Postinduction positron emission tomography assessment of N2 nodes is not associated with ypN2 disease or overall survival in stage IIIA non-small cell lung cancer

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ABSTRACT

Objective: Induction therapy is often recommended for patients with clinical stage IIIA-N2 (cIIIA/pN2) lung cancer. We examined whether postinduction positron emission tomography (PET) scans were associated with ypN2 disease and survival of patients with cIIIA/pN2 disease.

Methods: We performed a retrospective review of a prospectively maintained database to identify patients with cIIIA/pN2 non-small cell lung cancer treated with induction chemotherapy followed by surgery between January 2007 and December 2012. The primary aim was the association between postinduction PET avidity and ypN2 status; the secondary aims were overall survival, disease-free survival, and recurrence.

Results: Persistent pathologic N2 disease was present in 61% of patients (61 out of 100). PET N2-negative disease increased from 7% (6 out of 92) before induction therapy to 47% (36 out of 77) afterward. The sensitivity, specificity, and accuracy of postinduction PET for identification of ypN2 disease were 59%, 55%, and 57%, respectively. Logistic regression analysis indicated that postinduction PET N2 status was not associated with ypN2 disease. Of the 39 patients with both pre- and postinduction PET N2-avidity, 25 (64%) had ypN2 disease. The 5-year overall survival was 40% for ypN2 disease versus 38% for N2-persistent disease ($P = .936$); the 5-year overall survival was 43% for postinduction PET N2-negative disease versus 39% for N2-avid disease ($P = .251$). The 5-year disease-free survival was 34% for ypN2-negative disease versus 9% for N2-persistent disease ($P = .079$).

Conclusions: Postinduction PET avidity for N2 nodes is not associated with ypN2 disease, overall survival, or disease-free survival in patients undergoing induction chemotherapy for stage IIIA/pN2 disease. (J Thorac Cardiovasc Surg 2016;151:969-79)

Five-year overall survival was 43% for postinduction positron emission tomography N2-negative disease versus 39% for N2-avid disease.

Central Message

For stage IIIA/pN2 NSCLC, postinduction PET avidity of N2 nodes is not associated with ypN2 disease or overall survival.

Perspective

For patients with stage IIIA non-small cell lung cancer with pN2 disease treated with induction chemotherapy, persistence of postinduction positron emission tomography avidity in N2 nodes is not associated with ypN2 disease. The 5-year overall survival of 39% in this series highlights the steadily improving outcomes of multimodality therapy, including surgery.

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Patients with stage IIIA non-small cell lung cancer (NSCLC) have a 5-year overall survival (OS) of 24%, according to the international database reported by Goldstraw and

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Abbreviations and Acronyms

CIR	= cumulative incidence of recurrence
CT	= computed tomography
DFS	= disease-free survival
EBUS	= endobronchial ultrasound
MSKCC	= Memorial Sloan Kettering Cancer Center
NSCLC	= non-small cell lung cancer
OS	= overall survival
PET	= positron emission tomography
PORT	= postoperative radiotherapy
SUVmax	= maximum standardized uptake values
ypN2	= pathologic N2-persistent
ypN0-1	= pathologic N2-negative

colleagues.¹ Induction therapy for locally advanced NSCLC was developed to improve the poor outcomes among patients treated with surgery or radiotherapy alone.²⁻⁹ In a phase II study, Martini and colleagues⁷ found a 3-year survival of 41% for patients with N2 disease treated with induction therapy. They reported a significant survival advantage for patients with a major response to chemotherapy (3-year survival, 34% vs 7%) and for patients who underwent complete resection (3-year survival, 41% vs 5%). Martin and colleagues,¹⁰ as well as others,¹¹⁻¹³ reported that survival was significantly better among patients with N0 or N1 disease than among patients with persistent N2 disease (3-year survival, 43.3% vs 25.5%).

Preoperative prediction of response to therapy in N2 nodes is challenging and often inaccurate.¹⁰ Rebollo-Aguirre and colleagues¹³ found that the positive predictive value of positron emission tomography (PET) scans for persistent N2 disease ranged from 43% to 100%. Prior studies showed that PET assessment of N2 disease after induction therapy had a false-negative rate of 25%.¹⁰ Given that pathologic N2-persistent (ypN2) disease may be a predictor of improved OS, we sought to determine whether postinduction PET avidity in N2 nodes was associated with ypN2 disease for patients with stage IIIA/pN2 disease. We also reviewed the outcomes among patients who underwent resection after induction chemotherapy for stage IIIA/pN2 disease to help guide decisions about resection in the presence of persistent nodal disease and to ascertain outcomes and recurrence patterns.

PATIENTS AND METHODS**Data Collection**

We performed a retrospective review of a prospectively maintained database, from the Thoracic Surgery Service at Memorial Sloan Kettering Cancer Center (MSKCC), of patients who underwent surgery for NSCLC between January 1, 2007, and December 31, 2012. Because we have previously analyzed patients who underwent induction therapy before 2007,¹⁴ we chose this period to avoid any duplication. This study was approved by the MSKCC Institutional Review Board.

Consecutive patients with pathologically confirmed N2 metastatic NSCLC who were treated with induction chemotherapy followed by surgery were included. Before induction therapy, N2 disease was confirmed by endobronchial ultrasound (EBUS), diagnostic mediastinoscopy, endoscopic ultrasound, computed tomography (CT)-guided biopsy, or thoracoscopic biopsy. None of the patients had complete mediastinal nodal clearance. EBUS, the current preferred procedure, became more common during this period. In general, patients were considered for surgery if all N2 nodal disease was thought to be surgically resectable following induction therapy, regardless of the size or number of involved N2 nodal stations. Patients treated with induction chemoradiotherapy or who had synchronous primary, superior sulcus, or neuroendocrine lung cancers were excluded. Patients without pathologically confirmed N2 disease were excluded. All consecutive patients were included for determination of the secondary outcomes of survival and recurrence, regardless of whether pre- and postinduction PET scans were performed.

