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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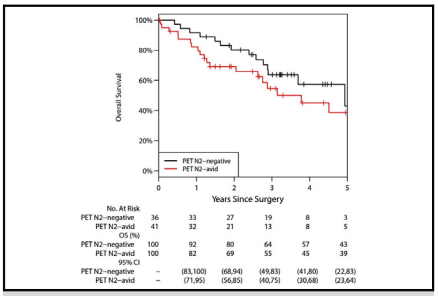
ABSTRACT

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.

See Editorial Commentary page 980.

See Editorial page 911.

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 colleagues[7] 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 colleagues[13] found that the positive predictive value of position 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.