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Lung: Short Report

# The Impact of Tumor Size on Node Involvement in Typical Lung Carcinoids

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## ABSTRACT

**BACKGROUND** Observation has been suggested as an alternative to surgical resection for small typical lung carcinoids. We sought to evaluate the potential impact of tumor growth and lymphatic spread during observation by examining predictors of node positivity and the impact of tumor size and node status on survival.

**METHODS** National Cancer Database cases of typical lung carcinoid resections from 2006 to 2016 were analyzed. Predictors of lymph node involvement and survival were determined.

**RESULTS** Overall, 1019 of 8257 patients who underwent typical carcinoid resection had at least 1 positive node (12.3%). The incidence of node positivity among the 921 patients with subcentimeter tumors was 5.4% (n = 50). Increasing tumor size was independently associated with nodal involvement. Patients with nodal involvement had significantly worse 5-year survival (89.5% vs 94.0%; $P < .001$). Increasing tumor size was not associated with worse survival in multivariable analysis, but node positivity did independently predict worse survival.

**CONCLUSIONS** More than 5% of patients with subcentimeter typical carcinoids of the lung have nodal metastases, and node involvement is an independent predictor of worse survival, whereas tumor size is not. These data suggest that even patients with small tumors should generally undergo resection when diagnosed.

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The incidence of lung neuroendocrine neoplasms has risen during the past 50 years.[1] On histologic evaluation, these tumors vary from well or moderately differentiated (typical and atypical carcinoids) to poorly differentiated (small cell carcinoma and large cell neuroendocrine carcinoma).[2] Typical and atypical carcinoids have much better prognosis than the poorly differentiated subtypes but are still considered incurable once they progress to unresectable metastatic disease.[1,3] The recommended treatment of typical carcinoids in the lung is anatomic resection with systematic node dissection.[4]

Watchful radiologic follow-up has been suggested as an alternative to surgical resection for small carcinoids.[5] However, this has an inherent risk of tumor growth and, more important, lymphatic and distant spread during the observation period. This study was undertaken to quantify the relationship between tumor size and node involvement and the impact of size and node status on

### IN SHORT

- More than 5% of patients with subcentimeter typical carcinoids of the lung have nodal metastases. Node involvement is an independent predictor of worse survival, whereas tumor size is not.
- These data suggest that even patients with small tumors should generally undergo resection with lymph node dissection when diagnosed.

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survival to better understand the potential implications of growth and spread during an observation period.

## PATIENTS AND METHODS

The National Cancer Database captures an estimated 70% of newly diagnosed cancers in the United States and includes >1500 facilities and >30 million records. Given the deidentified nature of the National Cancer Database, this retrospective analysis was considered exempt by the Stanford University institutional review board.

Patients who underwent wedge resection, segmentectomy, lobectomy, bilobectomy, or pneumonectomy for typical lung carcinoid from 2006 to 2016 were analyzed. Patients without an exact tumor size recorded or who had no nodes pathologically examined were excluded. Patients with prior malignant neoplasms, those who received chemotherapy or radiation therapy before surgical resection, and those with distant metastatic disease on initial clinical staging or with missing survival data were excluded (Supplemental Figure 1).

Patients were stratified by node involvement, and characteristics and outcomes were compared. The relationship of node involvement and tumor size was evaluated, and independent predictors of node positivity were estimated with a multivariable logistic regression model. Sensitivity analysis was performed on patients with clinical N0 status to address the possibility that clinical node status could influence the extent of surgical resection and node dissection.

Survival was assessed with the Kaplan-Meier method, log-rank test, and Cox proportional hazards modeling. Variables chosen a priori for inclusion in the Cox model were patient, treatment, and tumor characteristics previously shown or clinically accepted as likely to be associated with survival. The Cox model was adjusted for clustering by hospital by including specific facility in the model as a random effect.

Analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing). Baseline characteristics between groups were compared with Wilcoxon rank sum test for continuous variables and Pearson $\chi^2$ test for discrete variables. Fisher exact test was used for discrete variables with <5 outcomes.

