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Postinduction PET 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 (OS), disease-free survival (DFS), and recurrence.

Results—Persistent pathologic N2 disease was present in 61% of patients (61/100). PET N2-negative disease increased from 7% (6/92) before induction therapy to 47% (36/77) 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 OS was 40% for ypN2 disease versus 38% for N2-persistent disease (p=0.936); the 5-year OS was 43% for postinduction PET N2-negative disease versus 39% for N2-avid disease (p=0.251). The 5-year DFS was 34% for ypN2-negative disease versus 9% for N2-persistent disease (p=0.079).

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Central Message: For stage IIIA/pN2 non-small cell lung cancer, postinduction PET avidity of N2 nodes is not associated with ypN2 disease or overall survival.

Conclusions—Postinduction PET avidity for N2 nodes is not associated with ypN2 disease, OS, or DFS in patients undergoing induction chemotherapy for stage IIIA/pN2 disease.

Introduction

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 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 colleagues found a 3-year survival of 41% for patients with N2 disease treated with induction therapy.[7] 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/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 colleagues found that the positive predictive value of position emission tomography (PET) scans for persistent N2 disease ranged from 43% to 100%.[13] Prior studies showed that PET assessment of N2 disease after induction therapy had a false-negative rate of 25%.[10] Given that 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. As 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. Prior to induction therapy, N2 disease was confirmed by endobronchial ultrasound (EBUS), diagnostic mediastinoscopy, endoscopic ultrasound (EUS), 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 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, MRI 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 were not subjected to 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 “pathologic N2-persistent (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.

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 (≥ypIIIA vs <ypIIIA). The log-rank test was used to compare OS and DFS between groups. Cox proportional hazards 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 two-tailed, and $p<.05$ was considered to indicate statistical significance. No multiple comparison adjustment was made. All analyses were performed using Stata 13 (StataCorp, College Station, TX) and R 2.13.1 (R Development Core Team, 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%; 78/100). The majority of cases of N2 disease (95%; 95/100) were confirmed by EBUS or mediastinoscopy; the other 5 cases were confirmed by EUS, 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 (65/77) had a decrease in SUVmax T status, and 80% (61/76) had a decrease in SUVmax N status. The percentage of patients with PET N2-negative disease increased from 7% (6/92) before induction therapy to 47% (36/77) after. The median duration between pre- and postinduction PET was 4 months (range, 1.7 to 11.2); the median duration between postinduction PET and surgery was 0.7 months (range, 0.03 to 5.8).

Operative Management and Adjuvant Therapy

All patients received doublet induction therapy, with the majority (99/100; 99%) receiving a platin-based regimen. The most common operation was lobectomy (75%; 75/100). Eighty-

five patients had R0 resections, 8 had R1, and 7 had R2. Eight percent of patients (8/100) 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% (2/100); 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 (Table 1 and Supplemental Table 1).

Pathologic Staging and N2 Status

Postoperative pathologic staging revealed that 36% of patients had <ypIIIA disease (36/100) and 64% had ≥ypIIIA. Two patients had complete pathologic responses (Table 1). Pathologic staging found ypN2 disease in 61% of patients (pN2, 61/100) and ypN0-1 disease in 39% (pN0, 33/100; pN1, 6/100). 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 (Supplemental Table 2 and 3). 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(+)/Path(+)], 14 false-positives [PET(+)/Path(-)], 17 true-negatives [PET(-)/Path(-)], and 19 false-negatives [PET(-)/Path(+)]. 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%.

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% CI, 0.69–4.33; p=0.2). 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 = 0.045), 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 (OR 2.9; 95% CI, 1.09–7.63; p=0.032). Age, lung function, and method of preinduction N2 staging were not statistically significant (Supplementary Table 4).

