Survival Benefit of Surgery after Chemoradiotherapy for Stage III (N0–2) Non–Small-Cell Lung Cancer Is Dependent on Pathologic Nodal Response

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Introduction: The benefit of surgery (trimodality therapy [TMT]) after chemoradiotherapy (CRT) for patients with stage III non–small-cell lung cancer (NSCLC) is controversial, but nodal pathologic complete response (N-PCR) is accepted as a strong predictor of overall survival (OS). We compared the outcomes of patients treated with TMT versus CRT, focusing on the importance of N-PCR.

Methods: Patients with stage III NSCLC treated with CRT or TMT from December 2004 through December 2012 were included; patients with N3 disease were excluded. Pathologic nodal response dichotomized surgical patients into N-PCR versus residual nodal disease (RND) groups. Actuarial OS, progression-free survival (PFS), and distant metastasis-free survival (DMFS) were compared between patients treated with CRT and TMT and between CRT and N-PCR/RND.

Results: The cohort was composed of 138 patients (52% CRT and 48% TMT). The median OS was significantly higher after TMT than after CRT (81 versus 31.8 mo, $p = 0.0068$). This benefit was restricted to N-PCR (n = 50, 83.2 versus 31.8 mo, $p = 0.0004$), as RND (n = 19) experienced poor OS (16.1 mo). On multivariable analyses, N-PCR had superior OS (hazard ratio [HR], 0.38; $p = 0.0012$), PFS (HR, 0.42; $p = 0.0005$), and DMFS (HR, 0.42; $p = 0.0007$) compared with CRT. Conversely, there were trends for worse OS and PFS for RND versus CRT, although only inferior DMFS was significant (HR, 1.83; $p = 0.04$).

Conclusions: Surgical patients with complete nodal clearance experienced superior survival, but those with RND fared no better than CRT alone. Mediastinal response may play an important role in the decision to proceed with surgical resection after CRT for stage III NSCLC.

Key Words: Non–small-cell lung cancer, Chemoradiotherapy, Trimodality therapy, Mediastinal staging.

(*J Thorac Oncol.* 2015;10: 1475–1480)

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Disclosure: The authors declare no conflict of interest.

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DOI: 10.1097/JTO.0000000000000639

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ISSN: 1556-0864/15/1010-1475

Concurrent chemoradiotherapy (CRT) is typically the essential component of definitive treatment for patients with stage III non–small-cell lung cancer (NSCLC).[1] Indeed, the National Comprehensive Cancer Network gives definitive CRT alone a category 1 recommendation for most stage III NSCLC patients.[2] The Intergroup 0139 trial showed that trimodality therapy (TMT)—surgical resection following induction CRT—results in improved local control and progression-free survival (PFS) in appropriately selected patients with stage IIIA NSCLC.[3] However, this disease control improvement did not translate into an overall survival (OS) benefit, possibly because of treatment-related morbidity in the surgical arm.

In the absence of randomized data that firmly support the addition of surgery, treatment choice is often a function of institutional and/or physician preference,[4] especially because there are currently no reliable clinical, radiologic, or genomic tests that can establish the relative risk of local-only versus distant recurrence. Multiple prospective studies and retrospective series have shown that nodal pathologic complete response (N-PCR) after induction therapy is strongly prognostic for improved survival outcomes.[5–10] Patients with residual nodal disease (RND)—particularly positive mediastinal adenopathy—typically fare much worse. One may, therefore, question whether pathologic response should guide the decision to proceed with surgical resection.

At Rush University Medical Center, all patients with potentially curable stage III NSCLC first undergo CRT and are evaluated for resectability during and after treatment. Historically, we have aggressively pursued surgery after CRT given the first anticipated, and then proven, PFS benefit of resection. Although most patients with stage III disease were ultimately treated with definitive CRT, a sizeable percentage of individuals did undergo post-CRT resection. The objective of this retrospective study was to compare the outcomes of patients treated with TMT with those of patients treated with CRT alone, focusing on the differential survival results as a function of pathologic nodal status.

PATIENTS AND METHODS

Patient Selection

The study population included all adult patients with stage III (N0–2) NSCLC treated with curative intent CRT with or without surgery at Rush University Medical Center initiated

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between December 2004 and December 2012. Patients were excluded from the CRT cohort if they did not receive curative intent concurrent CRT (minimum 60 Gy). Patients treated with induction CRT (i.e., less than 60 Gy) but not proceeding to surgery were excluded from the TMT cohort; additional exclusion criteria included a prior diagnosis of lung cancer or history of malignancy other than nonmelanoma skin cancer within 5 years of starting treatment. Institutional review board approval was obtained for this retrospective study.

