow-up consisted of CT chest scanning every three months for a year, followed by scans every four months for two years, every six months for one year, and then scans annually. CT chest imaging also captured the upper abdomen and was performed with IV contrast if renal function allowed. All patients were followed with the institutional standard CT imaging schedule described above, unless a new patient symptom prompted imaging that deviated from this schedule. Brain imaging was not part of the institutional standard follow-up, though a subset of patients (n = 36) had routine CNS imaging as well, as part of two clinical trial protocols. Patients were classified according to whether their relapse was detected during a routine CT chest scan (F/U) or detected because they had symptoms related to their disease progression (SX). Patterns of recurrence were classified based on whether relapse was local (LR) versus systemic. Localized recurrence was defined as lesions found within the chest and included pericardial and pleural effusion as well as supraclavicular lymph nodes. If recurrence was extrathoracic, the patient was considered to have systemic relapse and was also categorized as having multiple metastatic sites (MM), a single extra-cranial metastatic site (SEM), or oligometastatic brain mestastases (OBM). Patients with OBM were defined as having < 3 brain lesions.

Several descriptive variables of the study cohort were assessed and included sex, race, age, tumor histology, treatment modality (chemoradiotherapy alone or chemoradiotherapy + surgery), and tumor stage. Cross-tabulations between the ordinal variables and how progression was detected (F/U versus SX) were tested using Chi-square tests, while

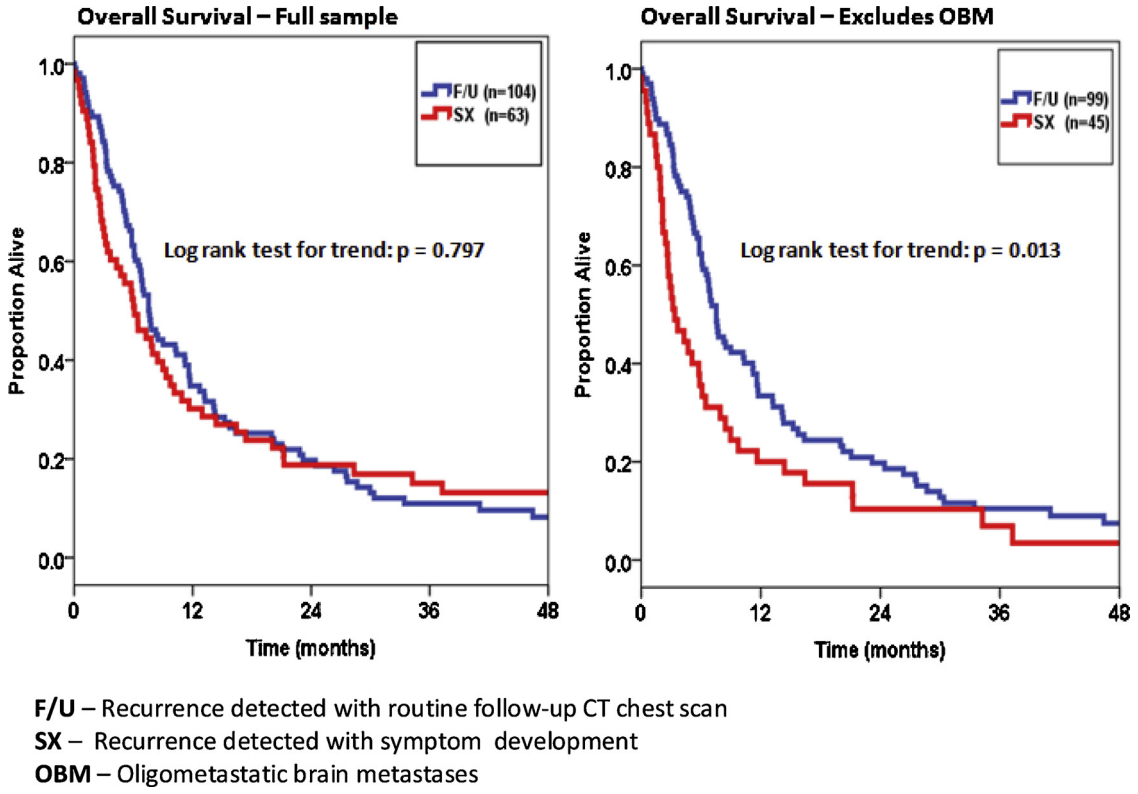

Fig. 1. Kaplan-Meier survival for full cohort (includes all relapse sites) and for sub-cohort (excludes patients with OBM) by method of recurrence detection.
F/U – Recurrence detected with routine follow-up CT chest scan.
SX – Recurrence detected with symptom development.
OBM – Oligometastatic brain metastases.