Factors Associated with OS

The median duration of follow-up was 2.7 years (range, 0.02 to 7.2). Forty-five patients died during follow-up. The majority (41/45; 92%) died of disease; 4 died of other causes. The median time to death was 1.6 years (range, 0.04–5.0). 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=0.936); 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 ≥ypIIIA disease (p=0.791). Among patients with valid postinduction PET N2 status, the 5-year OS was 43% (95% CI, 22%–83%) for PET N2-negative disease versus 39% (95% CI, 23%–64%) for PET N2-avid disease (p=0.251). Univariable analyses revealed that no factors, among those evaluated, were significantly associated with hazard of any death (Table 3). Pathologic T stage ≥IIA had a HR of 1.80 (95% CI, 0.98–3.31; p=0.058), 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=0.079); 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 ≥ypIIIA disease (p=0.054). Although not statistically significant, the HR for ypN2 disease was 1.58 (95% CI, 0.94–2.63; p=0.082), and the HR for ≥ypIIIA disease was 1.67 (95% CI, 0.99–2.85; p=0.056), 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=0.867). R2 resection, pathologic T stage ≥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 two variables: age (HR=0.97; 95% CI, 0.94–1.00; p=0.059) and pathologic T stage ≥IIA (HR=1.92; 95% CI, 1.12–3.31; p=0.018). 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 (Table 4 and Supplemental Table 5). The 3-year CIR for the entire cohort was 70% (95% CI, 60%–81%; Supplemental Figure

1). The 5-year CIR was 76% (95% CI, 58%–99%) for postinduction PET N2-negative disease versus 58% (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=0.049), indicating a worse prognosis for recurrence for patients with ≥ypIIIA disease. The CIRs were not significantly different by postinduction PET N2 status (p=0.571) or ypN2 status (p=0.077).

Discussion

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

Candela and Detterbeck reviewed the literature on restaging after induction therapy.[10] 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 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 25-30 patients, whereas we reported 100 patients included consecutively from 2006 to 2012. Only De Leyn and colleagues reported that all patients had preinduction pathologic confirmation of N2 disease.[11] 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 1A).[14] Albain and colleagues reported the results of Intergroup Trial 0139, in which patients randomized to receive induction chemoradiotherapy had a 5-year OS of 27%.[6] Our 5-year OS is higher, which we believe may be secondary to several factors. We postulate that the emphasis on adequate preresection DLCO, 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 colleagues 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.[17] In contrast, OS in our series was not different with regard to pathological staging (<ypIIIA) or ypN2 disease (Figure 1C-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, even though 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 (44/61) received adjuvant therapy; 61% (37/61) received PORT. Owing 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, from the German Lung Cancer Cooperative Group, reported that 55% of the patients in the surgical control group underwent complete resection.[22] Van Meerbeeck and colleagues, 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.[23] We believe that complete removal of all N2 nodes contributed to the favorable outcomes in our series. However, R1-R2 resections were not associated with decreased survival in our series. Since 85% of patients (85/100) underwent an R0 resection, the numbers of R1-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 endpoints 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ARDS	adult respiratory distress syndrome
CI	confidence interval
cIIIA/pN2	clinical stage IIIA–N2
CIR	cumulative incidence of recurrence
DFS	disease-free survival (DFS)
EBUS	endobronchial ultrasound
EGFR	endothelial growth factor receptor
EUS	endoscopic ultrasound
FEV1	forced expiratory volume in one second
HR	hazard ratio
KRAS	Kirsten rat sarcoma viral oncogene homolog
NIDDM	non-insulin dependent diabetes
OR	odds ratio
OS	overall survival
PET	positron emission tomography
PORT	postoperative radiotherapy
MSKCC	Memorial Sloan Kettering Cancer Center
NSCLC	non-small cell lung cancer
SUVmax	maximum standardized uptake values
VATS	video-assisted thoracic surgery
ypN2	pathologic N2-persistent
ypN0-1	pathologic N2-negative

Perspective Statement

For patients with stage IIIA non-small cell lung cancer with pN2 disease treated with induction chemotherapy, persistence of postinduction PET 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.

