Analysis of Relapse Events After Definitive Chemoradiotherapy in Locally Advanced Non–Small-Cell Lung Cancer Patients

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Abstract

The appropriate follow-up frequency after chemoradiotherapy (CRT) for locally advanced non–small-cell lung cancer patients is unknown. Our data on 211 patients found that most relapses happen within a year of completing CRT, and that symptomatic relapses portended worse outcomes versus relapses identified by surveillance imaging. More intensive surveillance imaging may identify asymptomatic relapses, which are more amenable to early salvage.

Background: The appropriate follow-up frequency after definitive chemoradiotherapy (CRT) for locally advanced non–small-cell lung cancer patients is unknown. Although surveillance guidelines have been proposed, very few data support current recommendations. Here we analyze relapse events after CRT and investigate whether symptomatic relapses versus those detected by surveillance imaging influences outcomes. **Patients and Methods:** Stage III non–small-cell lung cancer patients treated with CRT at our institution between 2005 and 2014 were retrospectively analyzed. Relapse events were grouped into posttreatment intervals and analyzed with cumulative tables. Time to relapse and overall survival (OS) were compared between patients with relapse detection via symptomatic presentation versus surveillance imaging. **Results:** A total of 211 patients were identified for analysis. The median follow-up was 43 months for patients alive at the time of analysis. The median age was 63 years, and equal proportions had IIIA or IIIB disease. A total of 135 patients (64%) experienced disease relapse, and of these, 74% did so within 12 months. In those who did not experience relapse at $\leq$ 12 months, 16%, 6%, and $<$ 5% experienced relapse during 12 to 24, 24 to 36, and $>$ 36 months of follow-up, respectively. In patients with relapse, 56% presented symptomatically, which led to inferior median OS compared to those identified by surveillance imaging (23 vs. 36 months; $P = .013$). **Conclusion:** This study identified that most relapses occur within 1 year of completing CRT, and approximately half of these occur within 6 months. A symptomatic relapse led to inferior OS. More aggressive surveillance imaging may therefore identify asymptomatic relapses that are amenable to earlier salvage therapy.

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Introduction

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-related death in the United States and worldwide.[1-3] Approximately half of newly diagnosed NSCLC patients present with locally advanced unresectable disease, which is primarily managed with definitive chemoradiotherapy (CRT).[4] Previous prospective trials have established that platinum-based doublet therapy concurrent with radiotherapy (RT) provides superior outcomes compared to sequential regimens.[5] Recently RTOG 0617, a randomized phase 3 trial, demonstrated a median overall survival (OS) of 28.7 months, a new survival benchmark for this concurrent CRT approach.[6] Yet despite advancements in multimodal approaches, NSCLC continues to be an aggressive disease with a high risk of recurrence after CRT or surgery.

Disease relapse dynamics after definitive therapy for NSCLC have mostly been described in heterogeneous retrospective surgical series,[7-9] which have informed the American College of Chest

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Physicians (ACCP) recommendations for postoperative surveillance.[10] The European Society for Medical Oncology (ESMO) guidelines for NSCLC currently recommend chest computed tomography (CT) imaging biannually for those deemed to be suitable for salvage treatment; otherwise CT imaging is recommended at least once at 12 and 24 months.[11] The National Comprehensive Cancer Network (NCCN) NSCLC guidelines previously recommended a similar follow-up schedule, but this was recently changed to a shorter surveillance interval of every 3 to 6 months for the first 3 years after definitive treatment.[12] Although these recommendations have been provided, there are no data from randomized trials and very few retrospective data that analyze posttreatment surveillance after definitive CRT.

We evaluated time-based events of relapse in stage III NSCLC patients after definitive CRT to characterize posttreatment intervals at high risk for relapse. We also analyzed whether symptomatic presentation versus identification on surveillance imaging influenced patient outcomes after initial relapse.

Patients and Methods

Study Cohort

After institutional review board approval, we performed a retrospective review of a prospectively collected clinical database of patients with pathologically confirmed unresectable locally advanced NSCLC treated with definitive CRT from 2005 through 2014. Over the span of this study, mediastinal staging was performed using combinations of imaging, endobronchial ultrasound, and mediastinoscopy or mediastinotomy. Patients were excluded if they presented with metastatic disease or had prior oncologic intervention for lung cancer.