Treatment

Details of radiation therapy and chemotherapy regimens have been reported previously by Gielda et al.[11] Radiation therapy for all patients was delivered with a split course technique using three-dimensional conformal radiation therapy or intensity modulated radiotherapy to a target volume consisting of the primary tumor and involved nodes plus a margin for setup error. Respiratory motion was assessed by fluoroscopy before 2006 and more recently with four-dimensional computed tomography (CT) simulation. Treatment was given in 1.8 to 2 Gy daily fractions. The total dose for patients receiving CRT alone was typically 60 to 64 Gy, whereas patients receiving TMT were typically treated to 44 to 46 Gy. All patients were treated with platinum-based chemotherapy regimens. Most patients received carboplatin and paclitaxel, but after 2008, patients with non–squamous-cell carcinoma typically received carboplatin and pemetrexed. Among the TMT cohort, the decision to pursue this treatment paradigm was made in a multidisciplinary setting before any oncologic treatment, and surgeons verified subsequent resectability based on clinical assessment and repeat chest CT after the delivery of neoadjuvant CRT. All patients underwent anatomical resection (lobectomy, bilobectomy, or pneumonectomy) approximately 4 to 6 weeks after induction CRT.

Posttreatment Evaluation

Radiation and medical oncologists performed clinical and radiographic follow-up, and surgeons also followed those patients treated with TMT. Chest CT was usually performed approximately 4 to 6 weeks after the end of definitive treatment. Surveillance then consisted of chest CT every 3 months for the first 2 years, and semiannually thereafter. Positron-emission tomography (PET)–CT was usually performed for further evaluation of suspicious findings on CT.

Data Collection

Patients were identified through a departmental database. Demographic, disease, and treatment characteristics were recorded from the electronic medical record. Findings on surveillance imaging of abnormal-appearing or enlarged nodes, growth of the primary lesion, or development of distant metastases were usually confirmed with short-interval reimaging (chest CT or PET–CT) or by biopsy before initiation of salvage or palliative therapies. If recurrence was confirmed through these methods, the date of failure was recorded as the date of the initial abnormal surveillance scan. Locoregional recurrences included progression within the ipsilateral lung and nodal failures in the hilum, mediastinum, and supraclavicular fossa. Recurrences consistent with positive M-classification in the current American Joint Committee on Cancer 7 staging system, including new pleural lesions and malignant effusions, were classified as distant recurrences. Pathology reports from postinduction surgery were evaluated to determine response to neoadjuvant CRT. Response within the primary lesion was classified separately from response in the lymph nodes. Patients in the TMT cohort were dichotomized as achieving N-PCR or RND.

Statistical Analysis

Differences in patient, disease, and treatment characteristics between those treated with CRT versus TMT were tested using Fisher's exact and χ^2 tests. OS, PFS, and distant metastasis-free survival (DMFS) were determined using Kaplan–Meier statistics from date of diagnosis, and the log-rank test was used to analyze differences in survival curves. Gray's test was used to assess differences in cumulative incidences of locoregional recurrence between the CRT cohort, the entire TMT cohort, and the two TMT subsets, with death serving as a competing risk.

Multivariable Cox regression analyses with stepwise selection were performed to compare adjusted survival outcomes between three cohorts of patients: CRT versus TMT (all), CRT versus TMT (N-PCR), and CRT versus TMT (RND). Clinicopathologic variables included in the initial multivariable model were age, sex, overall stage, T-stage, N-stage, and histology. SAS version 9.2 (Cary, NC) was used for all statistical analyses.

RESULTS

Patient, Disease, and Treatment Characteristics

A total of 138 patients were included in this retrospective analysis. Patient and pretreatment disease characteristics are shown in Table 1. There were 72 patients (52%) who received CRT alone, and 66 patients received TMT (48%). There was a trend for more frequent PET–CT staging in patients treated with CRT alone (85% versus 74%, $p = 0.14$), whereas pathologic staging with mediastinoscopy was more usually done in those treated with TMT (70% versus 39%, $p < 0.0001$). The median radiotherapy doses in the CRT and TMT cohorts were 60 Gy (interquartile range [IQR], 60–60 Gy) and 45 Gy (IQR, 44–46 Gy), respectively. The clinical T-N stage distribution for CRT patients was T1–3 N2 (N = 36, 50%), T4 N0–1 (N = 10, 14%), and T4 N2 (N = 26, 36%). The corresponding distribution for TMT patient was T1–3 N2 (N = 68, 88%), T4 N0–1 (N = 4, 6%), and T4 N2 (N = 4, 6%).

