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Natural History of Typical Pulmonary Carcinoid Tumors

A Comparison of Nonsurgical and Surgical Treatment

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BACKGROUND: The natural history of typical pulmonary carcinoid tumors has not been described and has important implications for counseling elderly patients or patients with high operative-risk about surgical resection.

METHODS: Data from the Surveillance, Epidemiology, and End Results Program were used to identify 4,111 patients with biopsy specimen-proven lymph node-negative typical carcinoid tumor of the lung between 1988 and 2010; 306 had no resection, 929 underwent sublobar resection, and 2,876 underwent lobectomy. Overall survival and disease-specific survival (DSS) were analyzed using Kaplan-Meier plots. Multivariate analysis was used to determine predictors of survival.

RESULTS: Five-year overall survival in patients who underwent lobectomy, sublobar resection, or no surgery was 93%, 92%, and 69%, respectively ($P < .0001$); 5-year DSS was 97%, 98%, and 88%, respectively ($P < .0001$). Among T1 tumors, DSS was 98% for patients who underwent lobectomy and sublobar resection and 92% for no surgery; among T2 tumors, DSS was 97%, 100%, and 87%, respectively, and among T3 and T4 tumors, it was 96%, 100%, and 75%, respectively. On multivariate analysis, nonoperative management was associated with an increased risk for disease-specific mortality compared with lobectomy (hazard ratio, 2.14; 95% CI, 1.35-3.40; $P = .0013$).

CONCLUSIONS: In this population-based cohort, surgical resection of lymph node-negative carcinoid tumors is associated with a survival advantage over nonoperative treatment. However, the DSS at 5 years was still high without any treatment, suggesting that observation of asymptomatic peripheral typical carcinoid tumors or endoscopic management of symptomatic central carcinoid tumors may be considered in patients at high risk for surgical resection.

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ABBREVIATIONS: DSS = disease-specific survival; HR = hazard ratio; ICD-O-3 = *International Classification of Diseases for Oncology, Version 3*; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results

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Little is known about the natural history of pulmonary carcinoid tumors. Pulmonary carcinoid tumors may present as incidental peripheral lung lesions or as symptomatic endobronchial lesions.[1] Typical carcinoid tumors, the most common pulmonary carcinoid tumors, are associated with 90% to 95% 5-year overall survival (OS) with surgical resection.[1,2] One small patient series reported that the doubling time of pulmonary carcinoid tumors averages 80 months for typical carcinoid tumors.[3] As the number of lung nodules detected incidentally on CT screening for lung cancer or other indications increases, it is important to understand the natural history of nonresected typical pulmonary carcinoid tumors. This information can be useful in informing elderly patients, patients with limited life expectancy, or patients at high operative risk about the expected outcomes with nonoperative management of asymptomatic peripheral carcinoid tumors or endobronchial treatment of central tumors. Using data from the Surveillance, Epidemiology, and End Results (SEER) program, we describe the survival of patients with biopsy specimen-proven, lymph node-negative typical carcinoid tumors who did not undergo surgical resection compared with who did.

Materials and Methods

Patients

Patient data were obtained from the SEER website.[4] The SEER catchment area covers approximately 28% of the United States, and the dataset contains clinicopathologic information, treatment specifics, OS, and disease-specific survival (DSS). Disease-specific death codes are used if the index cancer is the patient's first primary, with "disease specific" defined as death caused by cancer of the same site or cancer of the same body system. In addition, if the patient had only one cancer in his or her lifetime (sequence code = 00), any cause of death by cancer and death due to noncancer diseases related to the site of cancer are considered disease specific. Another cancer or cancers that develop (sequence code = 01) in addition to cancer of the same site and cancer of the same body system, death from cancer attributed to multiple cancers with an unknown primary, and death from noncancer diseases related to the site of first cancer diagnosis are coded as disease specific. Tumor location, grade, and histology were coded according to the *International Classification of Diseases for Oncology, Version 3* (ICD-O-3). Tumor stage was coded according to the seventh edition of the American Joint Committee on Cancer TNM staging system.[5] SEER requires registries to update disease and vital status on all cases annually. This study was reviewed by our institutional review board and was determined to be exempt research.

Table 1 summarizes the inclusion and exclusion of patients in the study. Included in the analyses were patients aged ≥ 18 years with histologically confirmed nonmetastatic lung cancer (ICD-O-3 site code C34) between January 1988 and December 2010. Only patients classified with typical carcinoid histology (ICD-O-3 morphology code 8240) were included in the study dataset. In addition, patients with lymph node-positive disease or insufficient staging information or who received radiation were excluded. Since 2002, SEER has provided information on whether lymph node status was determined based on clinical stage or pathologic examination of lymph nodes with or without excision of the primary tumor. In 1,796 patients with information on lymph node status, diagnosis in 1,181 (66%) was based on histologic examination of lymph nodes, 41 patients (2%) may have had lymph nodes examined without primary tumor, and diagnosis in 574 (32%) was based on clinical staging alone. Cases where T stage was not coded or unknown (TX) were included in the study but analyzed separately. Patients with a history of cancer were excluded, as were patients receiving a diagnosis at autopsy or while in hospice. Of the 782,468 patients with lung cancer in the SEER registry between 1988 and 2010, the final sample comprised 4,111 patients. Procedure codes available in SEER were then assigned to one of three groups: lobectomy, sublobar resection, and no surgery. Within the lobectomy category, we included sleeve lobectomy, bilobectomy, and pneumonectomy, and within the sublobar resection category, we included bronchial sleeve resection (resection of bronchus alone without lung parenchyma). Among patients coded as having no surgery, we included 51 who had local tumor destruction with laser, cautery/fulguration, or tumor destruction not otherwise specified.

Statistical Analysis

Patient demographic and clinical characteristics were compared across treatment groups using the Pearson χ^2 test for categorical nominal data and the Jonckheere-Terpstra nonparametric test for categorical ordinal data. As a continuous variable, age was compared across groups using the Student *t* test. Univariate and multivariate Cox proportional hazard models identified factors associated with improved DSS and OS, with results reported using hazard ratios (HRs) and 95% CIs. In addition, the proportional hazard assumptions for the Cox models were tested by calculating scaled Schoenfeld residuals. Results indicated model fit or flat residuals secondary to large sample sizes.

Kaplan-Meier curves were used to calculate median and 5- and 10-year DSS and OS rates, with the log-rank test used to determine statistical differences across groups. Survival time, in years, was calculated from the date of diagnosis until the date of death. If the patient was alive, he or she was censored at the date of last contact. For the DSS analyses, patients who died of lung cancer (SEER variable dth_class = 1) were identified using cause of death on the death certificate. Patients who died of causes unrelated to their lung cancer were censored at the date of death. Median follow-up time for the 3,494 patients (85%) alive at last contact was 5.8 years (interquartile range, 2.7-10.2 years; mean ± SD, 7.1 ± 5.5 years). All analyses were performed using SAS software (SAS Institute Inc) with two-sided $P \leq .05$ considered statistically significant.

Results

OS at 5 years was 93% for lobectomy, 92% for sublobar resection, and 69% without surgery ($P < .0001$) (Fig 1A). Median survival was not reached for the lobectomy or sublobar resection groups and was 10 years for nonsurgical patients (95% CI, 8-not reached years). DSS at 5 years (Fig 1B) was 97% for lobectomy, 98% for sublobar resection, and 88% without surgery. DSS at 10 years was 95%, 96%, and 85%, respectively ($P < .0001$, log-rank test). There was no clinically meaningful difference in 10-year DSS among patients undergoing lobectomy with increasing T stage (96% for T1 and 95% for T2,