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 under-

stand 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 $\pm$ SD, 7.1 $\pm$ 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,

TABLE 1 Stepwise Cohort Selection

Step	Selection Criterion	% Removed	No. Remaining
1	All lung cancer	0.0	949,904
2	All patients with lung cancer, 1988-2010	17.6	782,468
3	Carcinoid tumor-only code 8240	99.0	7,945
4	Exclude patients aged < 18 y	0.6	7,901
5	Exclude patients with metastatic/M1 disease	7.0	7,347
6	Exclude patients with node-positive results	20.0	5,879
7	Exclude patients who received radiation	2.4	5,735
8	Exclude patients with unknown surgical or radiation status	0.6	5,700
9	Exclude Louisiana registry patients from July-September 2005 Hurricane Katrina-impacted areas	0.1	5,694
10	Exclude patients who were not given a histologically confirmed diagnosis	1.9	5,587
11	Exclude patients receiving a diagnosis while in a nursing home or hospice, at autopsy, or on death certificate	1.0	5,530
12	Exclude patients with prior cancer	23.0	4,259
13	Exclude those with T stage group of in situ or error	3.5	4,111
14	Final dataset	0.0	4,111

$P = .012$) or sublobar resection (96% for T1 and 93% for T2, $P = .71$). However, among patients who did not undergo surgery, DSS at 10 years was 87% for T2

Figure 1 – A, B, Overall (A) and disease-specific (B) survival in patients with lymph node-negative typical pulmonary carcinoid tumors undergoing lobectomy, sublobar resection, or no surgery.

tumors and 92% for T1 tumors, although the difference was not statistically significant ($P = .16$). We did not include values for T3/T4 tumors because of the small numbers of nonsurgical patients with these tumors. Median DSS time was not reached in the lobectomy, sublobar resection, or nonsurgical groups. Among sublobar resections were 519 wedge resections and 129 segmentectomies; 10-year DSS was 96% for both categories ($P = .56$).

Patient characteristics stratified by lobectomy, sublobar resection, or nonsurgical treatment are summarized in Table 2. Nonsurgical patients were older; in fact, 23.2% of these patients were aged ≥ 80 years compared with 5.9% of the patients undergoing sublobar resection and 2.6% undergoing lobectomy ($P < .0001$). Black patients underwent surgery less often than nonblack patients ($P = .006$) and presented with higher T stages than nonblack patients ($P = .0027$). Patients who did not undergo surgical lung resection had a higher proportion of tumors within the mainstem bronchus (13.4% vs 4.3% for lobectomy, $P < .001$); however, due to limitations with the coding system, it is unclear how many patients with nonmainstem locations actually had centrally located vs peripheral tumors. Patients undergoing sublobar resection were more likely to have T1 disease than those undergoing lobectomy or nonsurgical treatment (79%, 65%, and 36%, respectively; $P < .001$), although a large proportion of nonsurgical patients had tumors coded as TX (35%). Not

TABLE 2] Patient, Tumor, and Treatment-Related Characteristics in Patients Stratified by Treatment Status

Characteristic	Lobectomy (n = 2,876)	Sublobectomy (n = 929)	No Treatment (n = 306)	P Value
Follow-up time, y	6.7 (3.1-10.8)	5.4 (2.4-9.1)	3.8 (1.6-6.6)	< .0001
Disease-specific status				< .0001
Alive	2,457 (85.4)	796 (85.7)	203 (66.3)	
Dead from other causes	310 (10.8)	109 (11.7)	72 (23.5)	
Dead from disease	109 (3.8)	24 (2.6)	31 (10.1)	
Vital status				< .0001
Alive	2,457 (85.4)	796 (85.7)	203 (66.3)	
Dead	419 (14.6)	133 (14.3)	103 (33.7)	
Age, y	54.6 ± 14.63	59.8 ± 13.9	65.6 ± 16.26	< .0001
Age group ^a				< .0001
18-49 y	1,018 (35.4)	200 (21.5)	49 (16.0)	
50-64 y	1,046 (36.4)	352 (37.9)	81 (26.5)	
65-79 y	738 (25.7)	322 (34.7)	105 (34.3)	
≥ 80 y	74 (2.6)	55 (5.9)	71 (23.2)	
Sex				.0018
Male	1,009 (35.1)	268 (28.8)	108 (35.3)	
Female	1,867 (64.9)	661 (71.2)	198 (64.7)	
Race/ethnicity				.0006
Nonblack	2,725 (94.7)	882 (94.9)	274 (89.5)	
Black	151 (5.3)	47 (5.1)	32 (10.5)	
Location				< .0001
Main	125 (4.3)	58 (6.2)	41 (13.4)	
Upper	862 (30.0)	304 (32.7)	84 (27.5)	
Middle	580 (20.2)	148 (15.9)	40 (13.1)	
Lower	1,196 (41.6)	377 (40.6)	110 (35.9)	
NOS/overlapping	113 (3.9)	42 (4.5)	31 (10.1)	
T stage group				< .0001
T1	1,873 (65.1)	731 (78.7)	109 (35.6)	
T2	801 (27.9)	98 (10.5)	72 (23.5)	
T3/T4	91 (3.2)	34 (3.7)	18 (5.9)	
TX	111 (3.9)	66 (7.1)	107 (35.0)	
No. nodes examined	5 (2-8)	0 (0-2)	0 (0-0)	< .0001
0	276 (9.6)	573 (61.7)	277 (90.5)	
1-4	947 (32.9)	218 (23.5)	10 (3.3)	
5-8	674 (23.4)	47 (5.1)	3 (1.0)	
9-13	361 (12.6)	30 (3.2)	2 (0.7)	
≥ 14	244 (8.5)	15 (1.6)	3 (1.0)	
Unknown	374 (13.0)	46 (5.0)	11 (3.6)	