Patient, tumor, treatment, and outcome data were abstracted from the electronic medical charts. Particularly, patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status (PS), disease stage according to American Joint Committee on Cancer (AJCC; 7th edition) staging for NSCLC,[13] smoking status during treatment, and total pack-years were evaluated.

Regarding treatment, all patients received concurrent platinum-based chemotherapy and RT delivered with 70 Gy in 35 fractions utilizing 3D-conformal RT or intensity-modulated RT planning, which has been the standard at our institution since 2005. Beginning in 2006, elective nodal irradiation was not part of the treatment approach. Additionally, treatment for all patients was planned with 4D-CT imaging, and strict normal tissue constraints were used.

Follow-up

All patients underwent routine posttreatment surveillance with physical examination, comprehensive metabolic panels, and imaging studies. Over the course of this analysis, the method of posttreatment surveillance was heterogeneous, although the majority of treating physicians followed our institutional standards and scheduled a follow-up evaluation every 3 months with CT or 18-fluorodeoxy-glucose positron emission tomography (^{18}FDG-PET)/CT imaging for the first 2 to 3 years and then annually thereafter. ^{18}FDG-PET/CT was used to confirm suspicious findings on CT imaging. Magnetic resonance imaging (MRI) brain scans with and without contrast were obtained when patient symptoms warranted further investigation. All posttreatment CT, ^{18}FDG-PET/CT images, or MRI brain scans were evaluated for first event of disease recurrence and compared to the radiologists' formal assessment. Of note, routine CT chest imaging at our institution extends to the level of the adrenal glands.

Assessment of Relapse Events

The events of local relapse (LR), regional relapse (RR), and distant relapse (DR) were evaluated from the conclusion of RT to the first evidence of relapse on posttreatment imaging; patients with multisite relapses were categorized by the most advanced site. Relapse events were defined as follows: LR indicated relapse within the RT field (overlapping the planning target volume); RR indicated relapse in hilar/mediastinal lymph nodes (defined in the 7th edition of AJCC staging for NSCLC) outside the RT field; and DR indicated any relapse in the contralateral lung parenchyma/pleura or outside the thorax. A major limitation to surveillance imaging after RT is the poor discriminatory ability of defining residual versus recurrent versus posttreatment changes in the lung.[14] For this reason, final designation of a relapse event required an additional oncologic intervention in the patients' care plans in addition to imaging findings. No distinction was made between a second primary tumor and recurrence.

Patients who experienced relapse were further stratified by detection of relapse on the basis of scheduled surveillance imaging or presentation with relapse-related symptoms. Examples of relapse-related symptomology included new-onset hemoptysis, increased shortness of breath or dyspnea, chest pain, nonthoracic pain related to metastatic disease, or neurologic symptoms resulting from brain metastases.

Statistical Analysis

A cumulative incidence table was generated by assigning relapse events into graded posttreatment intervals in the following manner: relapses within 0 to 12 months were grouped into 3-month intervals; relapse events from $>$ 12 to 24 months were grouped into 4-month intervals; and relapses $>$ 24 months were grouped into 6-month intervals. All relapses $>$ 48 months were within their own grouping. The Kaplan-Meier method was used to estimate time to relapse and OS between analyzed cohorts, and results were compared by log-rank test. Univariate analysis with chi-square comparison was used to assess for the significance of clinical variables in defined end points. All tests were 2 sided, and an α (type I) error $<$ 0.05 was considered to be statistically significant. Analyses were performed by SPSS 24.0 (IBM, Chicago, IL).

Results

A total of 211 patients with stage III NSCLC who were treated with definitive CRT met our inclusion criteria. Table 1 summarizes the baseline patient demographics and treatment characteristics. The median age at diagnosis was 63 years (range, 36-84 years), and 51% were female. The majority of patients (89%) had an excellent ECOG PS (0-1) at the beginning of treatment. In this cohort, 22% of patients continued to smoke during CRT; the median pack-years of tobacco use was 40 (range, 0-150).

All patients underwent staging with ^{18}FDG-PET/CT imaging; 34% of patients had their mediastinum staged by imaging alone.