continuous variables were tested using the Mann-Whitney test. Outcomes analyzed included median time to progression (TTP) and median overall survival (OS) using Kaplan Meier curves. TTP was defined as the time between the date of original diagnosis to date of recurrence. OS was calculated from the date of recurrence. Comparisons between F/U and SX cases and patterns of recurrence (LR versus SEM versus MM versus OBM) were assessed using the log rank test-for-trend. Outcomes were first assessed between F/U and SX cases using the entire cohort and including all relapse sites (n = 167). The cohort was then stratified by pattern of recurrence, and survival curves were computed to assess outcomes between F/U and SX cases for each recurrence subgroup. A sub-cohort (n = 144), that excluded the twenty-three patients with OBM, was then examined and compared outcomes between F/U cases and SX cases. All analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, New York). Given the relatively small number of events, we did not perform a multivariate analysis. This retrospective cohort study was performed in accordance with the Institutional Review Board of the University of Maryland.

3. Results

Of the cohort of 167 patients, 104 (62%) patients had recurrence detected via a routine follow-up CT chest scan while 63 (38%) patients had recurrence detected by the development of symptoms. Table 1 shows that gender, race, age, tumor histology, and tumor stage did not significantly vary between the F/U and SX cases. Most patients in the cohort were treated with chemoradiotherapy alone (74%). FU and SX cases had an equal percentage of patients who additionally underwent surgery. Pattern of recurrence significantly differed between FU and SX cases. A significantly greater proportion of patients evaluated with scans had localized recurrence compared with symptomatic patients (p = 0.001). There were 23 cases of OBM and these were more likely to be detected on the basis of symptoms. There were 15 cases of solitary extra-cranial metastases and these were detected more often with routine scans and commonly occurred in the liver, bone, or adrenal glands. There was no difference in the patterns of recurrence between patients who underwent chemoradiotherapy or those who underwent chemoradiotherapy and surgery.

Median time to progression (Table 2) for the entire cohort did not differ between F/U and SX patients (p = 0.446). TTP also did not significantly vary between F/U and SX cases once stratified by patterns of recurrence, except for patients with OBM (LR: 12.3 months versus 11.1 months, p = 0.91; MM: 11.9 months versus 8.1 months, p = 0.32; SEM: 7.5 months versus 8.9 months, p = 0.85). The five patients who underwent routine brain imaging as part of the clinical trials they were enrolled in at the time, had a slightly shorter median TTP as compared to patients who had their solitary brain metastases discovered via symptoms (7.5 months versus 8.0 months, p = 0.043). This should be interpreted with caution though, given the small sample size in this subgroup.

Median overall survival for the patients with recurrence detected by routine follow-up CT scans was 7.6 months while patients with symptoms had a survival time of 6.1 months (p = 0.797,Table 2, Fig. 1). After stratifying by patterns of recurrence, F/U patients with localized recurrence had a trend toward longer survival, though this was not statistically significant (10.3 months versus 4.7 months, p = 0.14). The same trend was seen for F/U patients with multiple metastases (5.0 months versus 2.9 months, p = 0.14). Patients with a single extra-cranial or OBM did not show this same trend and there were no differences seen between F/U and SX cases. (SEM: 7.5 months versus 8.9 months, p = 0.85; OBM: 12.7 months versus 12.9 months, p = 0.79) (Table 2, Fig. 2).