PET scans from other institutions were included in the analysis. Recorded data were maximum standard uptake value (SUVmax), nonavid description, and a nonnumerical descriptor of T and N2 status. Typically, "nonavid" reflected SUVmax equivalent to or lower than that in the blood pool. However, the reports came from multiple referring institutions; therefore, a uniform definition did not exist. "Nonnumerical descriptor" refers to studies that reported the SUVmax as "increased," "decreased," or "improved" but did not provide a specific SUVmax.

Clinical Assessment

Preoperative assessment included history and physical examination, laboratory assessment, pulmonary function tests, CT of the chest/upper abdomen, magnetic resonance imaging of the brain, and PET scan. Staging was performed using the seventh edition of the American Joint Committee on Cancer staging manual (www.cancerstaging.org).

All patients had surgery at MSKCC, although some received induction therapy at other institutions. Complete mediastinal lymph node dissections were performed for all patients before attempted pulmonary resection. If the mediastinal lymph nodes were unresectable, the operation was aborted and patients did not undergo lobectomy or a larger operation.

Postoperative surveillance was based on National Comprehensive Cancer Network guidelines (www.nccn.org). In general, patients underwent a clinical interview with interval history, physical examination, and CT of the chest/upper abdomen every 6 months for the first 2 to 3 years, then annually thereafter.

Primary and Secondary Study Aims

The primary aim of the study was to determine whether postinduction PET avidity was associated with pathologic persistence of N2 nodes. Secondary aims were 30- and 90-day mortality, OS, disease-free survival (DFS), and the cumulative incidence of recurrence (CIR).

Statistical Analysis

Postinduction PET N2 status was categorized as PET N2-avid or PET N2-negative. The reference standard was determined by pathologic N2 status and categorized as ypN2 or pathologic N2-negative (ypN0-1).

The performance of postinduction PET for the detection of persistent mediastinal disease was quantified using the subset of patients with both postinduction PET scans and pathologic N2 status reports. A positive identification was defined as postinduction PET N2-avid, and a negative identification was defined as PET N2-negative. Performance measures (sensitivity, specificity, and positive and negative predictive values) were determined using the standard definitions. Logistic regression was performed to investigate factors associated with persistent mediastinal disease. Other factors included age, sex, smoking status, comorbidities, lung function, histologic profile, method of mediastinal staging, and resection status. Given that the PET scans were performed at multiple institutions, absolute SUVmax and changes in SUVmax were not evaluated.

TABLE 1. Patient demographic, clinical, and operative characteristics (N = 100)

Characteristic	Result
Demographic details	
Sex	
Woman	49 (49)
Man	51 (51)
Age (y)	65.0 (58.5-71.0)
Smoking status	
Current	10 (10)
Former	73 (73)
Never	17 (17)
Comorbidities	
Pulmonary (n = 84)	32 (38)
Cardiac (n = 85)	53 (62)
Noninsulin-dependent diabetes (n = 75)	9 (12)
Forced expiratory volume in 1 s (%) (n = 98)	87.0 (79.0-99.0)
Diffusion (%) (n = 94)	77.0 (63.0-96.0)
Operative details	
Procedure	
Wedge	8 (8.0)
Lobectomy	75 (75)
Bilobectomy	7 (7.0)
Pneumonectomy	8 (8.0)
Segmentectomy	2 (2.0)
Location of tumor	
Right	80 (80)
Left	20 (20)
Operative approach	
Open	97 (97)
Video-assisted thoracoscopic surgery	3 (3.0)
Resection	
R0	85 (85)
R1	8 (8.0)
R2	7 (7.0)
Mortality	
30-d	2 (2.0)
90-d	2 (2.0)
Adverse events	27 (27)
Prolonged air leak	5 (5.0)
Respiratory failure/acute respiratory distress syndrome	2 (2.0)
Supraventricular tachycardia	7 (7.0)
Clinical and pathologic details	
Method of preinduction mediastinal staging	
Mediastinoscopy only	35 (35)
Endobronchial ultrasound only	52 (52)
Mediastinoscopy + endobronchial ultrasound	8 (8.0)
Other	5 (5.0)
Pathology	
No viable tumor	2 (2.0)
Adenocarcinoma	78 (78)
Squamous cell carcinoma	18 (18)
Large cell carcinoma	2 (2.0)
Pathologic N status	
N0	33 (33)
N1	6 (6.0)
N2	61 (61)

(Continued)

TABLE 1. Continued

Characteristic	Result
Postoperative pathologic stage	
0	2 (2.0)
IA	14 (14)
IB	11 (11)
IIA	4 (4.0)
IIB	5 (5.0)
IIIA	59 (59)
IIIB	3 (3.0)
IV	2 (2.0)
Adjuvant therapy	
None	39 (39)
Postoperative radiotherapy only	37 (37)
Adjuvant chemotherapy only	16 (16)
Postoperative radiotherapy + adjuvant chemotherapy	8 (8.0)

Data are presented as n (%) or median (25th-75th percentile).