Data are presented as median (interquartile range), No. (%), or mean ± SD. P values for follow-up time reflect nonparametric testing using the Kruskal-Wallis test. NOS = not otherwise specified.

^aP values shown are based on the Jonckheere-Terpstra test for ordinal data. All other P values are based on χ^2 test across groups.

surprisingly, fewer lymph nodes were examined among patients undergoing sublobar resection or no surgery (82% and 94%, respectively, had 0-4 lymph nodes examined vs 35% of patients undergoing lobec-

tomy; $P < .001$). At least nine patients (3%) who did not undergo surgery had lymph nodes sampled by mediastinoscopy, endobronchial ultrasound, or other methods.

On multivariate analysis, nonsurgical patients were more than twice as likely to die than patients who underwent lobectomy (OS HR, 2.23; 95% CI, 1.67-2.96; $P < .0001$) after controlling for age, sex, race/ethnicity, and T stage. Based on DSS data, the risk of dying from disease was also twice as likely in nonsurgical patients than in patients who underwent lobectomy (HR, 2.14; 95% CI, 1.35-3.40; $P = .001$). Increasing age was associated with disease-specific mortality, with patients aged ≥ 80 years having an HR of 14.10 (95% CI, 6.53-29.10; $P < .001$) compared with patients aged 18 to 49 years.

Blacks had a higher rate of disease-specific mortality (HR, 2.13; 95% CI, 1.26-3.59; $P = .005$) than whites on multivariate analysis. Comparing various clinical variables, blacks were less likely to undergo surgery than whites (no surgery, 14% vs 7%, respectively; $P = .0004$) and were less likely to have T1 disease (56% vs 67%, respectively; $P = .0054$). Among the 306 patients who did not undergo a resection, 156 (51%) were not recommended surgery, 51 (17%) underwent bronchoscopic management instead of resection (reasons not given), 18 (6%) refused recommended surgery, 13 (4%) had conditions that contraindicated surgery, and 68 (22%) had unknown or other reasons for not undergoing resection. Table 3 lists the reasons for not undergoing resection stratified by age category.

Discussion

In this population-based cohort, surgical resection of typical carcinoid tumors is associated with greater OS and DSS than nonsurgical treatment in patients with lymph node-negative biopsy specimens. Patients undergoing lobectomy, sublobar resection, and no surgery had different clinical characteristics, which may influence survival. Specifically, patients who did not undergo surgical resection were older. In addition, patients who underwent sublobar resection were more likely to have

T1 disease than those undergoing lobectomy or no surgery. These and other unmeasured variables may have led to decreased survival rates in patients undergoing nonoperative treatment. Despite this, the DSS at 10 years is still high without resection. Specifically, we found that 10-year DSS was 85% for those undergoing nonsurgical treatment compared with 95% for those undergoing lobectomy.

Patients who underwent no surgery were more likely to have mainstem bronchus involvement than those who underwent surgery. It is possible that the presence of main bronchial involvement was a reason for nonoperative treatment because resection would have involved a more complex procedure than that for a peripheral carcinoid tumor. We did not identify any significant survival difference between patients with a mainstem vs a nonmainstem location undergoing nonsurgical treatment. However, aside from mainstem location, SEER does not provide data on whether a tumor was peripheral or central, which limits the interpretation of data on tumor location and outcome.