**TABLE 1 Baseline Characteristics of Patients Undergoing Resection of Typical Lung Carcinoid**

| Variable | Overall Cohort (N = 8257) | Node Negative (n = 7238) | Node Positive (n = 1019) | *P* Value |
|---|---|---|---|---|
| Age, y | 59 (49-68) | 60 (50-68) | 56 (45-66) | <.001 |
| Female sex | 5751 (69.6) | 5075 (70.1) | 676 (66.3) | .016 |
| Race | | | | .22 |
| White | 7494 (91.8) | 6586 (92) | 908 (90.3) | |
| Black | 527 (6.5) | 451 (6.3) | 76 (7.6) | |
| Other | 145 (1.8) | 124 (1.7) | 21 (2.1) | |
| Charlson Comorbidity Index | | | | .002 |
| 0 | 5520 (67.9) | 4790 (67.2) | 730 (72.7) | |
| 1 | 2104 (25.9) | 1877 (26.3) | 227 (22.6) | |
| 2+ | 505 (6.2) | 458 (6.4) | 47 (4.7) | |
| Education above median | 4610 (61.7) | 4043 (61.8) | 567 (61.1) | .71 |
| Income above median | 4769 (63.9) | 4189 (64.1) | 580 (62.5) | .38 |
| Insured | 7931 (97.3) | 6956 (97.3) | 975 (96.9) | .50 |
| Facility type | | | | .068 |
| Community program | 294 (4.9) | 259 (4.9) | 35 (5) | |
| Comprehensive community program | 2631 (43.5) | 2352 (44.1) | 279 (39.5) | |
| Research/academic program | 3117 (51.6) | 2725 (51.1) | 392 (55.5) | |
| Tumor size, cm | | | | <.001 |
| 0.1-1 | 921 (11.2) | 871 (12) | 50 (4.9) | |
| 1-2 | 3485 (42.2) | 3184 (44) | 301 (29.5) | |
| 2-3 | 2197 (26.6) | 1879 (26) | 318 (31.2) | |
| 3-5 | 1309 (15.9) | 1046 (14.5) | 263 (25.8) | |
| 5-7 | 256 (3.1) | 188 (2.6) | 68 (6.7) | |
| >7 | 89 (1.1) | 70 (1) | 19 (1.9) | |
| Clinical N stage | | | | <.001 |
| 0 | 5043 (61.1) | 4599 (63.5) | 444 (43.6) | |
| 1 | 310 (3.8) | 95 (1.3) | 215 (21.1) | |
| Not recorded | 2904 (35.2) | 2544 (35.1) | 360 (35.3) | |
| No. of examined nodes | 7 (4-11) | 6 (3-11) | 9 (6-14) | <.001 |
| Extent of resection | | | | <.001 |
| Lobectomy | 6809 (82.5) | 5933 (82) | 876 (86) | |
| Pneumonectomy | 370 (4.5) | 278 (3.8) | 92 (9) | |
| Sublobar resection | 1078 (13.1) | 1027 (14.2) | 51 (5) | |
| Positive margin | 248 (3) | 190 (2.6) | 58 (5.8) | <.001 |

Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range).

## RESULTS

There were 8257 patients who met inclusion criteria. Overall, 1019 patients (12.3%) had at least 1 positive node. Baseline patient and tumor characteristics are shown in Table 1. Specific nodal station involvement was recorded for 733 of the patients with N+ disease: 488 (66.6%) had N1 disease, 241 (32.9%) had N2 disease, and 4 (0.5%) had N3 disease.

The rate of node positivity by tumor size is shown in Figure 1A; even subcentimeter tumors had a node positivity rate of 5.4%, whereas the node positivity rate was >20% in tumors >3 cm. In multivariable logistic regression modeling, increasing tumor size was an independent predictor of node positivity (Table 2). Younger age and increasing extent of surgical resection also had statistically significant associations with nodal involvement. In the subset analysis of patients with cN0 disease, baseline characteristics were generally similar (Supplemental Table 1). The rate of nodal positivity was 8.8%, and nodal positivity in subcentimeter tumors was 4.0%. The rate of nodal positivity increased with tumor size (Figure 1B), and