The median length of hospitalization after surgery for the TMT patients was 5 days (IQR, 3–7 days). Postoperative cardiac complications were seen in six patients (9%): atrial fibrillation (N = 4), supraventricular tachycardia (N = 1), and nonfatal myocardial infarction (N = 1). Overall, serious complications as a result of surgery were rare. Two patients (4%) developed pneumonia/empyema, and two patients (4%) were reintubated for hypoxia but were subsequently stabilized; all patients recovered from these acute events. Only one patient died within 30 days of surgery after experiencing asystole in

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TABLE 1. Patient Characteristics

Characteristic	Total	CRT	TMT	*P* Value
Number	138	72	66	—
Age, yr, median (IQR)	65 (59,70)	68 (63,73)	65 (56,70)	0.03
Gender				
Male	69 (50%)	41 (57%)	28 (57%)	0.12
Female	69 (50%)	31 (43%)	38 (42%)	
TN stage				
T1–3 N2	94 (68%)	36 (50%)	58 (88%)	0.33
T4 N0–1	14(10%)	10 (13%)	4 (6%)	
T4 N2	30 (22%)	26 (37%)	4 (6%)	
Histology				
Adenocarcinoma	74 (54%)	37 (51%)	37 (56%)	0.68
Squamous-cell carcinoma	59 (43%)	33 (46%)	26 (39%)	
NSCLC, unspecified	5 (3%)	2 (3%)	3 (5%)	
ECOG performance status				
0–1	99 (72%)	65 (90%)	34 (52%)	<0.0001
≥2	13 (9%)	7 (10%)	6 (9%)	
Unknown	26 (19%)		26 (39%)	
Pretreatment PET–CT				
Yes	110 (80%)	61 (85%)	49 (74%)	0.14
No	28 (20%)	11 (15%)	17 (26%)	
Pretreatment mediastinoscopy				
Yes	74 (54%)	28 (39%)	46 (70%)	<0.0001
No	64 (46%)	44 (61%)	20 (30%)	

CRT, chemoradiotherapy; TMT, trimodality therapy; IQR, interquartile range; ECOG, Eastern Cooperative Group; PET–CT, positron emission tomography–computed tomography; TN stage, clinical American Joint Committee on Cancer tumor and nodal stage, at diagnosis.

the immediate postoperative period. No patients died from radiotherapy complications.

Treatment Response at Time of Surgery

The median interval between the end of radiotherapy and surgery was 32 days (IQR, 26–40). Forty-seven of the 66 patients (71%) in the TMT cohort had complete pathologic clearance of nodal disease in response to neoadjuvant CRT. Only 3 of 19 patients with RND had downstaging of nodal status, all from N2 to N1, but these patients were not differentiated within the RND subset due to small numbers. Twenty patients (30%) had complete pathologic response of the primary tumor, whereas 24 patients (36%) had some decrease in T-stage noted at the time of surgery.

Survival

The median follow-up for surviving patients was 37 months (IQR, 22.7–51.3 mo). Survival data are shown in Table 2. OS was significantly longer in patients treated with TMT versus CRT, with median survival times of 81 and 32 months, and 3-year survival probabilities of 63% and 46%, respectively (p = 0.019). However, stratification based on pathologic nodal response showed that the improved outcomes in the TMT cohort were restricted to those patients achieving N-PCR (Fig. 1). This subset had a median OS of 83 months and 3-year survival probability of 73%, which was significantly better than those treated with CRT alone (p = 0.0009). In contrast, OS for RND patients was clearly inferior to that for the N-PCR cohort (16.1 mo and 35% at 3 years, p = 0.0029), but did not differ significantly from those treated with CRT alone (p = 0.45).

When restricting the analysis to clinical N2 patients, there was improved survival in the TMT cohort (median OS 80.6 versus 31.8 mo, log-rank p = 0.007). The significant difference was again strictly driven by the N-PCR population (median OS 83.2 versus 31.8 mo for CRT, log-rank $p < 0.0001$).

