Incidence and Prognostic Significance of Carcinoid Lymph Node Metastases

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Background. **Pulmonary carcinoid tumors are often considered indolent tumors. The prognostic significance of lymph node (LN) metastases and the need for mediastinal dissection is controversial. We sought to determine the incidence, risk factors, and prognosis of LN metastases in resected carcinoid patients.**

Methods. **Patients undergoing lung resection for carcinoid and removal of ≥10 LNs were identified in the National Cancer Database from 2004 to 2014. Typical (TCs) and atypical carcinoids (ACs) were included. Clinical and pathologic LN status was assessed. Overall survival (OS) was analyzed using log-rank test and Cox hazard regression analysis.**

Results. **A total of 3,335 patients (TC 2,893; AC 442), underwent resection (lobectomy/bilobectomy 84%, pneumonectomy 8%, sublobar resection 8%). LN involvement was present in 21% of patients (N1 15%, N2 6%) and increased with tumor size and AC histology. Tumor size was an independent predictor of LN disease. The rate of nodal upstaging was 13% (TC 11%, AC 24%). Independent predictors of OS were AC type (HR 3.25 [95% CI 2.19-4.78]) and LN metastases (HR 2.3 [1.49-3.58]). LN disease was associated with worse survival for TC > 2 cm (5-year OS 87% versus 94%, $p = 0.005$) and AC (58% versus 88%, $p = 0.001$), but not for small (≤ 2 cm) TC patients (5-year OS 93% versus 92%, $p = 0.67$).**

Conclusions. **A substantial number of well-staged carcinoid patients had LN metastases. Large tumor size is a valuable predictor of carcinoid nodal disease. LN involvement was an independent predictor of worse survival. Nodal dissection in tumors > 2 cm and in atypical subtype can yield important prognostic information.**

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Carcinoid tumors are a type of neuroendocrine tumor of the lung (NET) that arise from Kulchitsky cells. They account for 1% to 2% of all primary lung malignancies, with increasing incidence over the past 3 decades [1, 2]. According to World Health Organization classification, NETs are categorized by grade, mitotic count, and presence of necrosis [3]. Carcinoid tumors represent the less aggressive end of the NET spectrum and include well-differentiated typical carcinoid (TC) and the less common moderately differentiated atypical carcinoid (AC) tumors. As a group, they are generally considered indolent tumors, but can exhibit a significant variation in their malignant behavior [4, 5].

One key question considering surgical treatment for carcinoid tumors is the propensity for lymph node metastases. Currently, the true incidence of carcinoid lymph node metastases remains ill defined, as current data are derived mostly from small, single-institution analyses or registry data with varying degree of lymph node assessment [6–9]. It has been established that TCs have been associated with a lower risk of lymph node metastases as compared with ACs. Nevertheless, studies have shown that even small TCs may present with significant nodal disease [10, 11]. Given the lack of definitive data, significant variability in treatment exists. Although most surgeons advocate for systematic lymph node dissection in all carcinoid patients, others may feel that, given their favorable characteristics, a routine lymph node dissection is not warranted. Recent population-based studies demonstrated that up to one fourth of patients with small TCs had no surgical lymph node assessment performed and 30% had a sublobar resection [9, 10].

The objective of this study were (1) to determine the incidence of lymph node metastases in patients with carcinoid tumors who underwent pulmonary resection with a thorough lymph node dissection documented in a large national cancer registry, (2) to examine clinical predictors of lymph node metastases, and (3) to assess the prognostic significance of nodal disease based on tumor size and histology of surgically resected carcinoids.

Patients and Methods

The National Cancer Database (NCDB) was queried for all patients with pulmonary carcinoid tumors diagnosed between 2004 and 2014. The NCDB is a comprehensive

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nationwide cancer outcomes database, jointly sponsored by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which captures some 70% of all newly diagnosed cancers in the United States from over 1,500 institutions. The database is accessible to CoC-accredited programs by request through a Web-based application process.

We selected patients with pathologic confirmed typical carcinoid (TC) or atypical carcinoid (AC) based on ICD-9 histology codes (8240 and 8246) and the International Classification of Disease for Oncology, Third Edition (ICD-O-3) site codes (c340-c343 and c348-c349). The study cohort was limited to patients with nonmetastatic disease, who had upfront surgery with a pulmonary resection, and 10 or more lymph nodes removed based on pathologic lymph node count (Fig 1). The minimum of 10 lymph nodes is currently defined as a quality measure for adequate lymph node sampling by the CoC for early-stage non-small cell lung cancer [12].