When examining the entire study sample that includes both F/U and SX cases, most patients with solitary or oligometastatic recurrences had

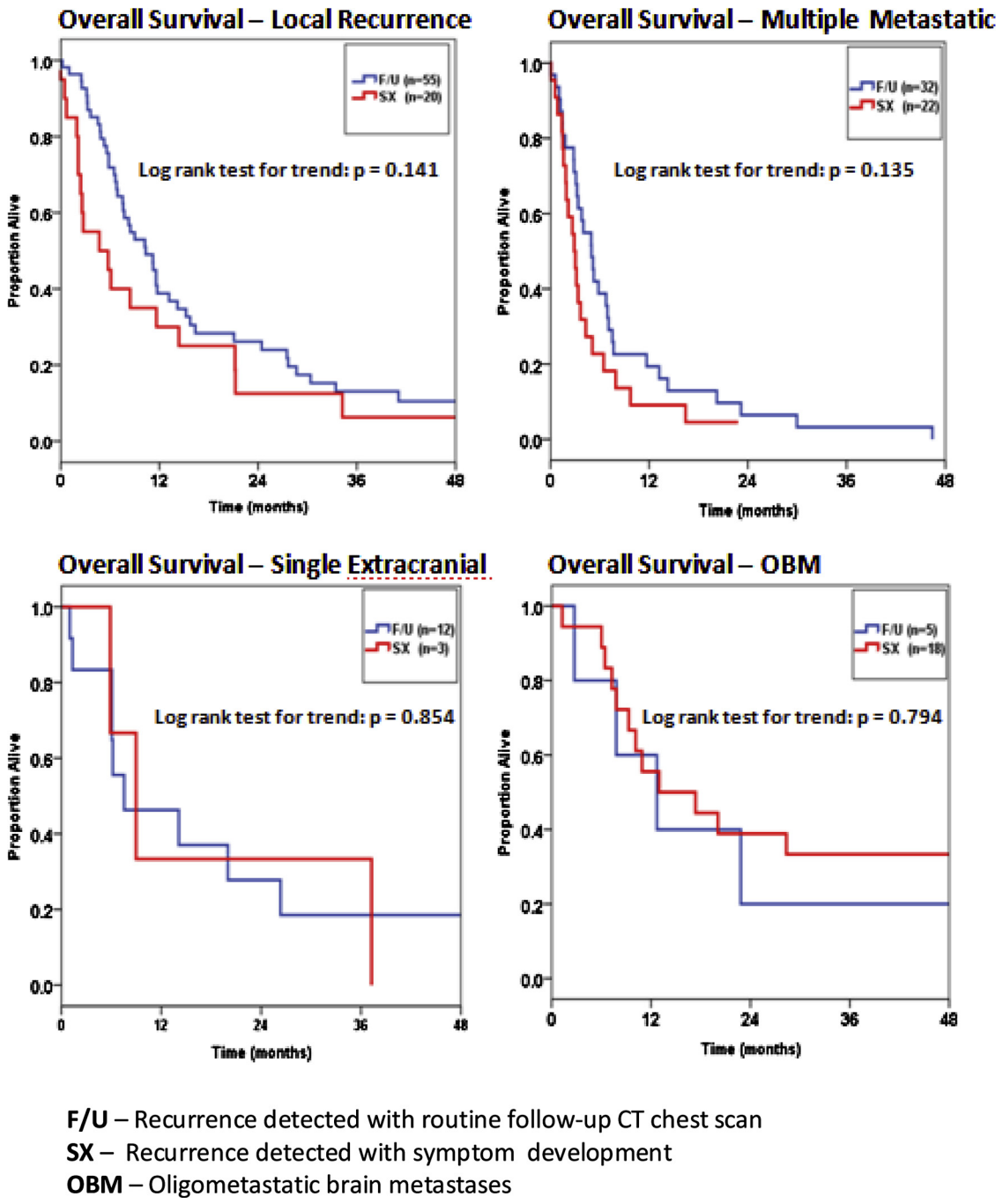

Fig. 2. Kaplan-Meier survival by method of recurrence detection and pattern of recurrence.
F/U – Recurrence detected with routine follow-up CT chest scan.
SX – Recurrence detected with symptom development.
OBM – Oligometastatic brain metastases.

the brain as the site of disease (n = 23). Overall, these OBM patients had the best outcomes with a median survival time of 12.9 months as compared to 8.9 months for single extra-cranial relapse or 8.5 months for those with local recurrences or 3.7 months for those with multiple metastatic sites ($p < 0.001$) (Table 2).