Table 1 Patient, Tumor, and Treatment Characteristics of 211 Subjects

Characteristic	Value
Sex	
Male	148 (49)
Female	154 (51)
Age at time of diagnosis (y), median (range)	63 (36-84)
ECOG PS	
0-1	188 (89)
2	23 (11)
Tumor Histology	
Adenocarcinoma	102 (48)
Squamous-cell carcinoma	69 (33)
Other	40 (19)
T Group	
Tx	20 (9)
T1	31 (15)
T2	46 (22)
T3	50 (24)
T4	64 (30)
N Group	
N0	11 (5)
N1	6 (3)
N2	136 (65)
N3	58 (27)
Tumor Stage	
IIIA	105 (50)
IIIB	106 (50)
Current smoker	47 (22)
Pack-years of tobacco use, median (range)	40 (0-150)
Chemotherapy	
Concurrent	211 (100)
Induction	23 (11)
Consolidation	47 (22)
Weekly	112 (53)
Chemotherapy Cycle Start With RT	
Cycle 1-2	190 (90)
Cycle 3 or higher	21 (10)

Data are presented as n (%) or median (range).
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; RT = radiotherapy.

Table 2 Patterns of Relapse After Definitive Chemoradiotherapy

Pattern of Relapse	N (%)
Total Relapses	135 (64)
Local	57 (27)
Regional	61 (29)
Distant	117 (55)
Site of Distant Metastases	
Brain	35 (30)
Adrenal	14 (12)
Bone	32 (27)
Liver	15 (13)
Contralateral lung	32 (27)
Extrathoracic lymph node	10 (9)
Other	5 (4)

Pathologic confirmation of ^{18}FDG-PET/CT results was performed with an endobronchial ultrasound or mediastinoscopy/mediastinotomy approach in 45% and 21% of patients, respectively. In this cohort, 81% (n = 170) of patients underwent pretreatment assessment of the brain with an MRI, whereas 19% underwent CT head imaging. Using these staging approaches, equal proportions of patients had stage IIIA and IIIB disease, with 48% having adenocarcinoma histology. The majority of patients (94%) received platinum doublet chemotherapy concurrent with RT, and 53% received this in a weekly regimen. Twenty-three (11%) and 47 (22%) patients received induction and consolidative chemotherapy, respectively. Most (90%) started RT treatment with cycle 1 or 2 of chemotherapy.

The median follow-up for all patients was 18 months (range, 3-126 months), and 43 months (range, 5-126 months) for those alive at analysis. A total of 135 patients (64%) experienced disease relapse during our study period. LR and RR occurred in 27% and 29%, respectively, as the first site of relapse. DR was the most common pattern (55%) of disease relapse. Of those who experienced distant recurrence, intracranial relapse was the most common (30%). The second most frequent sites of DR were the contralateral lung and bone (27% each). Table 2 lists patterns of relapse and categorization of the sites of metastatic relapse. Of note, some patients had local, regional, and/or DR simultaneously. In this study, we found that 28%, 57%, and 26% of patients had ^{18}FDG-PET/CT-detected LR, RR, and DR events, respectively.

Of the 135 patients with disease relapse, 74% had disease that recurred within 1 year of completing CRT. In those who did not experience disease recurrence at $\leq$ 12 months, 16%, 6%, and < 5% experienced recurrence during > 12 to 24, > 24 to 36, and > 36 months of follow-up, respectively (Table 3). Figure 1A depicts the cumulative incidence of relapse events for patients with a relapse event. Note that at 6 months and 12 months, approximately one half and three fourths of total relapse events occurred, respectively. When stratified by disease stage, we found the median onset of relapse was more rapid in patients with IIIB versus IIIA disease (8.1 vs. 14.9 months; $P = .02$). Of the patients with relapse, approximately 51% of patients with IIIB disease experienced recurrence within the first 6 months, compared to 41% in the IIIA cohort. In both stage groups, about 90% of relapse events occurred by 24 months (Figure 1B).