OS was the duration between surgery and death from all causes. DFS was calculated as the time from surgery to locoregional recurrence, distant metastasis, or death without evidence of recurrence or progression. These analyses were supplemented by analyses of time to recurrence. The Kaplan-Meier method was used to construct OS and DFS curves. CIR curves were generated using a competing risk approach in which death from any cause before recurrence was treated as a competing risk event. Although plots show data through 5 years, all follow-up data were used in the statistical calculations. OS and DFS curves were separated by postinduction PET N2 status (PET N2-avid vs PET N2-negative), pathologic N2 status (pathologic N2-persistent vs pathologic N2-negative), and pathologic staging ($\geq$ ypIIIA vs $<$ ypIIIA). The log-rank test was used to compare OS and DFS between groups. Cox proportional hazard models were used to compute hazard ratios (HRs). Comparison of CIRs was performed using the method of Gray.¹⁵ Multivariate regression models were constructed, starting with all variables with $P < .10$ in univariate analyses. All statistical tests were 2-tailed, and $P < .05$ was considered to indicate statistical significance. No multiple comparison adjustment was made. All analyses were performed using Stata 13 (Stata-Corp, College Station, Tex) and R 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and PET Details

One hundred consecutive patients with stage IIIA/pN2 NSCLC at diagnosis were identified (Table 1). The most common histologic profile was adenocarcinoma (78%; 78 out of 100). The majority of cases of N2 disease (95%; 95 out of 100) were confirmed by EBUS or mediastinoscopy; the other 5 cases were confirmed by endoscopic ultrasound, CT-guided biopsy, or thoracoscopic biopsy.

Preinduction PET scans were available for 99 patients (98 with reported T and N values) (Table 2). Postinduction PET scans were available for 80 patients (79 with reported T and N status). The median SUVmax for N2 nodes was 6.5 for patients with preinduction PET with numerical values and 3.3 for those with postinduction PET with numerical values. Eighty-four percent (65 out of 77) had a decrease in SUVmax T status, and 80% (61 out of 76) had a decrease

TABLE 2. Pre- and postinduction positron emission tomography (PET) results

Variable	Preinduction PET n = 99	Postinduction PET (n = 80)
T status		
Nonavid	1 (1.0)	10 (13)
No value reported	1 (1.0)	—
Nonnumerical value reported	4 (4.0)	1 (1.3)
Numerical value reported	93 (94)	69 (86)
SUVmax T among numerical values	9.8 (6.2-14.7)	5.0 (3.0-9.8)
N status		
Nonavid	6 (6.1)	36 (45)
No value reported	1 (1.0)	1 (1.3)
Nonnumerical value reported	6 (6.1)	2 (2.5)
Numerical value reported	86 (87)	41 (51)
SUVmax N among numerical values	6.5 (3.8-9.5)	3.3 (2.7-4.5)
N2 status		
N2-Negative	6/92 (6.5)	36/77 (47)
N2-Avid	85/92 (93)	41/77 (53)

PET response to induction therapy: Change from pre- to postinduction values*	SUVmax T (n = 77)	SUVmax N (n = 76)
No change	1 (1.3)	6 (7.9)
Decreased	65 (84)	61 (80)
Increased	11 (14)	9 (12)
Not interpretable	2	3

Values are presented as n (%) or median (25th-75th percentile). PET, Positron emission tomography; SUVmax, maximum standardized uptake value. *Pre- and post-PET scans available for 79 patients; 77 with interpretable change in SUVmax T and 76 with interpretable change in SUVmax N2. Nonnumeric descriptions in postinduction PET cannot be categorized as a change unless preinduction PET is also a nonnumeric description.

in SUVmax N status. The percentage of patients with PET N2-negative disease increased from 7% (6 out of 92) before induction therapy to 47% (36 out of 77) after. The median duration between pre- and postinduction PET was 4 months (range, 1.7-11.2 months); the median duration between postinduction PET and surgery was 0.7 months (range, 0.03-5.8 months).

Operative Management and Adjuvant Therapy

All patients received doublet induction therapy, with the majority (99 out of 100; 99%) receiving a platin-based regimen. The most common operation was lobectomy (75%; 75 out of 100). Eighty-five patients underwent R0 resections, 8 underwent R1, and 7 underwent R2. Eight percent of patients (8 out of 100) underwent a nonanatomic wedge resection. Resection of N2 nodal disease was attempted before pulmonary resection. If the mediastinal disease was unable to be completely resected (R2), the planned pulmonary resection was aborted. In such patients, if possible, the primary tumor was resected by a wedge resection to limit the subsequent radiation field. Thirty- and 90-day mortalities were 2% (2 out of 100);

both patients experienced adult respiratory distress syndrome after a segmentectomy and a lobectomy. There were no deaths following pneumonectomy (Table 1).

Sixty-one patients (61%) received adjuvant therapy, 37 received postoperative radiotherapy (PORT) only, 16 received adjuvant chemotherapy only, and 8 received both PORT and adjuvant chemotherapy (Tables 1 and E1).

Pathologic Staging and N2 Status

Postoperative pathologic staging revealed that 36% of patients had less than ypIIIA disease (36 out of 100) and 64% had $\geq$ ypIIIA. Two patients had complete pathologic responses (Table 1). Pathologic staging found ypN2 disease in 61% of patients (pN2, 61 out of 100) and ypN0-1 disease in 39% (pN0, 33 out of 100; pN1, 6 out of 100). Of the 39 patients with N2-avid disease on both pre- and postinduction PET, 25 (64%) had ypN2 disease.

Accuracy and Performance of Postinduction PET N2 Staging

We quantified the ability of postinduction PET N2 nodal assessment to identify persistent pathologic N2 disease. Postinduction PET scans and corresponding ypN2 status reports were available for 77 patients (Tables E2 and E3). Postinduction PET scan indicated N2-negative disease in 36 patients (47%) and N2-avid disease in 41 (53%). Pathologic N2-staging confirmed ypN0-1 disease in 31 patients (40%) and ypN2 disease in 46 (60%). There were 27 true-positives [PET(+)/pathology(+)], 14 false-positives [PET(+)/pathology(-)], 17 true-negatives [PET(-)/pathology(-)], and 19 false-negatives [PET(-)/pathology(+)]. The sensitivity, specificity, and accuracy of postinduction PET for the detection of ypN2 disease were 59%, 55%, and 57%, respectively; positive and negative predictive values were 66% and 47%, respectively.