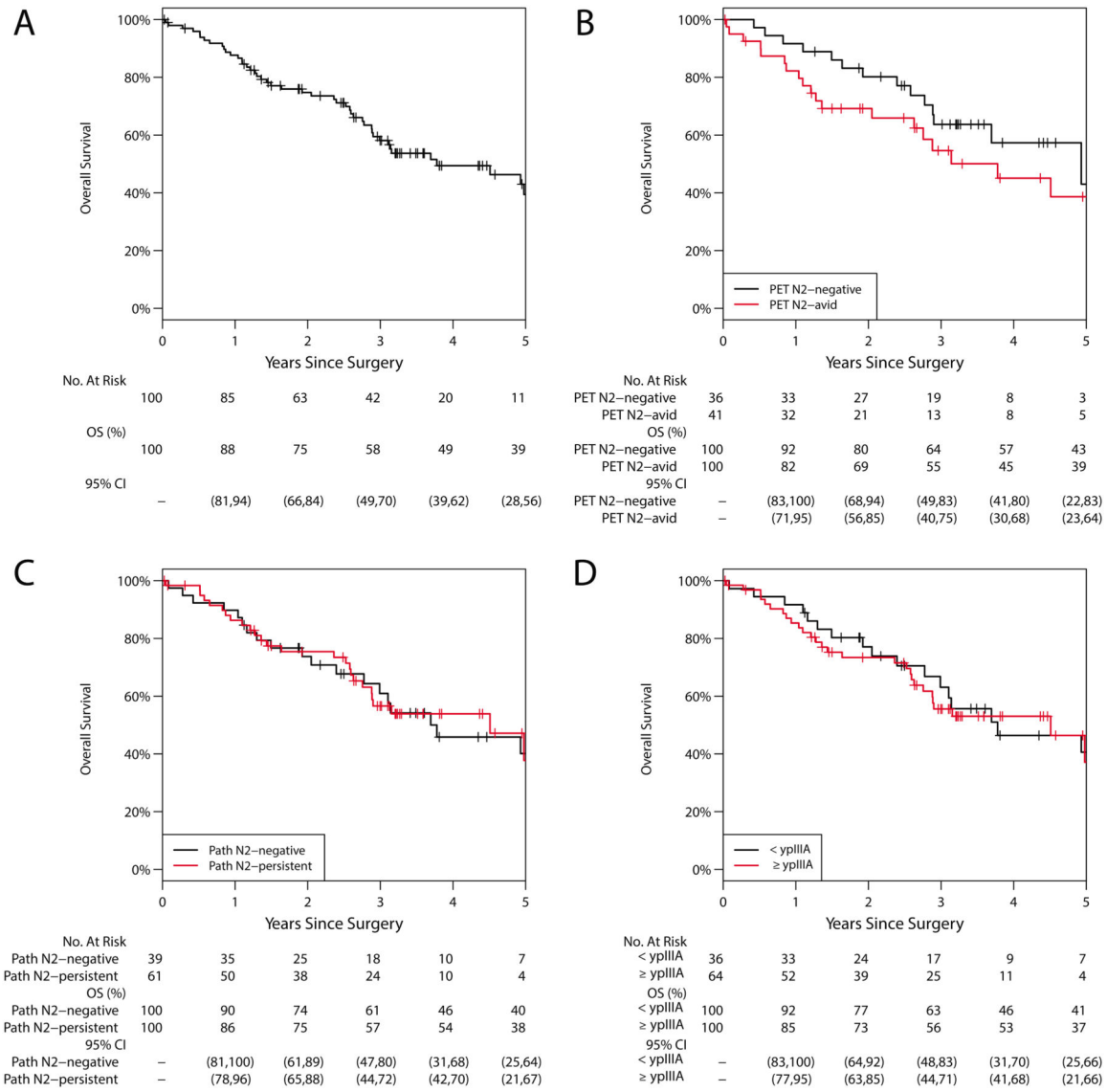


Figure 1.