Next, we evaluated whether the method of relapse identification (surveillance imaging vs. symptomatic presentation) influenced patient outcomes. There were no differences in the proportions of patients with stage IIIA (n = 59) versus IIIB (n = 76) disease between the two groups ($P = .29$). Of the 135 patients who experienced relapse, 56% (n = 76) had recurrence first identified by a symptomatic presentation. There was no significant difference in the overall onset of any relapse ($P = .78$), RR ($P = .55$), or DR

Table 3 Cumulative Incidence of Defined Relapse Events by Follow-up Interval

Relapse Event	Variable	Event (Total)	Month											
			3	6	9	12	16	20	24	30	36	42	48	>48
LR	Incidence (% total of LR)	—	5 (9)	8 (14)	12 (21)	5 (9)	6 (11)	6 (11)	3 (5)	5 (9)	2 (4)	2 (4)	1 (2)	2 (4)
	Cumulative events (remain at risk)	57 (211)	5 (188)	13 (162)	25 (129)	30 (107)	36 (91)	42 (79)	45 (66)	50 (55)	52 (46)	54 (36)	55 (33)	—
RR	Incidence (% total of RR)	—	4 (7)	15 (25)	11 (18)	8 (13)	7 (11)	5 (8)	6 (10)	2 (3)	0	1 (2)	1 (2)	1 (2)
	Cumulative events (remain at risk)	61 (211)	4 (189)	19 (155)	30 (125)	38 (106)	45 (88)	50 (78)	56 (66)	58 (56)	58 (47)	59 (37)	60 (34)	—
DR	Incidence (% total of DR)	—	31 (26)	24 (21)	22 (19)	12 (10)	2 (2)	12 (10)	4 (3)	4 (3)	3 (3)	1 (1)	1 (1)	1 (1)
	Cumulative events (remain at risk)	117 (211)	31 (166)	55 (131)	77 (102)	89 (86)	91 (78)	103 (63)	107 (57)	111 (47)	114 (41)	115 (33)	116 (31)	—
Any relapse	Incidence (% total of any relapse)	—	32 (24)	31 (23)	23 (17)	14 (10)	10 (7)	7 (5)	6 (4)	6 (4)	3 (2)	1 (1)	1 (1)	1 (1)
	Cumulative events (remain at risk)	135 (211)	32 (165)	63 (126)	86 (97)	100 (81)	110 (67)	117 (57)	123 (49)	129 (41)	132 (36)	133 (29)	134 (28)	—
	Follow-up interval (mo)		≤12				12-24			24-36			>36	
	Relapse per follow-up interval		74%				16%			6%			3%	

Incidence is represented as percentage of total of defined relapse event.
Abbreviations: DR = distant relapse; LR = local relapse; RR = regional relapse.

(P = .54) between the imaging and symptomatic groups (Figure 2A). However, patients with a symptomatic LR experienced relapse more quickly than those identified by surveillance imaging (7.2 vs. 16.4 months; P = .04) (Figure 2B). Patients who continued to smoke during CRT had more frequent symptomatic LR events than those who did not smoke (P = .003). In addition, patients with symptomatic relapses had a worse median OS compared to those with relapse identified by surveillance imaging (23 vs. 36 months; P = .013) (Figure 2C).

Discussion

The appropriate follow-up of NSCLC patients after curative-intent treatment has long been debated. Currently available data address this question inadequately because of the spectrum of disease stages, treatment approaches, and frequency and type of surveillance imaging used. To our knowledge, this study represents the largest analysis to date evaluating surveillance in stage III NSCLC patients treated with curative-intent modern-day delivery of CRT at a high-volume cancer center.

In this study, we found that approximately 75% of relapse events occurred within 1 year after CRT, and this risk gradually declined to < 5% at 3 years (Table 3). Additionally, we found that identification of relapse based on symptomatic presentation versus surveillance imaging portended a worse OS (23 vs. 36 months, respectively).

Presently the ACCP guidelines for NSCLC recommend at least biannual surveillance CT chest imaging along with history and clinical examination for the first 2 years, and annual follow-up thereafter. The ESMO guidelines have been recently updated to recommend CT chest imaging every 6 months for those patients who are suitable for salvage therapy; otherwise, annual imaging is the minimum recommendation.[11] Although the NCCN guidelines previously had similar recommendations, suggestions for surveillance after definitive treatment were recently updated to include a CT chest with or without contrast every 3 to 6 months for the first 3 years.[12] Although these have been proposed, to our knowledge, there are no data to support the current recommendations, especially in the setting of definitive CRT.