Factors Associated with ypN2 Disease

We investigated the association between postinduction PET N2 staging and ypN2 disease among 77 patients with known postinduction PET N2 status. The results of logistic regression indicated that the odds of ypN2 disease were 1.73-times higher for patients with PET N2-avid disease than for patients with PET N2-negative disease, although this relationship was not statistically significant (95% confidence interval [CI], 0.69-4.33; $P = .2$). Having a postinduction PET SUVmax of N2 nodes that was higher than the median value of 3.3 was significantly associated with greater odds of ypN2 disease (HR, 4.6; $P = .045$), although the 95% CI was large secondary to a small sample size. Expanding to the entire cohort of 100 patients, the only factor that was statistically significant in univariable models was adenocarcinoma (odds ratio, 2.9; 95% CI, 1.09-7.63;

FIGURE 1. Overall survival (OS). A, Entire cohort: the 5-year OS was 39% (95% confidence interval [CI], 28%-56%). B, Postinduction positron emission tomography (PET) N2 status: The 5-year OS for N2-negative was 43% (95% CI, 22%-83%) versus 39% (95% CI, 23%-64%) for N2-avid disease ($P = .251$). C, Pathologic N2 status: The 5-year OS for N2-negative was 40% (95% CI, 25%-64%) versus 38% (95% CI, 21%-67%) for N2-persistent disease ($P = .936$). D, Pathologic staging: The 5-year OS for < ypIIIA was 41% (95% CI, 25%-66%) versus 37% (95% CI, 21%-66%) for $\geq$ ypIIIA ($P = .791$).

$P = .032$). Age, lung function, and method of preinduction N2 staging were not statistically significant (Table E4).

Factors Associated with OS

The median duration of follow-up was 2.7 years (range, 0.02-7.2 years). Forty-five patients died during follow-up. The majority (41 out of 45; 92%) died of disease; 4 died of other causes. The median time to death was 1.6 years (range, 0.04-5.0 years). The 5-year OS was 39% (95% CI, 28%-56%) (Figure 1); median survival was 3.78 years.

Median survival for ypN0, ypN1, and ypN2 disease was 3.8, 2.0, and 4.5 years, respectively. The 5-year OS was 40% (95% CI, 25%-64%) for patients with ypN0-1 disease versus 38% (95% CI, 21%-67%) for patients with ypN2 disease ($P = .936$); median survival was 3.7 years and 4.5 years. The 5-year OS was 41% (95% CI, 25%-66%) for patients with < ypIIIA disease versus 37% (95% CI, 21%-66%) for patients with $\geq$ ypIIIA disease ($P = .791$). Among patients with valid postinduction PET N2 status, the 5-year OS was 43% (95% CI,

TABLE 3. Univariable Cox models for overall survival and disease-free survival analyses

Variable	Overall survival			Disease-free survival		
	Hazard ratio	95% Confidence interval	P value	Hazard ratio	95% Confidence interval	P value
Postinduction PET*	1.50	0.75-3.00	.3	1.05	0.59-1.86	.9
Pathologic N2 status†	0.98	0.54-1.77	.9	1.58	0.94-2.63	.082
Pathologic staging‡	1.09	0.59-1.99	.8	1.67	0.99-2.82	.056
Age at surgery	0.99	0.96-1.03	.6	0.97	0.94-1.00	.044
Male	1.49	0.82-2.70	.2	1.07	0.66-1.75	.8
Smoking, yes	1.02	0.48-2.20	.9	0.93	0.48-1.78	.8
Smoking pack-years >30, yes	0.98	0.54-1.75	.9	0.71	0.43-1.16	.2
Pulmonary comorbidity, yes	1.07	0.55-2.10	.8	0.77	0.44-1.35	.4
Cardiac comorbidity, yes	0.95	0.48-1.88	.9	0.69	0.40-1.21	.2
NIDDM, yes	1.43	0.50-4.09	.5	1.73	0.68-4.41	.3
FEV1 (%)	0.99	0.97-1.01	.2	0.99	0.97-1.00	.10
Diffusion (%)	1.00	0.99-1.02	.6	1.01	1.00-1.02	.2
Adenocarcinoma, yes	1.07	0.52-2.23	.9	1.65	0.88-3.10	.12
EGFR, present	0.74	0.26-2.12	.6	0.79	0.35-1.75	.6
KRAS, present	1.66	0.81-3.40	.2	1.18	0.64-2.20	.6
Adjuvant therapy						
PORT only vs none	1.19	0.61-2.33	.6	1.14	0.65-2.01	.6
Adjuvant chemotherapy only vs none	0.64	0.26-1.58	.3	0.78	0.37-1.63	.5
PORT + adjuvant chemotherapy vs none	0.60	0.17-2.08	.4	0.94	0.38-2.31	.9
Resection						
R1 vs R0	2.08	0.87-4.97	.10	1.46	0.66-3.22	.3
R2 vs R0	1.33	0.41-4.34	.6	2.32	0.92-5.88	.075
Pathologic T stage (≥IIA vs <IIA)§	1.80	0.98-3.31	.058	2.22	1.33-3.73	.002

PET, Positron emission tomography; NIDDM, noninsulin dependent diabetes; FEV1, forced expiratory volume in 1 second; EGFR, endothelial growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; PORT, postoperative radiation therapy. *N2-avid versus N2-negative. †N2-persistent versus N2-negative. ‡Greater than or equal to ypIIIA versus less than ypIIIA. §Forty-five patients had <IIA (0, IA, and IB) and 55 had ≥IIA (includes IIA, IIB, IIIA, III, and IV).

22%-83%) for PET N2-negative disease versus 39% (95% CI, 23%-64%) for PET N2-avid disease ($P = .251$). Univariable analyses revealed that no factors, among those evaluated, were significantly associated with hazard of any death (Table 3). Pathologic T stage $\geq$ IIA had an HR of 1.80 (95% CI, 0.98-3.31; $P = .058$), suggesting a potential worse prognosis with higher T stage. No multivariable analysis was performed.