Overall survival (OS). A, Entire cohort: the 5-year OS was 39% (95% CI, 28%–56%). B, Postinduction PET N2 status: the 5-year OS for N2-negative was 43% (95% CI, 22%–83%) *vs* 39% (95% CI, 23%–64%) for N2-avid disease (p=0.251). C, Pathologic N2 status: the 5-year OS for N2-negative was 40% (95% CI, 25%–64%) *vs* 38% (95% CI, 21%–67%) for N2-persistent disease (p=0.936). D, Pathologic staging: the 5-year OS for <ypIIIA was 41% (95% CI, 25%–66%) *vs* 37% (95% CI, 21%–66%) for ≥ypIIIA (p = 0.791).

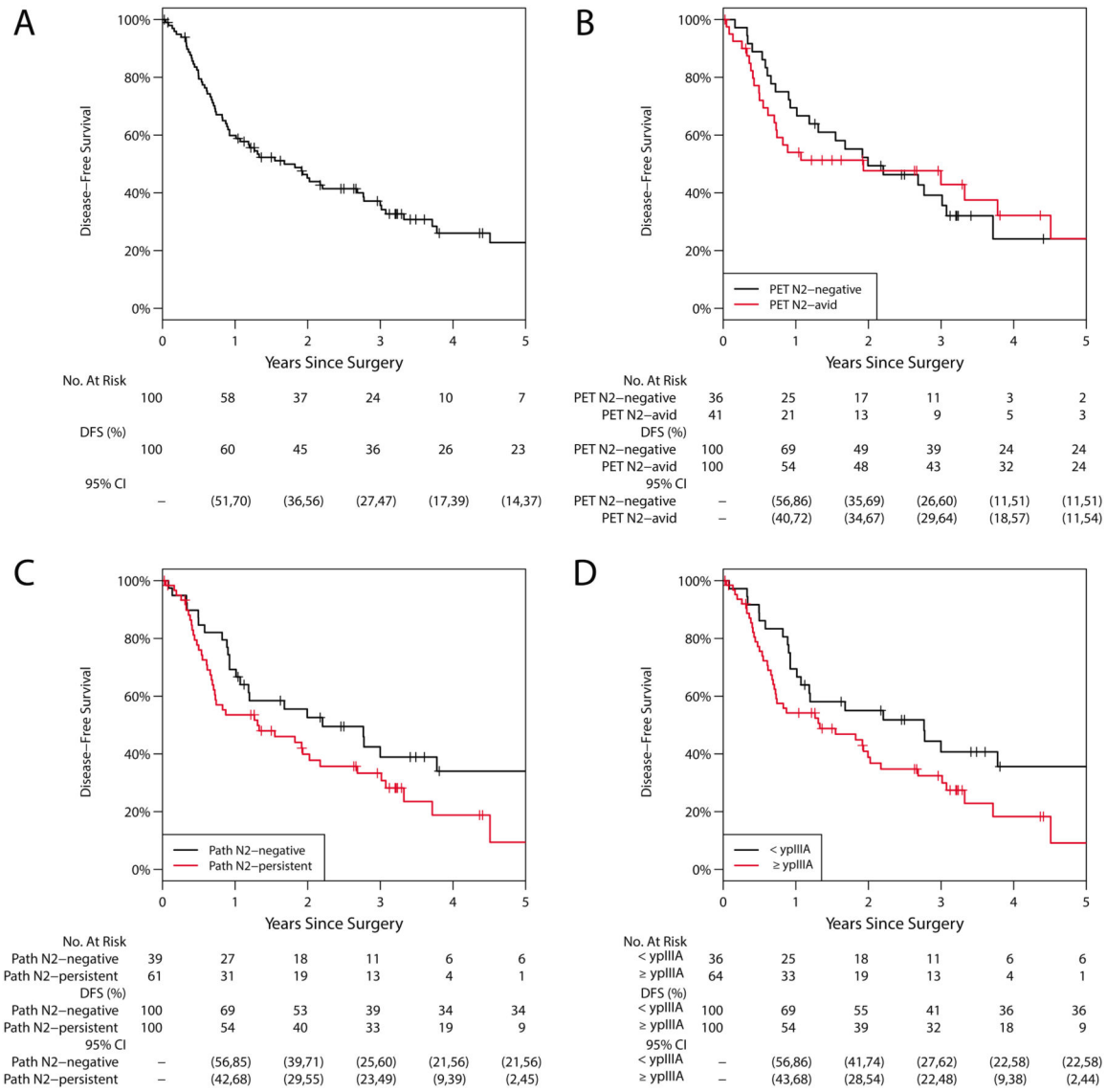
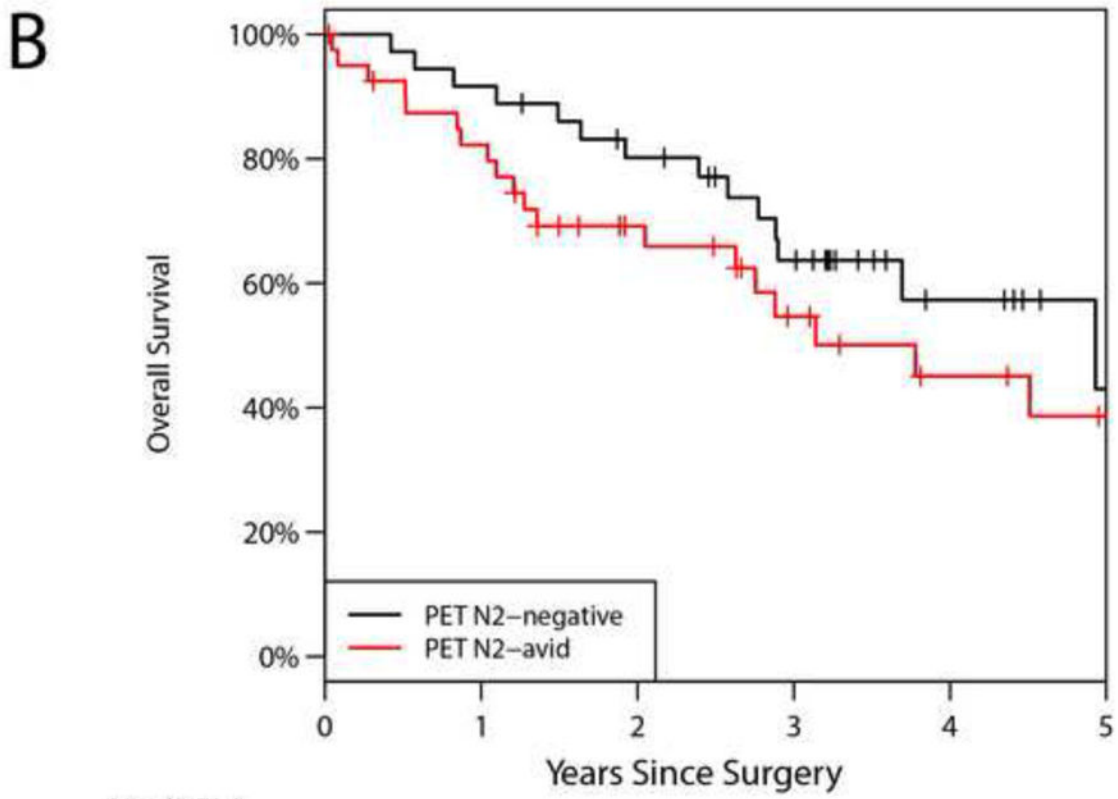


Figure 2.