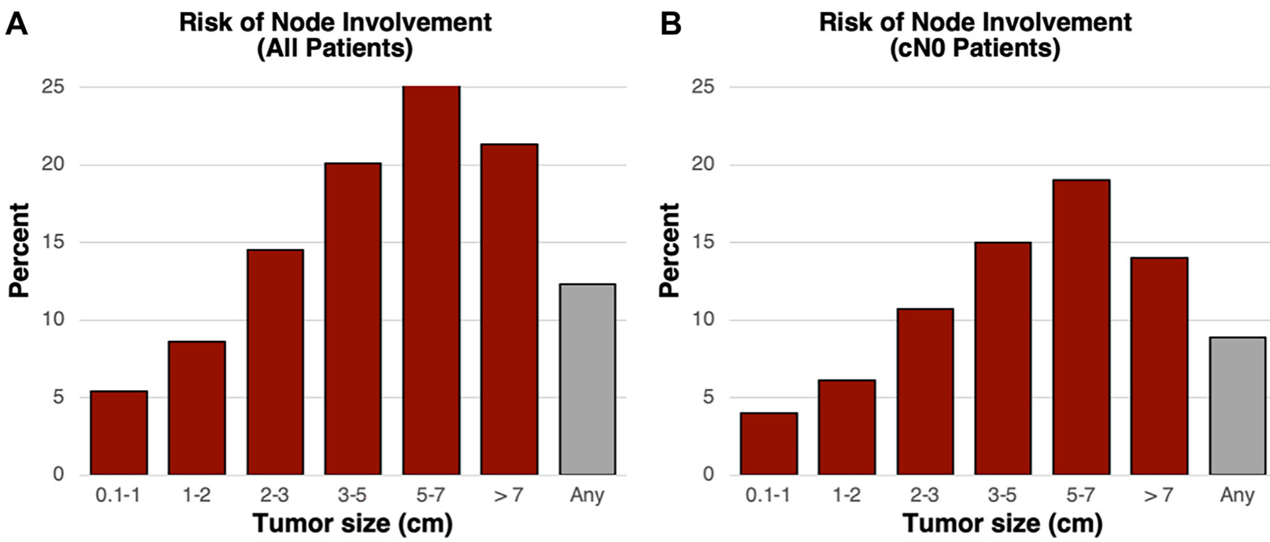


**FIGURE** Risk of node involvement in typical carcinoid tumors of the lung, stratified by tumor size, shown for (A) the entire cohort and (B) the subset of patients with cN0 tumors.

increasing tumor size remained an independent predictor of nodal positivity in multivariable analysis (Supplemental Table 2).

Five-year survival of the cohort was 93.4%. Patients with nodal involvement had significantly worse survival (Supplemental Figure 2). Five-year survival for node-negative vs node-positive patients was 94.0% vs 89.5% ($P < .001$). In multivariable analysis, increasing tumor size was not associated with worse survival, but node positivity did independently predict worse survival (Table 3). Patients with pathologic N2/N3 disease had significantly worse survival than patients with pathologic N1 disease (5-year survival, 87.2% vs 92.2%; $P = .012$; Supplemental Figure 3).

## COMMENT

In this analysis of cases of typical lung carcinoid from the National Cancer Database, we sought to determine predictors of lymph node positivity to delineate the relationship of tumor size and lymph node status on patient survival and to determine the potential consequences of observation of small typical carcinoids. The rate of lymph node involvement in this large cohort of >8000 patients was 12.3% overall, did indeed increase with tumor size, and was >5% even in subcentimeter tumors. Although the overall 5-year survival for the entire cohort was >90%, node positivity was associated with significantly worse survival. Interestingly, we found that increasing tumor size did not independently predict worse survival. The clinical implication of these findings is that observation of patients with known typical carcinoid tumors will increase the likelihood of nodal metastasis if the tumor grows during observation, which ultimately portends a worse prognosis. These results can inform the treatment decision-making process when patients are found to have small carcinoid tumors.

The optimal extent of surgical resection needed for carcinoid tumors has been a matter of study.[6,7] Overall, less aggressive surgical management with sublobar

**TABLE 2** Logistic Regression Model Showing Predictors of Node Positivity for Patients Undergoing Resection of Typical Carcinoid Tumors of the Lung

| Variable | Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Age (per decade) | 0.91 | 0.86-0.95 | <.001 |
| Female sex | 0.96 | 0.82-1.12 | .57 |
| Race (reference: White) | | | |
| Black | 1.04 | 0.78-1.37 | .81 |
| Other | 1.24 | 0.76-2.03 | .39 |
| Insured (reference: uninsured) | 1.18 | 0.78-1.80 | .43 |
| Charlson Comorbidity Index (reference: 0) | | | |
| 1 | 0.91 | 0.76-1.08 | .26 |
| 2+ | 0.84 | 0.60-1.17 | .29 |
| Income above median | 0.95 | 0.80-1.14 | .58 |
| Education above median | 1.03 | 0.87-1.23 | .73 |
| Tumor size, cm (reference: 0.1-1) | | | |
| 1-2 | 1.75 | 1.24-2.48 | .002 |
| 2-3 | 2.87 | 2.02-4.07 | <.001 |
| 3-5 | 3.77 | 2.64-5.40 | <.001 |
| 5-7 | 5.30 | 3.41-8.27 | <.001 |
| >7 | 3.56 | 1.86-6.81 | <.001 |
| Extent of resection (reference: lobectomy) | | | |
| Pneumonectomy | 1.69 | 1.28-2.22 | <.001 |
| Sublobar resection | 0.49 | 0.36-0.66 | <.001 |