DFS and Factors Associated with DFS

Sixty-five patients experienced recurrence or progression or died (Figure 2). Sixty-one patients (61%) experienced recurrence or progression: 7 locoregional only, 28 distant only, and 26 locoregional and distant (Table 4). Five patients died without a reported recurrence or progression. The 5-year DFS was 23% (95% CI, 14%-37%); median DFS was 1.68 years. Median DFS for pN0, pN1, and pN2 disease was 2.8, 1.5, and 1.3 years, respectively. The 5-year DFS was 34% (95% CI, 21%-56%) for ypN0-1 disease versus 9% (95% CI, 2%-45%) for ypN2 disease ($P = .079$); median survival was 2.2 years and 1.3 years. The 5-year DFS was 36% (95% CI, 22%-58%) for patients with < ypIIIA disease versus 9% (95% CI, 2%-44%) for patients with $\geq$ ypIIIA disease ($P = .054$). Although not statistically significant, the HR for ypN2 disease was 1.58 (95% CI, 0.94-2.63; $P = .082$), and the

HR for $\geq$ ypIIIA disease was 1.67 (95% CI, 0.99-2.85; $P = .056$), suggesting a worse prognosis for ypN2 disease or higher pathologic stage. Among patients with postinduction PET N2 status, the 5-year DFS was 24% (95% CI, 11%-51%) for patients with PET N2-negative disease versus 24% (95% CI, 11%-54%) for patients with N2-avid disease ($P = .867$). R2 resection, pathologic T stage $\geq$ IIA, and younger age at surgery were also significantly associated with worse prognosis (Table 3). With acknowledgment of the limitations in terms of power, we present the final multivariable Cox model stratified by resection status with only 2 variables: age (HR, 0.97; 95% CI, 0.94-1.00; $P = .059$) and pathologic T stage $\geq$ IIA (HR, 1.92; 95% CI, 1.12-3.31; $P = .018$). Postinduction PET N2 status showed evidence of violating the proportionality assumption, but adjusting for this assumption did not affect the significance of the other factors. We did not include postinduction N2 nodal avidity in the final multivariable model.

CIR

Sixty-one patients experienced recurrence postoperatively (Tables 4 and E5). The 3-year CIR for the entire cohort was 70% (95% CI, 60%-81%) (Figure E1). The 5-year CIR was 76% (95% CI, 58%-99%) for postinduction PET N2-negative disease versus 58%

FIGURE 2. Disease-free survival (DFS). A, Entire cohort: The 5-year DFS was 23% (95% confidence interval [CI], 14%-37%). B, Postinduction positron emission tomography (PET) N2 status: The 5-year DFS for N2-negative was 24% (95% CI, 11%-51%) versus 24% (95% CI, 11%-54%) for N2-avid disease ($P = .867$). C, Pathologic N2 status: The 5-year DFS for N2-negative was 34% (95% CI, 21%-56%) versus 9% (95% CI, 2%-45%) for N2-persistent disease ($P = .079$). D, Pathologic staging: The 5-year DFS for < ypIIIA was 36% (95% CI, 22%-58%) versus 9% (95% CI, 2%-44%) for ≥ ypIIIA ($P = .054$).

(95% CI, 41%-80%) for N2-avid disease. The 5-year CIR was 59% (95% CI, 44%-79%) for ypN0-1 disease versus 80% (95% CI, 66%-96%) for ypN2 disease. The 5-year CIR was 57% (95% CI, 41%-78%) for < ypIIIA disease versus 80% (95% CI, 67%-96%) for ≥ ypIIIA disease (Gray's test, $P = .049$), indicating a worse prognosis for recurrence for patients with ≥ ypIIIA disease. The CIRs were not significantly different by postinduction PET N2 status ($P = .571$) or ypN2 status ($P = .077$).

DISCUSSION

We found that postinduction N2 nodal PET activity was not associated with ypN2 disease following induction chemotherapy for known pN2 disease. Not surprisingly, a difference in 5-year OS, with or without residual PET avidity in N2 nodes, was not detected.

Candela and Detterbeck¹⁰ reviewed the literature on restaging after induction therapy. Across the 10 studies they analyzed, the aggregate false-positive rate was 33%, and the false-negative rate was 25%, with no subset in which

TABLE 4. Patient outcomes and recurrence and progression patterns by resection status

Outcome	Overall (n = 100)	Resection status		
		R0 (n = 85; 85%)	R1 (n = 8; 8.0%)	R2 (n = 7; 7.0%)
Pathologic N2 status				
N2-Negative	39 (39)	33 (39)	4 (50)	2 (29)
N2-Persistent	61 (61)	52 (61)	4 (50)	5 (71)
Status				
Alive with disease	18 (18)	14 (16)	1 (13)	3 (43)
Died of other causes	4 (4.0)	3 (3.5)	1 (13)	0 (0)
Died of disease	41 (41)	33 (39)	5 (63)	3 (43)
No evidence of recurrence	37 (37)	35 (41)	1 (13)	1 (14)
Recurrence or progression*				
Locoregional only	7 (11)	7 (14)	0 (0)	0 (0)
Distant only	28 (46)	26 (52)	2 (33)	0 (0)
Both locoregional and distant	26 (43)	17 (34)	4 (67)	5 (100)

Values are presented as n (%). *n = 61.

PET performed sufficiently well. However, only 3 of the studies reported N2 data for PET restaging after induction chemotherapy only. These 3 studies had false-positive rates of 25% to 40% and false-negative rates of 23% to 36%.^{11,12,16} These studies were published from 2004 to 2006 and reported the outcomes of only 25 to 30 patients, whereas we reported 100 patients included consecutively from 2006 to 2012. Only De Leyn and colleagues¹¹ reported that all patients had preinduction pathologic confirmation of N2 disease. By including only patients with pathologically confirmed N2 disease, and as a result of our institution's routinely performing systematic, complete mediastinal lymph node dissections, we believe that our data represent a reliable assessment of postinduction PET scans. We still report positive and negative predictive values of 66% and 47%, which do not support the reliability of postinduction PET assessment of N2 nodal disease. We also found that the 5-year OS was the same with or without residual PET avidity in N2 nodes. This strongly suggests that N2 PET avidity is not reliably associated with ypN2 node disease following induction therapy. Furthermore, an important and incremental advance of this study is that postinduction PET assessment of N2 nodes is not associated with OS.