Many of the surgical series that guide the current posttreatment surveillance recommendations combined early and locally advanced stage patients in their time-to-event analyses, which may skew the representation of the optimal follow-up interval in unresectable locally advanced disease. In contrast to these studies, we evaluated time-based relapse events in a relatively homogenous cohort of stage III NSCLC patients treated with CRT, which would remove bias created by grouping relapse patterns across different disease stages. Similar to previous retrospective surgical series,[7,8] we found the majority of relapse events in stage III patients occurred within 1 year of completing treatment. Of note, approximately half of these relapses occurred within 6 months of completing CRT, which is the minimum surveillance interval recommended by the ACCP and ESMO. These results suggest that patients are at the highest risk of relapse within the first 6 months of completing CRT.

Prior studies suggest symptomatic relapses may occur in 40% to 76% of NSCLC patients.[8,15,16] In our study, 56% of patients with relapse sought medical attention as a result of relapse-related symptoms before scheduled surveillance imaging. We observed no differences in the median onset of any relapse, RR, or DR when

Figure 1 Cumulative Relapse Incidence Per Follow-up Interval in Patients With Disease Relapse After Definitive Chemoradiotherapy. (A) Relapse Events Are Binned Into Defined Follow-up Intervals. Incidence Is Represented as Percentage of Total Relapse Events. (B) Cumulative Relapse Incidence Stratified by Disease Stage

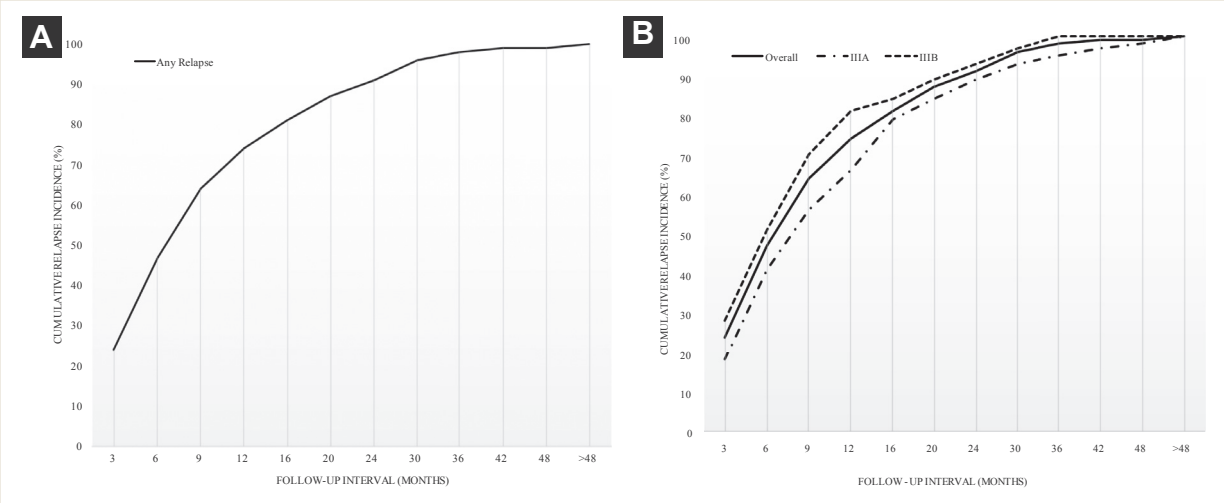
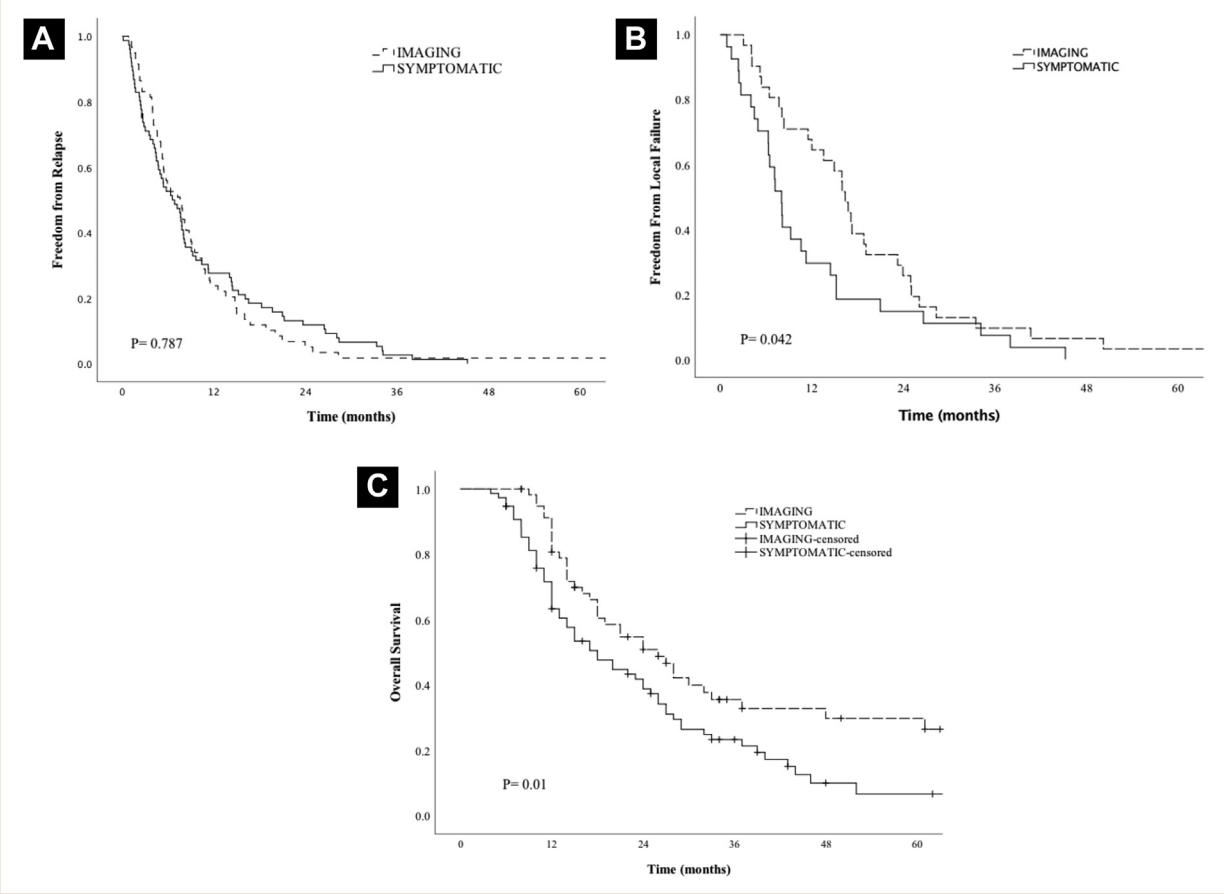