Disease-free survival (DFS). A, Entire cohort: the 5-year DFS was 23% (95% CI, 14%–37%). B, Postinduction PET N2 status: the 5-year DFS for N2-negative was 24% (95% CI, 11%–51%) *vs* 24% (95% CI, 11%–54%) for N2-avid disease (p=0.867). C, Pathologic N2 status: the 5-year DFS for N2-negative was 34% (95% CI, 21%–56%) *vs* 9% (95% CI, 2%–45%) for N2-persistent disease (p=0.079). D, Pathologic staging: the 5-year DFS for <ypIIIA was 36% (95% CI, 22%–58%) *vs* 9% (95% CI, 2%–44%) for ≥ypIIIA (p=0.054).



No. At Risk						
PET N2–negative	36	33	27	19	8	3
PET N2–avid	41	32	21	13	8	5
OS (%)						
PET N2–negative	100	92	80	64	57	43
PET N2–avid	100	82	69	55	45	39
95% CI						
PET N2–negative	–	(83,100)	(68,94)	(49,83)	(41,80)	(22,83)
PET N2–avid	–	(71,95)	(56,85)	(40,75)	(30,68)	(23,64)

Central Picture Figure 1B.
5-year overall survival was 43% for postinduction PET N2-negative disease versus 39% for N2-avid disease.

Table 1
Patient demographic, clinical, and operative characteristics

	N=100
Sex	
Female	49 (49%)
Male	51 (51%)
Age	65.0 (58.5, 71.0)
Smoking Status	
Current	10 (10%)
Former	73 (73%)
Never	17 (17%)
Comorbidities	
Pulmonary (N=84), yes	32 (38%)
Cardiac (N=85), yes	53 (62%)
NIDDM (N=75), yes	9 (12%)
FEV1 (%) (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%)
VATS	3 (3.0%)
Resection	
R0	85 (85%)
R1	8 (8.0%)
R2	7 (7.0%)
Mortality	
30-day mortality	2 (2.0%)
90-day mortality	2 (2.0%)
Adverse Events, yes	27 (27%)
Prolonged Air Leak, yes	5 (5.0%)
Respiratory Failure/ARDS, yes	2 (2.0%)

	N=100
Supraventricular Tachycardia, yes	7 (7.0%)
Clinical and Pathological Details	
Method of Pre-induction Mediastinal Staging	
Mediastinoscopy-only	35 (35%)
EBUS-only	52 (52%)
Mediastinoscopy + EBUS	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%)
Pathological N Status	
N0	33 (33%)
N1	6 (6.0%)
N2	61 (61%)
Post-operative Pathological 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%)
PORT-only	37 (37%)
Adjuvant Chemotherapy-only	16 (16%)
PORT + Adjuvant Chemotherapy	8 (8.0%)

Data presented as N(%) or median (25^{th}, 75^{th} percentile). VATS = video-assisted thoracic surgery; PORT = post-operative radiation therapy; NIDDM = non-insulin dependent diabetes; EBUS = endobronchial ultrasound; ARDS = Adult respiratory distress syndrome.

Table 2

Pre- and Post-induction PET Results

	Pre-induction PET (N=99)	Post-induction PET (N=80)
T Status		
Non-avid	1 (1.0%)	10 (13%)
No value reported	1 (1.0%)	--
Non-numerical value reported	4 (4.0%)	1 (1.3%)
Numerical value reported	93 (94%)	69 (86%)
SUVmax N among numerical values	9.8 (6.2, 14.7)	5.0 (3.0, 9.8)
N Status		
Non-avid	6 (6.1%)	36 (45%)
No value reported	1 (1.0%)	1 (1.3%)
Non-numerical value reported	6 (6.1%)	2 (2.5%)
Numerical value reported	86 (87%)	41 (51%)
SUVmax T 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 Post-induction values*	SUVmax T (N=77)	SUVmax N (N=76)
Pre- to Post-induction		
No change	1 (1.3%)	6 (7.9%)
Decreased	65 (84%)	61 (80%)
Increased	11 (14%)	9 (12%)
Not interpretable	2	3

Data presented as N(%) or median (25^{th}, 75^{th} percentile).