The previously reported 5-year OS after induction chemotherapy and surgical resection ranges from 17% to 36%; the 5-year OS in our series was 39% (Figure 1, A).¹⁴ Albain and colleagues⁶ reported the results of Intergroup Trial 0139, in which patients randomized to receive induction chemoradiotherapy had a 5-year OS of 27%. Our 5-year OS is higher, which we believe may be secondary to several factors. We postulate that the emphasis on adequate preresection diffusing capacity of the lungs for carbon monoxide, the avoidance of surgery in patients with severe comorbid conditions, the increase in adenocarcinoma relative to squamous cell carcinoma histologic profile, the lack of

radiotherapy in the induction regimens, the low rate of pneumonectomy, and evolution of chemotherapy are all likely contributors to more favorable outcomes.

N2 nodal downstaging has been associated with improved survival,¹⁷⁻²⁰ yet it was not a significant prognostic factor in our series. This finding is in contrast with older reports from our institution and others.^{5,7,17,19,21} Betticher and colleagues¹⁷ reported that clearance of N2 lymph node involvement was a significant predictor of OS; 3-year OS was 11% with ypN2 disease versus 61% for those without it. In contrast, OS in our series was not different with regard to pathologic staging (< ypIIIA) or ypN2 disease (Figure 1, C and D). Despite the lack of difference in OS for ypN2 disease, we cannot conclude ypN2 disease is equivalent to no residual N2 disease; rather, we believe this finding reflects the lack of statistical power. In all likelihood, although this series had a relatively large number of patients with stage IIIA disease, 100 patients is sufficiently small that differences that cannot be detected may exist (type II error). Some improvement in OS may be secondary to the use of adjuvant therapy, given that 72% of patients with N2 disease (44 out of 61) received adjuvant therapy; 61% (37 out of 61) received PORT. Due to the small numbers and the heterogeneity of adjuvant therapies, we cannot determine the efficacy of adjuvant therapies with statistical confidence in this series.

Complete resection has been a significant predictor of survival.^{3,7,22} Thomas and colleagues,²² from the German Lung Cancer Cooperative Group, reported that 55% of patients in a surgical control group underwent complete resection. Van Meerbeeck and colleagues,²³ from the European Organization for the Research and Treatment of Cancer, reported that only approximately half of the patients underwent complete resection, which was a significant predictor of survival on multivariate analysis. We believe that complete removal of all N2 nodes contributed to the favorable outcomes in our series. However, R1 to R2 resections were not associated with decreased survival in our series. Because 85% of patients (85 out of 100) underwent an R0 resection, the numbers of R1 to R2 resections are most certainly too small to detect a difference.

The limitations of our study include a selection bias on the basis of the inability to identify the number of patients with cIIIA/pN2 disease who were not offered resection. The biases that influenced the decision of definitive chemoradiotherapy versus induction chemotherapy followed by resection cannot be evaluated. However, a recent prospective, randomized trial suggests the addition of radiation to chemotherapy induction regimens followed by surgery for stage IIIA NSCLC offers no benefit to chemotherapy alone.²⁴ Although we could speculate that patients with poor performance status or marginal lung function were excluded from surgery, we do not have the data to know with certainty. Second, whether some patients

had progression or newly detected metastatic disease on postinduction PET scan and never underwent resection is unknown. This limitation prevents us from recommending not performing postinduction PET scans. Third, although we report all consecutive patients to determine secondary end points of survival and recurrence, only 80% had postinduction PET scans. However, we believe that reporting consecutive patients is most reflective of the overall experience at our institution. Last, on the basis of the review of PET scan documentation from multiple institutions, we were unable to accurately discern the extent (single vs multistation) of N2 disease, and we were unable to evaluate changes in SUVmax accurately. To accurately compare PET scans, the pre- and postinduction scans would need to be performed on the same scanners, with clearly defined protocols. In addition, assessment of single versus multistation disease would need to be similarly investigated. We chose to include all scans regardless of the institution from which they were performed, because that most accurately reflects the referral practice of our group. We do not routinely repeat pre- or postinduction PET scans if those studies are deemed to be of high quality.

CONCLUSIONS

Our experience indicates that the persistence of postinduction PET avidity in N2 nodes is not associated with ypN2 disease or decreased OS. We offer surgical resection to all postinduction patients in whom an R0 resection is thought to be possible, regardless of postinduction PET imaging. We do not perform mediastinal surgical restaging procedures to assess for N2 nodal response to induction therapy. Finally, we believe a complete R0 N2 nodal dissection is mandatory in these patients.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2015/Video/Wednesday/04-29-15_608_0919_Ripley.mp4.

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Key Words: stage III NSCLC, induction, surgery

Discussion

Dr Arjun Pennathur (*Pittsburgh, Pa*). That was a great presentation and congratulations to you and your colleagues for a very interesting study. I want to thank the Association for the privilege of discussing this topic.

You have addressed a very challenging topic; that is, the treatment of stage IIIA, N2-positive disease, which comprises a very heterogeneous group of patients ranging from a tiny focus of single-station N2 disease to bulky multistation N2 disease. With a very heterogeneous spectrum of N2 disease, the role of surgery for treatment of N2 disease after neoadjuvant therapy is an interesting and in some ways controversial topic. You have reported that fluorodeoxyglucose (FDG) avidity did not appear to correlate with downstaging or overall survival. You reported that the disease-free survival is worse with persistent N2 disease. This study is very interesting and raises important questions regarding the management of N2 disease, and I congratulate the authors for their efforts.