Given this latter result, we re-evaluated the efficacy of routine CT scans by excluding all patients who relapsed with OBM (n = 23). Therefore there were now 99 patients with a non-CNS relapse detected by routine scans compared to 45 symptom detected patients. There was now a significantly superior outcome for those detected with routine follow-up vs. by symptoms, 7.5 months vs. 3.4 months ($p = 0.01$) (Table 2, Fig. 1).

4. Discussion

This study found that overall survival from the time of recurrence did not vary significantly between patients diagnosed with recurrence detected by routine CT chest follow-up and patients whose recurrence was detected by evaluations obtained with the development of symptoms in the intervals between those scans. Among patients with localized recurrence or recurrence with multiple metastatic sites, those diagnosed with follow-up scans had a trend towards better survival compared to symptomatic patients, though this was not statistically significant. Interestingly, the patients diagnosed with symptom driven evaluation did not have shorter times to progression suggesting that the

trend towards better survival was not related to finding recurrences at an earlier time point than with scheduled scans.

There have been a number of studies that have evaluated follow-up strategies in lung cancer. [3–6] These have been conducted almost exclusively in resected patients, primarily stage I and II [7–10]. Most failed to find an advantage from a more intensive evaluation. Benamore et al. noted a 5% reduced risk of death among stage I patient followed with intensive follow-up, though no benefit was seen for lung specific survival and no benefit was found in the pooled analyses that included all stage I – III patients [11]. A recent prospective randomized clinical trial involving resected stage I – III non-small cell lung cancer patients, found no significant difference in survival at three years and at eight years between patients followed with a clinical exam and chest x-ray versus a more intensive scheme that also included CT scan +/- bronchoscopy [12].

While routine surveillance by CT chest alone did not improve outcomes for LANSCLC over symptom guided imaging in our study, this null result was largely driven by the favorable outcomes seen for patients with OBM. After excluding the patients with OBM, a significantly better outcome was seen for patients whose recurrence was found on follow-up CT scans as compared to those with symptoms. This suggests that earlier intervention in patients with local or systemic relapse does result in patient benefit, a finding consistent with data that patients with better performance status in advanced disease have superior outcomes. However, it is also possible that those who present symptomatically have more aggressive disease than those found by scanning, i.e. length time bias.

The pattern of relapse was the strongest predictor of overall survival in this current study. Consistent with prior studies, those with OBM had the best outcomes [13,14]. The large majority of these patients were diagnosed via symptoms, though five patients were discovered via routine brain imaging, as a subset of patients were enrolled in clinical trials at the time that involved serial brain scans. This raises the question of whether routine brain imaging should be part of surveillance. Yokoi et al., proposed the use of surveillance brain CTs as early as 1996 [15]. The brain as the sole site of recurrence has been recognized as a problem after the use of multimodality therapy for stage III disease and addressed in a randomized trial of prophylactic cranial irradiation (PCI, Radiation Therapy Oncology Group study 0214) [16]. This study demonstrated that PCI decreased recurrence in the brain without improvement in survival, and at the expense of decreased cognition. Though patients with OBM do comparatively better than others, the outcomes are still poor. The results of stereotactic radiotherapy for CNS disease are dependent upon disease volume and therefore investigation of active surveillance with the objective of identifying smaller metastases is justified [17]. Another factor that will enter into this process is the emerging use of immunotherapy after concurrent chemoradiotherapy for LANSCLC. Notably, this approach decreased the risk for brain metastases [18].

In summary, this is the largest study of follow-up strategy for patients treated with chemoradiotherapy for LANSCLC and suggests that a strategy of routine chest CT and CNS imaging may be beneficial as opposed to studies triggered only by symptoms. However, our study is limited by its retrospective nature and relatively small number of events. Given that this was a retrospective cohort, the two groups compared were not made through randomization, though the basic characteristics of sex, race and age were comparable. As noted above, it is certainly possible that the better outcomes for patients with extracranial disease detected by F/U is due to the detection of more indolent disease by scan and more aggressive disease by symptoms, analogous to the length time bias seen in disease screening. This can only be answered in the setting of a randomized study.

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