Figure 2 Time to Relapse and Overall Survival Stratified by Symptomatic Presentation or Asymptomatic Detection by Surveillance Imaging. (A) Freedom From Any Relapse. (B) Freedom From Local Relapse. (C) Overall Survival



comparing the two methods of relapse detection. In contrast, patients with symptomatic LR had a substantially more rapid median onset compared to those identified by surveillance imaging (7.2 vs. 16.4 months; $P = .04$) (Figure 2B). It can be inferred that patients with LR symptoms presented earlier because of lung cancer–associated symptoms, such as airway compression, hemoptysis, and increased shortness of breath. There was likely no difference in symptomatic presentation versus surveillance imaging in the onset of DR because the majority of these patients equally presented with pain or neurologic symptoms from osseous and brain metastases, respectively.

The data regarding outcomes resulting from symptomatic versus nonsymptomatic relapse identification are conflicting. A study evaluating patients enrolled onto the neoadjuvant CRT Intergroup 0160 and 0139 trials demonstrated no survival benefit with more intensive imaging surveillance.[15] Additionally, a study of patients managed with complete resection found that relapse detection in asymptomatic patients did not afford any OS benefit[16]; of note, more than half of the patients in this particular study had stage I disease. In contrast, Westeel et al[17] examined 192 patients followed with an aggressive postsurgical surveillance regimen of CT imaging and fiberoptic bronchoscopy, and found improved OS in patients with asymptomatic recurrences. Our study found that patients with symptomatic relapses compared to those detected by surveillance imaging had inferior median OS (23 vs. 36 months; $P = .013$). In our analysis, the definition of relapse required both evidence of progressive disease on imaging as well as a change in oncologic care. Thus, all patients with relapsed disease in our analysis underwent salvage therapy with either systemic therapy or repeat irradiation. The survival curves indicate that detection of first relapse was not dependent on symptomatic presentation (Figure 2A); therefore, the improved OS in our study is likely not inflated by lead-time bias but rather is due to earlier oncologic intervention.