I have a few questions. First of all, the analysis of positron-emission tomography (PET) scans does not appear to be in fashion across the institutions. Was this an integrated PET-computed tomography (CT) scan or a standalone PET? There are several factors that could affect the results of the FDG-PET scan, including, for example, the duration of fasting, the baseline blood glucose level, and the timing between administration of the isotope and the acquisition of images on the PET-CT scan. In addition, the time interval between completion of the neoadjuvant therapy and the performance of the CT scan is an important factor. Similarly, the time interval between the posttreatment PET scan and the surgical resection can have an influence on the results. How did you control these variables and factor these into your analysis?

Dr Ripley. The PET scans in this study are from multiple institutions. Most of the patients who presented with PET scans to our institution did not have a repeat scan. The inclusion of scans from multiple institutions is a limitation of this study, but it also reflects the referral and practice pattern at Memorial Sloan Kettering Cancer Center (MSKCC). For example, several patients actually presented to our clinic already undergoing neoadjuvant therapy; therefore, it was not meaningful to obtain another scan. To overcome this obstacle, we have a couple of options. We could re-review all the scans from MSKCC and exclude those that were not done at our institution. That would decrease the number of patients to evaluate and would undermine the secondary aims of reviewing the outcomes of all consecutive patients over this time period. Alternatively, a prospective evaluation of patients could clarify this question, but obviously that is beyond the possibilities of a retrospective review. Regardless of the comparison of institutional scans, I think the message that patients should not

automatically be excluded based on PET imaging alone is still valid, although we have included this as a limitation.

Dr Pennathur. Yes, I agree that patients should not be automatically excluded. The issue is how much the PET predicts the persistence of disease, which some of the studies you are proposing would address that.

Also, in describing the PET data, FDG avidity is mentioned. Did you, for example, look at the percentage decrease in the maximum standardized uptake value after neoadjuvant therapy? Other investigators—for example, Drs Cerfolio and Mountz—have previously presented at this Association and also published their data on integrated PET-CT scan being better, as well as the percentage decrease in maximum standardized uptake value actually predicting nodal downstaging after neoadjuvant chemoradiation for lung cancer. Have you attempted to quantitate the changes in FDG uptake in this fashion? Also, did you correlate the nodal station that was actually resected with the PET activity in that station? For example, you could have an R4 station that you resect that may be PET-negative and your path may correlate, but the patient could be N2 disease simply because level 8 is positive. Did you look into station-by-station comparison when you looked into the accuracy of PET scan to detect whether there was persistent N2 disease?

Dr Ripley. You asking several very good questions that we have discussed internally. Unfortunately, our data is not granular enough with a retrospective review of PET scans from multiple institutions. First, we did not report specific changes of PET values because the scans were not uniform; therefore, we thought that a comparison of specific maximum standardized uptake value or average standardized uptake value would be inaccurate. Second, we did not compare multistation versus single-station PET activity. Similar to the previous comment, we thought that the scans from multiple institutions created too much variability; therefore, I haven't presented that data.

Dr Pennathur. And then the final thing: Patients with N2-positive disease is an extremely heterogeneous group, from a tiny focus to bulky multistation disease. This is a highly selected population where patients were selected for surgery, and patients who had invasive procedures after induction therapy were excluded from the study. What about the patients who did not get operated on for persistent positive nodal disease or who you did not operate on because the PET scan showed a distant metastasis? One might expect that an isolated single station or one with distant metastasis would do worse. Also, in the multivariate analysis in your manuscript—in addition to the lack of impact of persistent N2 disease or increased FDG uptake—other factors, such as R2 resections and T status, had no influence on overall survival. Why do you think

this is the case? Is it because it's a very limited population or because you need longer follow-up for maturity of survival end points?

Dr Ripley. I think you are exactly right. One of your points, that the R0 resections were not a prognostic factor, speaks to 2 conclusions: First, the limitation of small numbers, and second, the potentially highly selective nature of this population—as you pointed out. Although the study is relatively large for N2 disease, only 16 patients had incomplete resections, including R1 and R2 resections. More than 80% of the patients with an R1 or R2 recurred, whereas 59% with an R0 resection recurred. I did not present that data during this presentation today, but those findings are in the manuscript. We believe with larger numbers, a significant difference would exist. Also, we want to stress that mediastinal lymph node dissections were performed before pulmonary resections. If the lymph nodes were deemed unresectable, the patients were not subjected to lobectomy or pneumonectomy.

The 84% resection rate in our series leads to the another point. Eighty-four percent is higher than most trials, which is likely secondary to the highly selective nature of our patient population. I think that surgeons and/or medical oncologists who deemed a patient unresectable have good judgment which resulted in a highly selected group of patients.

Dr Scott J. Swanson (*Boston, Mass*). Thanks. Great paper. I have a basic question. Given all those data, what do you do now at MSKCC with N2 disease? How do you restage them? Who gets surgery? What value is a PET scan if half the time it does not mean anything?

Dr Jones. Great question. Everyone gets a postinduction PET. With those studies, we really are looking for presence of distant metastatic disease. We initially make the decision whether we can perform an R0 resection, including all nodal disease. If we can, we do not restage the mediastinum. If there is some concern that the patient may not be a good operative candidate or we think there is persistent multistation, bulky disease that may not be resectable, we may redo an endobronchial ultrasound or perform another staging procedure. However, in general, we make the decision whether we are going to operate up front, meaning before the patient gets the induction therapy. It really is the presence of distant metastatic disease on postinduction PET imaging before we would not explore them.

Unidentified voice. Pneumonectomy?

Dr Ripley. Eight percent of patients underwent a pneumonectomy without any mortalities.