There was a trend for patients treated with TMT to experience improved PFS (p = 0.06) and DMFS (p = 0.06), and subset analyses based on pathologic nodal response paralleled the OS results. Compared with the CRT cohort, the subset achieving N-PCR had significantly improved 3-year PFS (56% versus 25%, p = 0.0013) and DMFS probabilities (56% versus 25%, p = 0.0011). Those with RND had 3-year PFS and DMFS probabilities of 11% for both endpoints, which were both significantly worse (p = 0.02 and 0.01 for PFS and DMFS, respectively) than the CRT cohort.

Multivariable Cox regression showed a persistent OS advantage in the TMT cohort (hazard ratio [HR], 0.56; p = 0.02) after adjusting for clinical nodal stage (Table 3). This survival gain was seen exclusively in the patients who experienced nodal clearance. When performing the regression with stratification by N-PCR status, patients with N-PCR had significantly improved OS (HR, 0.38; p = 0.0012), PFS (HR,

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TABLE 2. Survival Outcomes and Univariable Analyses

	CRT		TMT		TMT, RND		TMT, N-PCR	
Outcome	Median (mo)	3-year (%)	Median (mo)	3-year (%)	Median (mo)	3-year (%)	Median (mo)	3-year (%)
OS	31.8	46	81[a]	63[a]	16.1	35	83.2[a]	73[a]
PFS	14.3	25	22.5	44	7.8[a]	11[a]	41[a]	56[a]
DMFS	18.7	25	23.3	45	8.6[a]	11[a]	62.3[a]	56[a]

[a]Statistical significance ($p < 0.05$) in comparison with CRT.

CRT, chemoradiotherapy; TMT, trimodality therapy; N-PCR, nodal pathologic complete response; RND, residual nodal disease; OS, overall survival; PFS, progression-free survival; DMFS, distant metastasis-free survival.