Among the inherent weaknesses to retrospective analyses, there are additional limitations to our study. For instance, all patients did not undergo invasive mediastinal staging, which could affect the incidence of RRs. Also, the modality of relapse detection was not uniform among all patients, which could bias the occurrence of a relapse event by the imaging quality or interpretation by the radiologist. Although a potential confounder, as stated above, a change in oncologic management in addition to imaging findings was needed to define a relapse event in our study. We found that 28%, 57%, and 26% of patients had ^{18}FDG-PET/CT-detected LR, RR, and DR events, respectively, although this method of surveillance was not uniformly used by all physicians and may not accurately reflect detection rates by ^{18}FDG-PET/CT. Previous evidence suggests ^{18}FDG-PET/CT has superior sensitivity and specificity in detecting NSCLC recurrences compared to standard CT imaging, especially when relapse is within the mediastinum.[18] Although ^{18}FDG-PET/CT may be more robust in detecting relapses, a prospective study of 100 NSCLC patients of varying disease stages found that ^{18}FDG-PET/CT imaging 3 months after RT detected more relapses than CT alone, but only 3% of patients had disease amenable to salvage treatment.[19] Reddy et al[20] also recently reported no differences in survival outcomes in patients who experienced relapse identified by ^{18}FDG-PET/CT versus CT $>$ 6 months after completing definitive RT. These findings are reflected in various guidelines, which currently recommend against the use of ^{18}FDG-PET/CT for routine surveillance imaging after curative-intent interventions in NSCLC.

Approximately 15% to 30% of stage III NSCLC patients will have intracranial relapses after definitive therapy.[21,22] An analysis of 422 stage III NSCLC patients enrolled onto 4 prospective protocols of combined modality therapy demonstrated that approximately 60% of intracranial relapses occur within 6 months of treatment.[23] Furthermore, a study of 455 NSCLC patients of differing stages found the rate of symptomatic brain metastases was $<$ 10% over a period of 16 months.[24] Intracranial relapses were the most common site of DR in our study (30%) and were mostly identified by symptomatic presentation, despite 81% of patients undergoing pretreatment assessment by MRI. Because the majority of patients underwent pretreatment evaluation of the brain, our higher rate of symptomatic brain metastases is likely a reflection of aggressive biology and not profound underestimates of the pretreatment intracranial tumor burden.

This study found that most relapses happen within the first year of completing definitive CRT, and just over half of these are identified after symptomatic presentation. Although we found that symptomatic relapses correlated with worse OS, a more intensive surveillance regimen within the first 6 months of completing treatment may help identify more asymptomatic relapses. This would be advantageous because it may provide an opportunity to initiate salvage therapy sooner, possibly in patients with better PS and with a lower burden of disease. Of note, adjuvant therapy with durvalumab after CRT is now the standard of care in stage III disease and has been proven to increase the time to progression.[25] Thus, before symptomatic recurrence, administration of durvalumab may improve OS when the disease burden is lower or via the synergistic interactions between RT and immunotherapies.[26]

We provide what to our knowledge is the first evidence to support the recently changed NCCN guidelines recommending post-surveillance imaging and examination at 3 to 6 months after definitive treatment. Of note, however, our findings suggest that somewhat more frequent follow-up than this is probably preferable, because patients with asymptomatic recurrences detected on imaging fared better in our cohort. These findings also raise the question of whether periodic repeat brain imaging might be of benefit in the asymptomatic patient. Optimally, our findings should be validated in a prospective randomized controlled trial or (more realistically) a larger retrospective analysis of pooled patients from multiple institutions to better define an optimal posttreatment surveillance interval after curative-intent CRT.

Clinical Practice Points

- The optimal surveillance frequency after definitive CRT for stage III NSCLC patients is unknown.
- Most relapses after definitive CRT for stage III NSCLC happen within 1 year of completing treatment.
- Symptomatic relapses result in worse OS compared to asymptomatic relapses identified by surveillance imaging.
- More aggressive surveillance imaging may improve outcomes by identifying asymptomatic relapses that are amenable to earlier salvage therapy.

Disclosure

The authors have stated that they have no conflict of interest.

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