Unidentified voice. I tend personally to steer away from a pneumonectomy with multistation N2 disease. But if you are doing the nodes straight up, first thing in the operation, you should know if it's multistation.

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State of the Art: Precision Therapy for Lung Cancer: Tyrosine Kinase Inhibitors and Beyond. *David Schrupp*. *Semin Thorac Cardiovasc Surg* 2015; Spring; 27(1):36-48.

FIGURE E1. Cumulative incidence of recurrence (CIR). A, Entire cohort: The 5-year CIR was 70% (95% confidence interval [CI], 60%-81%). B, Post-induction positron emission tomography (PET) N2 status: The 5-year CIR for N2-negative was 76% (95% CI, 58%-99%) versus 58% (95% CI, 41%-80%) for N2-avid disease (Gray's test, $P = .571$). C, Pathologic N2 status: The 5-year CIR for N2-negative was 59% (95% CI, 44%-79%) versus 80% (95% CI, 66%-96%) for N2-persistent disease (Gray's test, $P = .077$). D, Pathologic staging: The 5-year CIR for < ypIIIA was 57% (95% CI, 41%-78%) versus 80% (95% CI, 67%-96%) for ≥ ypIIIA (Gray's test, $P = .049$).

TABLE E1. Adjuvant therapy based on nodal status

Therapy	pN0 (n = 33; 33%)	pN1 (n = 6; 6.0%)	pN2 (n = 61; 61%)	P value
Adjuvant therapy				
None	22 (67)	0 (0)	17 (28)	<.0001
PORT only	2 (6.1)	5 (83)	30 (49)	
Adjuvant chemotherapy only	8 (24)	1 (17)	7 (11)	
PORT + adjuvant chemotherapy	1 (3.0)	0 (0)	7 (11)	
Any adjuvant therapy				
No	22 (67)	0 (0)	17 (28)	<.0001
Yes	11 (33)	6 (100)	44 (72)	

Values are presented as n (%). *PORT*, Postoperative radiation therapy.

TABLE E3. Preinduction and Postinduction positron emission tomography (PET) N2-status for those with both pre- and postinduction PET scans*

Preinduction PET N2 status (n = 73)	Postinduction PET N2 status	
	N2-Negative (n = 36; 47%)	N2-Avid (n = 41; 53%)
N2-Negative (n = 6; 8%)	5 (15)	1 (2.5)
N2-Avid (n = 67; 92%)	28 (85)	39 (98)

Values are presented as n (%). *PET*, Positron emission tomography. *Seventy-three patients had valid preinduction and postinduction avidity reported on PET scans.

TABLE E4. Univariable logistic regression models to investigate association between factors and odds of pathologic N2-persistent disease

Variable	Odds ratio	95% Confidence interval	P value
Postinduction PET*	1.73	0.69-4.33	.2
Age at surgery	0.98	0.94-1.03	.4
Male	0.83	0.37-1.86	.6
Smoking, yes	1.12	0.39-3.23	.8
Pack-years >30, yes	0.77	0.34-1.73	.5
Pulmonary comorbidity, yes	0.71	0.29-1.73	.4
Cardiac comorbidity, yes	0.99	0.40-2.45	1
NIDDM, yes	0.72	0.17-3.14	.7
FEV1 (%)	1.00	0.97-1.03	1
Diffusion (%)	1.00	0.98-1.02	.8
Adenocarcinoma, yes	2.89	1.09-7.63	.032
EGFR, present	0.91	0.21-4.01	.9
KRAS, present	0.70	0.24-2.08	.5
Type of mediastinal stage			
EBUS vs medication only	1.46	0.61-3.50	.4
EBUS + medication vs medication only	5.89	0.65-53.11	.11
Others vs medication only	0.56	0.08-3.79	.6
Preinduction PET SUVmax N > 6.5†	1.66	0.68-4.04	.3
Preinduction PET SUVmax T > 9.75‡	0.67	0.29-1.56	.3
Postinduction PET SUVmax N > 3.3§	4.58	1.04-20.24	.045
Postinduction PET SUVmax T > 5.0	0.36	0.13-0.98	.046

PET, Positron emission tomography; *NIDDM*, noninsulin dependent diabetes; *FEV1*, forced expiratory volume in 1 second; *EGFR*, endothelial growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *EBUS*, endobronchial ultrasound; *SUVmax*, maximum standardized uptake values. *N2-avid versus N2-negative. †The median of 86 numerical SUVmax N was 6.5; 43 out of 86 had SUVmax N > 6.5. ‡The median of 93 numerical SUVmax T was 9.75; 46 out of 93 had SUVmax T > 9.75. §The median of 41 numerical SUVmax N was 3.3; 18 out of 41 had SUVmax N > 3.3. ||The median of 69 numerical SUVmax T was 5.0; 33 out of 69 had SUVmax N > 5.0.

TABLE E2. Results of postinduction N2 avidity in detecting pathologic mediastinal (N2-persistent) disease*

Pathologic N2 status	Postinduction PET N2 status	
	N2-Negative (n = 36; 47%)	N2-Avid (n = 41; 53%)
N2-Negative (n = 31; 40%)	17 (47)	14 (34)
N2-Persistent (n = 46; 60%)	19 (53)	27 (66)

Values are presented as n (%). *PET*, Positron emission tomography. *A total of 77 patients with available postinduction PET and pathologic N2 report.

TABLE E5. Locations of distant recurrences*

Location	Result n (%)
Single distant site	37 (67)
Multiple distant sites	18 (33)
Brain	21 (38) [†]
Lung	18 (33) [†]
Bone	10 (18) [†]
Pleural	6 (11) [†]
Liver	7 (13) [†]
Adrenal	1 (2) [†]
Extrathoracic lymph nodes	9 (16) [†]

*Fifty-five total patients with distant metastasis was used as the denominator.

[†]>100% because of multiple site recurrences.