The present findings are consistent with a report from our institution describing an average doubling time of close to 7 years for typical carcinoid tumors.³ The present results are also consistent with series reporting no difference in outcomes between sublobar resection and lobectomy for typical carcinoid tumors.^{6,7} The OS and DSS rates described herein are in line with other series of treated pulmonary carcinoid tumor, which show very few cases of disease recurrence among patients with typical carcinoid tumors.^{1,2}

We also observed that black race and older age were associated with a higher rate of disease-specific mortality on multivariate analysis. These findings have not been reported elsewhere to our knowledge, and the reasons for these findings are unclear. Erroneous attribution

TABLE 3] Reasons for No Surgery, Stratified by Age Group

Reason	< 60 y	60-74 y	≥ 75 y	P Value
Surgery not recommended	45 (28.8)	49 (31.4)	62 (39.7)	.0065
Surgery contraindicated	1 (7.7)	2 (15.4)	10 (76.9)	...
Patient died before surgery	0 (0)	0 (0)	1 (100.0)	...
Unknown	22 (35.5)	22 (35.5)	18 (29.0)	...
Patient or guardian refused	5 (27.8)	3 (16.7)	10 (55.6)	...
Recommended, unknown if done	3 (60.0)	1 (20.0)	1 (20.0)	...
Minor surgical procedure ^a	26 (51.0)	15 (29.4)	10 (19.6)	...

Data are presented as No. (%).

^aMinor surgical procedures included local tumor destruction, laser excision, and cryosurgery.

of cause of death to carcinoid tumor is possible, which would account for an increased disease-specific mortality with increasing age. Blacks with carcinoid tumors were less likely than whites to undergo surgery and had a more advanced T stage, two variables that were associated with increased mortality. However, these variables should have been controlled for in multivariate analysis. It is unclear whether higher disease-specific mortality in blacks in multivariate modeling is a result of incompletely controlled confounding variables, such as socioeconomic status or access to care, or whether the biology of carcinoid tumors in blacks is more aggressive. This possible disparity should be addressed with further research. Consistent with prior reports, we also found that the proportion of women with typical carcinoid tumors was double that of men, but sex did not seem to have an effect on prognosis.⁸

The present findings have important implications for counseling patients with incidentally detected carcinoid tumors. Patients who can tolerate surgical resection seem to have a survival benefit compared with no treatment, although the magnitude of that difference is unclear due to selection bias. However, patients with limited life expectancy or those at high risk for surgery may have excellent survival long term without surgical resection. Unfortunately, the data do not provide any insight into the degree to which symptoms may develop over time or into the quality of life of patients who choose not to undergo resection. It is possible that respiratory symptoms develop with time in patients who do not undergo resection of peripheral carcinoid tumors, and this should be factored into the decision-making regarding continued expectant management. Although the data do not have the granularity to address this specific question, patients with endobronchial tumors who are not fit for thoracotomy and surgical resection may be considered for palliation with endobronchial tumor resection. Stereotactic body radiation therapy is another option for treatment of small peripheral lung tumors, although there are few data on its efficacy in pulmonary carcinoid tumors.

This study has several limitations. Patients who did not undergo surgical resection were older and more likely to have comorbidities that precluded surgical resection than patients who underwent surgical resection. We did not have sufficient data on comorbidities to analyze the effect of this variable on survival in this study cohort. Nonetheless, we had data on DSS and reasons for not undergoing surgical resection. DSS may overestimate

true DSS in an indolent disease such as carcinoid tumor in patients with competing risk factors for death. In other words, because patients in this population are much more likely to die of a disease other than their carcinoid tumor, it is difficult to estimate a precise DSS. Therefore, the present estimate of DSS should be interpreted with caution, especially when counseling patients with a life expectancy of at least 5 to 10 years. Moreover, patients who did not undergo surgical resection were unlikely to have mediastinal or hilar lymph nodes sampled and, therefore, may have had occult nodal metastases, leading to understaging. This would have resulted in worse-than-expected DSS among nonsurgical patients and would not have altered the conclusion that survival without surgical resection is still high. The lack of nodal sampling in nonsurgical patients may lead to an underestimation of the true long-term survival. In addition, biopsy specimens from nonsurgical patients were likely to be small in the amount of material for examination, which may have resulted in misclassification of tumor type.^{9,10} In this study, we only included patients given a histologic diagnosis based on, for example, endobronchial forceps biopsy or core needle biopsy and excluded patients given a diagnosis based on cytology or unspecified methods to minimize the possibility of tumor misclassification. Finally, these data came from SEER, a cancer registry database. There are limitations of using SEER, such as a lack of individual case review and variability in treatment patterns. Although a prospective study of expectant management of asymptomatic typical carcinoid tumors would be ideal, such a study is unlikely to ever be organized.

To our knowledge, this study is the largest of untreated lung carcinoid tumors reported to date. It provides important information for counseling patients with asymptomatic typical carcinoid tumors of the lung regarding the outcome with and without surgical resection. We emphasize that patients who are fit for surgery should still undergo resection. Although there was selection bias in the assignment of treatment in this study, the data demonstrate a survival benefit to resection on multivariate analysis. Moreover, the mortality of lobectomy in high-volume centers is approximately 1%, whereas the mortality of sleeve lobectomy and sleeve resection is only about 2%.^{11,12} In patients with limited life expectancy who are symptomatic, these data may be useful regarding palliation of endobronchial lesions with endobronchial therapies. Although surgical resection is probably associated with improved survival, survival without resection is still excellent.

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