* Pre- and post-PET scans available for 79 patients; 77 with interpretable change in SUVmax T and 76 with interpretable change in SUVmax N2. Non-numeric descriptions in post-induction PET cannot be categorized as a change unless pre-induction PET is also a non-numeric description.

PET = positron emission scan; SUVmax = Maximum standardized uptake values

Table 3

Univariable Cox models for Overall Survival and Disease-Free Survival Analyses

	Overall Survival			Disease-Free Survival		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Post-induction PET (N2-avid *v* N2-negative)	1.50	0.75, 3.00	0.3	1.05	0.59, 1.86	0.9
Pathological N2 Status (N2-persistent *v* N2-negative)	0.98	0.54, 1.77	0.9	1.58	0.94, 2.63	0.082
Pathologic Staging (≥ypIIIA *v* <ypIIIA)	1.09	0.59, 1.99	0.8	1.67	0.99, 2.82	0.056
Age at Surgery	0.99	0.96, 1.03	0.6	0.97	0.94, 1.00	0.044
Male	1.49	0.82, 2.70	0.2	1.07	0.66, 1.75	0.8
Smoking, yes	1.02	0.48, 2.20	0.9	0.93	0.48, 1.78	0.8
Smoking Pack-years >30, yes	0.98	0.54, 1.75	0.9	0.71	0.43, 1.16	0.2
Pulmonary comorbidity, yes	1.07	0.55, 2.10	0.8	0.77	0.44, 1.35	0.4
Cardiac comorbidity, yes	0.95	0.48, 1.88	0.9	0.69	0.40, 1.21	0.2
NIDDM, yes	1.43	0.50, 4.09	0.5	1.73	0.68, 4.41	0.3
FEV1 (%)	0.99	0.97, 1.01	0.2	0.99	0.97, 1.00	0.10
Diffusion (%)	1.00	0.99, 1.02	0.6	1.01	1.00, 1.02	0.2
Adenocarcinoma, yes	1.07	0.52, 2.23	0.9	1.65	0.88, 3.10	0.12
EGFR, present	0.74	0.26, 2.12	0.6	0.79	0.35, 1.75	0.6
KRAS, present	1.66	0.81, 3.40	0.2	1.18	0.64, 2.20	0.6
Adjuvant Therapy						
PORT-only only vs None	1.19	0.61, 2.33	0.6	1.14	0.65, 2.01	0.6
Adjuvant Ch-only vs None	0.64	0.26, 1.58	0.3	0.78	0.37, 1.63	0.5
PORT+Adjuvant Ch vs None	0.60	0.17, 2.08	0.4	0.94	0.38, 2.31	0.9
Resection: R1 vs R0	2.08	0.87, 4.97	0.10	1.46	0.66, 3.22	0.3
Resection: R2 vs R0	1.33	0.41, 4.34	0.6	2.32	0.92, 5.88	0.075
Pathologic T-Stage (≥IIA *v* <IIA)[a]	1.80	0.98, 3.31	0.058	2.22	1.33, 3.73	0.002

[a] Pathologic T-stage: 45 had <IIA (0, IA, IB) and 55 had ≥IIA (includes IIA, IIB, IIIA, III and IV). NIDDM = non-insulin dependent diabetes; PORT = post-operative radiation therapy; Ch = chemotherapy

PET = positron emission scan; NIDDM = non-insulin dependent diabetes; FEV1 = Forced expiratory volume in one second; EGFR = Endothelial growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homolog; PORT = post-operative radiation therapy.

Table 4
Patient Outcomes and Recurrence and Progression Patterns by Resection Status

		Resection Status		
	Overall (N=100)	**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 (N=61)				
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%)