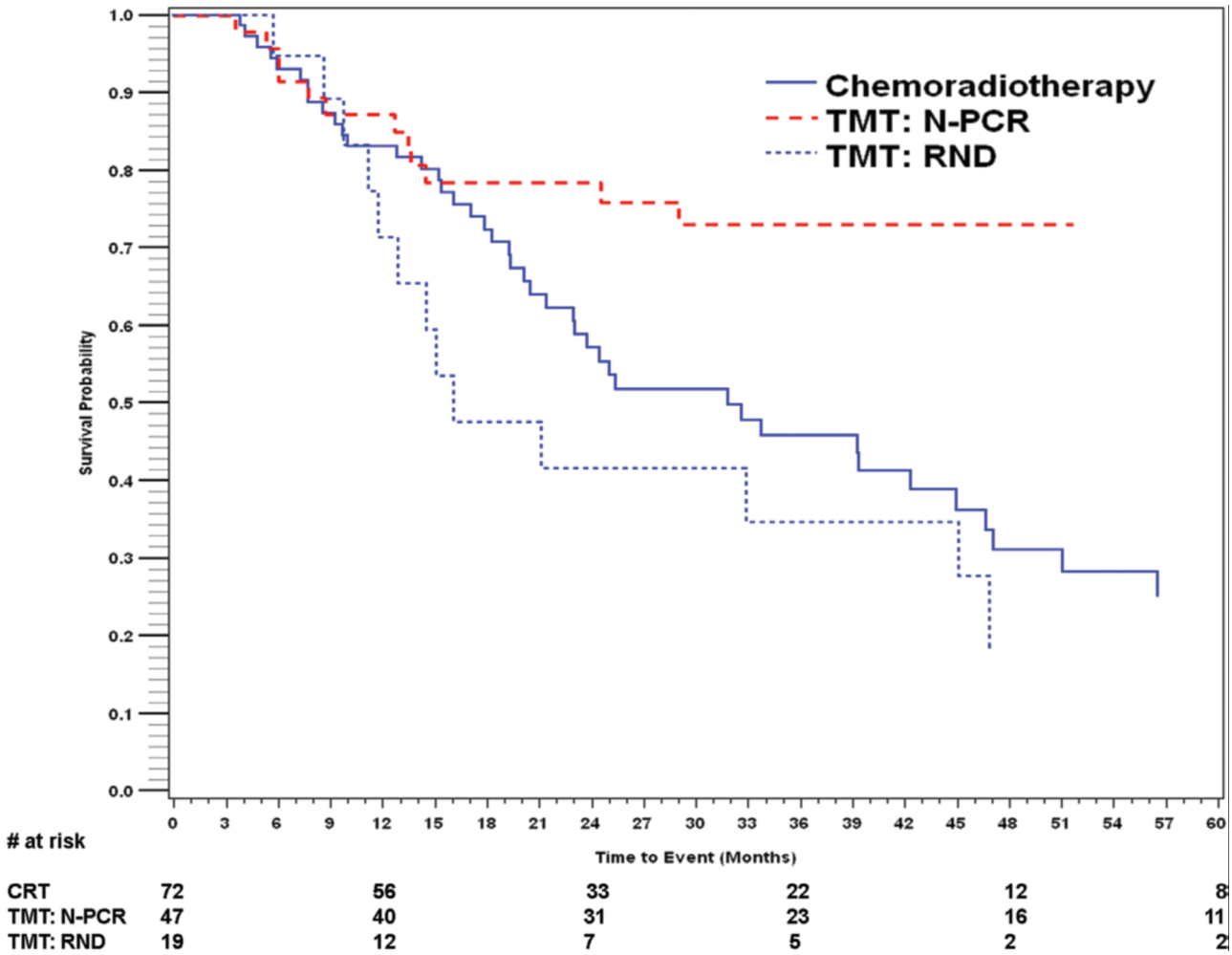

FIGURE 1. Overall survival as a function of treatment and nodal response. TMT, trimodality therapy; N-PCR, nodal pathologic complete response; RND, residual nodal disease.

0.42; $p = 0.0005$), and DMFS (HR, 0.42; $p = 0.0007$) compared with individuals treated with CRT. Conversely, those with RND consistently had worse outcomes compared with the CRT cohort, although only inferior DMFS was statistically significant (HR, 1.82; $p = 0.04$).

Locoregional Recurrence

The cumulative incidences of locoregional recurrence are shown in Table 4. Locoregional recurrence outcomes were superior for the patients in the TMT cohort achieving N-PCR with 1-year, 3-year, and 5-year recurrence rates of 12%, 22%, and 30%, respectively. These results compared favorably with recurrence rates of 27%, 50%, and 55% in the CRT cohort ($p = 0.0048$). In contrast, the surgical patients experiencing RND had the highest risk of locoregional recurrence, although the difference compared with the CRT cohort fell short of statistical significance ($p = 0.0859$).

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TABLE 3. Multivariate Analyses of Survival Outcomes

	OS		PFS		DMFS	
Predictor	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Treatment type						
CRT	Ref	0.0015	Ref	<0.0001	Ref	<0.0001
TMT, RND	1.28 (0.68–2.41)	0.44	1.71 (0.98–2.99)	0.06	1.83 (1.04–3.23)	0.04
TMT, N-PCR	0.38 (0.21–0.68)	0.0012	0.42 (0.26–0.68)	0.0005	0.42 (0.25–0.69)	0.0007
N stage						
0	Ref	0.0313	Ref	0.0019	Ref	0.0096
1	6.37 (1.51–26.9)	0.01	14.1 (3.25–61.0)	0.0004	9.53 (2.24–40.6)	0.02
2	1.48 (0.59–3.72)	0.41	2.48 (1.0–6.17)	0.05	2.29 (0.92–5.72)	0.08

CRT, chemoradiotherapy; TMT, trimodality therapy; N-PCR, nodal pathologic complete response; RND, residual nodal disease; OS, overall survival; PFS, progression-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio, CI, confidence interval.

TABLE 4. Cumulative Incidence of Locoregional Recurrence

Time (yr)	TMT, RND (%)	TMT, N-PCR (%)	CRT (%)
1	55	13	27
3	68	22	50
5	75 ($p = 0.0859$)	30 ($p = 0.0048$)	55

P value reflects comparison with CRT alone.

TMT, trimodality therapy; CRT, chemoradiotherapy; N-PCR, nodal pathologic complete response; RND, residual nodal disease.

DISCUSSION

Consistent with previous reports,[5–10] our retrospective analysis found that N-PCR predicted for superior outcomes in patients with stage III NSCLC treated with TMT. Dichotomization of TMT patients based on nodal pathologic response allowed comparison of each subset to patients treated with CRT alone. We found significantly better outcomes for those with N-PCR and equivalent or worse outcomes for the RND subset compared with CRT alone. Indeed, the finding of N-PCR at the time of surgery independently predicted for decreased risks of death from any cause, progression, and distant metastasis after the incorporation of known confounders in multivariable analyses. In contrast, the RND subset of patients experienced significantly inferior DMFS in comparison with patients receiving CRT alone, although the differences in OS and PFS did not reach statistical significance on adjusted analyses.