Patient characteristics for analysis included age, sex, race, Charlson comorbidity score, and type of treating facility. Disease factors included tumor site and laterality, clinical T-stage, and nodal status. Treatment data included extent of resection, operative approach, and adjuvant therapy. Pathologic tumor size, histology, nodal status, and margin status were analyzed.

Outcomes

The primary outcome was the presence of pathologic lymph node (LN) metastasis. Secondary endpoints included the presence of nodal upstaging in clinically staged, node-negative patients and survival. Overall survival was calculated from date of diagnosis to the last follow-up or death.

Statistical Analysis

Descriptive analysis was performed to report demographics and clinical and pathological characteristics. Median number and interquartile range (IQR) as well as mean values with SD were used to describe continuous data, with discrete variables displayed as total and frequencies. Variables were compared between TC and AC patients using χ^2 test or Fisher's exact test for categorical variables and the two-sample t test or Wilcoxon rank-sum test for continuous variables. Binary logistic regression analysis was performed to test the association of preoperative and procedural factors with presence of pathologic lymph node metastases. Univariate predictors with p less than 0.1 were included in the multivariate model. A receiver operating characteristic (ROC) curve of the true positive rate (sensitivity) against the false positive rate (1 – specificity) of tumor size for node positivity was plotted to determine a cutoff point. Kaplan Meier survival curves were created based on histology and compared using log rank test. Univariate and multivariate Cox regression analysis was performed for factors associated with survival. Variables with p values of less than 0.1 from the univariate analysis were included in the multivariate model. Statistical significance was defined as 2-tailed p value of less than 0.05. All data analysis was performed using SPSS version 20 for Microsoft Windows (LEAD Technology, Chicago, IL) statistical software package.

Results

There were 13,293 carcinoid patients registered in the NCDB from 2004 to 2014 with available LN counts, who had a median number of 4 LNs sampled. We identified 3,335 patients (2,893 TC, 442 AC) who met the inclusion

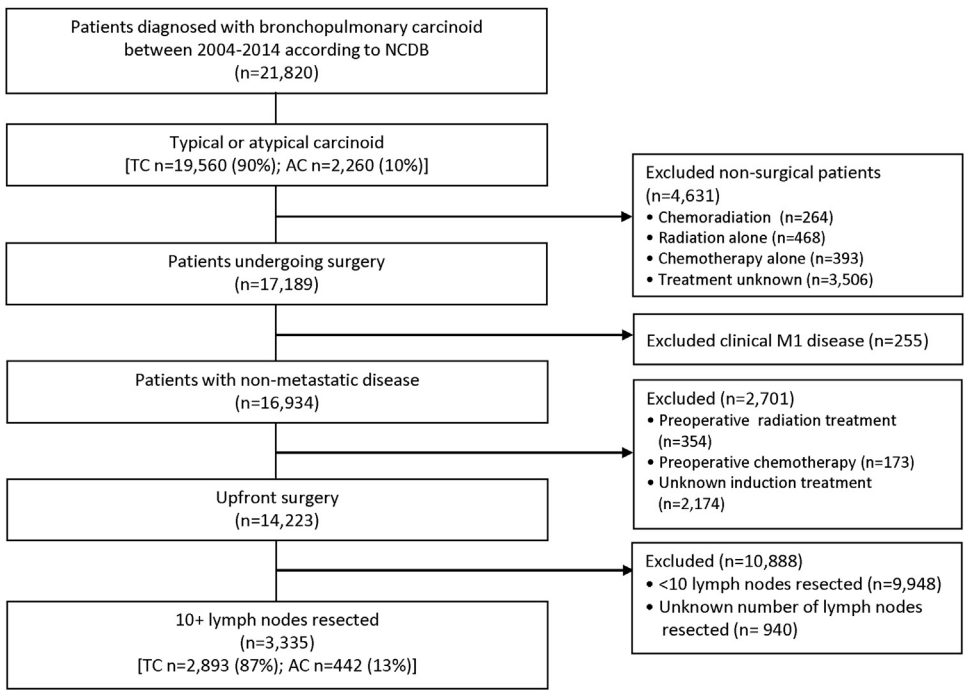

Fig 1. CONSORT diagram detailing selection of patient cohort. (AC = atypical carcinoid; NCDB = National Cancer Database; TC = typical carcinoid.)

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