The association between improved survival and pathologic nodal response is well documented in other studies of surgery after neoadjuvant therapy for stage III NSCLC. The Intergroup 0139 trial reported a statistically significant difference in median OS of 34.4 months for N0 status versus 26.4 months in those with N1–3 status at the time of surgery.[3] The European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized trial of neoadjuvant chemotherapy followed by either surgery or radiation for patients with stage IIIA (N2) disease, finding that median OS for ypN0–1 status was 22.7 months versus 14.9 months for ypN2 ($p = 0.04$ on multivariable analyses).[12] Similarly, the German Lung Cancer Cooperative Group conducted exploratory post hoc analyses in a large randomized trial of patients with stage III NSCLC comparing two neoadjuvant regimens before surgery. Among those patients in both arms having complete resection of initial N2–3 disease, the median OS was 57.5 months in those with mediastinal downstaging to N0–1 disease and 25.1 months in those with residual N2–3 disease ($p = 0.003$).[13]

One fundamental question in resectable stage III disease is whether the decision to proceed with surgical resection should depend on the pathologic nodal status after neoadjuvant therapy. Although it is clear that patients with mediastinal downstaging experience superior survival in comparison with patients who do not, whether those most favorable patients gain additional benefit from surgery remains an open question. The patients with favorable tumor biology may do well regardless of the intensity of local therapy, although our results suggest superb outcomes after TMT for this cohort. Patients with evidence of persistent primary tumor and nodal response may gain particular benefit from resection, as the primary oncologic gain from surgery is local-only control.[3]

On the other hand, it is also unknown whether patients with recalcitrant nodal disease should proceed with aggressive surgery given their significantly poorer prognosis. The data presented in this article support an extremely cautious approach when considering resection in patients with residual mediastinal adenopathy, as their survival results are clearly not superior—and potentially worse—than outcomes in individuals treated with CRT alone.

Reliable and accurate mediastinal restaging after neoadjuvant CRT remains a challenge in optimizing patient-specific decisions in this setting. Multiple studies have demonstrated a correlation between the amount of residual fluorodeoxyglucose avidity and pathological response, but this association is much stronger for tumor rather than nodal response, the former of which is significantly less informative. For example, one prospective study of 93 patients using PET–CT for restaging after neoadjuvant CRT showed mediastinal false-negative and false-positive rates of 20% and 25%, respectively, which are inadequate for decision making.[14] Available methods for pathologic restaging include endobronchial and/or esophageal ultrasonography with fine-needle aspiration and repeat mediastinoscopy. However, sensitivity of endoscopic needle biopsy for restaging has proven disappointing.[15] Repeat

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mediastinoscopy is often technically more difficult and less sensitive in comparison with the pretreatment setting due to fibrosis from neoadjuvant CRT and initial invasive staging.[16] Thus, our own clinical practice now trends toward pretreatment endobronchial ultrasonography for confirmation of N2 disease, reserving cervical mediastinoscopy for assessment after induction treatment.

This study has several limitations, several of which are inherent in any retrospective analysis. Selection bias and the potential influence of unknown confounders may have contributed to the differences in outcomes, especially considering that patients who ultimately went on to surgery were perceived at the time to gain benefit from it. For example, pathologic staging was not uniform between cohorts, and we were not able to quantify the volume or number of nodal stations involved at the time of initial or subsequent staging.[17–19] Similarly, the general approach for follow-up and surveillance imaging was applied consistently in our practice for all stage III NSCLC patients, but one cannot exclude the possibility that subtle imbalances in restaging between CRT and TMT patients could partially explain progression outcomes. Another consideration is the use of split-course CRT at our institution. This regimen is an uncommon practice,[11] and its use may limit the applicability of our data to patients receiving uninterrupted CRT.

Nevertheless, our results from a consistently treated cohort support the favorable survival outcomes after TMT for patients with a N-PCR. However, the survival outcomes in patients with RND were clearly not better than those treated with definitive CRT, and the latter population is obviously not exposed to the risk of surgical morbidity and mortality. Thus, as the sensitivity and specificity of mediastinal restaging modalities improve, these data support using pathologic response as a key informant on the utility of resection, with evidence of residual disease serving as a criterion to defer surgery.

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