**TABLE 3 Cox Proportional Hazards Model of Factors Independently Associated With Survival After Resection of Typical Carcinoid Tumors of the Lung**

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Age (per decade) | 1.99 | 1.86-2.13 | <.001 |
| Female sex | 0.62 | 0.54-0.72 | <.001 |
| Race (reference: White) | | | |
| Black | 1.04 | 0.78-1.37 | .81 |
| Other | 1.24 | 0.76-2.03 | .39 |
| Insured (reference: uninsured) | 1.18 | 0.78-1.80 | .43 |
| Positive nodes | 1.81 | 1.49-2.20 | <.001 |
| Charlson Comorbidity Index (reference: 0) | | | |
| 1 | 1.48 | 1.27-1.72 | <.001 |
| 2+ | 1.76 | 1.38-2.25 | <.001 |
| Income above median | 0.95 | 0.80-1.14 | .58 |
| Education above median | 1.03 | 0.87-1.23 | .73 |
| Tumor size, cm (reference: 0.1-1) | | | |
| 1-2 | 0.80 | 0.63-1.00 | .05 |
| 2-3 | 0.82 | 0.64-1.05 | .10 |
| 3-5 | 1.12 | 0.86-1.47 | .40 |
| 5-7 | 1.28 | 0.84-1.95 | .25 |
| >7 | 1.12 | 0.59-2.11 | .70 |
| Positive margin | 0.89 | 0.58-1.38 | .60 |
| Extent of resection (reference: lobectomy) | | | |
| Pneumonectomy | 2.11 | 1.58-2.84 | <.001 |
| Sublobar resection | 1.00 | 0.81-1.24 | .90 |
| Adjuvant radiation | 1.21 | 0.65-2.27 | .60 |
| Adjuvant chemotherapy | 2.34 | 1.52-3.62 | <.001 |

resection to spare lung parenchyma is considered potentially acceptable for peripheral tumors <2 cm.[4] Whereas sublobar resection may be appropriate if it is technically feasible to achieve complete resection, our findings suggest that some degree of pathologic lymph node evaluation should be performed. Indeed, others have shown a significant rate of upstaging in patients whose clinical stage did not initially suggest lymph node involvement,[6,8] further underscoring the need for lymph node evaluation in all cases (with consideration of extensive lymph node dissection if nodal involvement is demonstrated) as nonsurgical therapies to treat lymph node involvement have limited efficacy. Although several systemic treatment strategies have been used in metastatic lung carcinoids, including somatostatin analogs, everolimus, traditional cytotoxic chemotherapy, and novel targeted agents such as peptide receptor radioligand therapy,[5] there is a paucity of high-quality data to guide indications for these therapies. Their use is typically limited to symptomatic carcinoid syndrome or significant progression of tumor burden. Thus, resection of all disease—including any lymph node involvement—should be pursued aggressively.[9]

Our study is subject to limitations inherent in retrospective database studies, including selection bias in treatment and confounding by variables not controlled for in the analysis. Specifically, there is likely to be selection bias in how aggressively a surgeon approaches a given resection, which may include factors such as patient age and baseline health, imaging characteristics of the tumor or nodal stations, and peripheral vs central location of the tumor. Indeed, we found that younger age and greater extent of resection (pneumonectomy or lobectomy compared with sublobar resection) were independently associated with node involvement. This may indicate that when more aggressive surgical resection is performed—because the patient is younger, the surgeon believes it is preferred from an oncologic standpoint, or this is anatomically necessary on the basis of tumor location—better nodal assessment may be inherently obtained. In addition, by including patients with only 1 lymph node examined, we may underestimate occult node involvement in those patients. Similarly, patients undergoing sublobar resection may have inadequate staging of hilar nodes. Conversely, the exclusion from analysis of patients who did not have any nodes pathologically examined may result in an overestimation of node involvement. Our study also cannot provide comparisons with patients managed nonoperatively. However, even considering these limitations, this study clearly highlights the risk of lymph node involvement with typical pulmonary carcinoid tumors. The strength of our study is that by analyzing a national database containing a large number of cases generalizable across a wide spectrum of institutions, patients, and surgeons and by focusing on typical carcinoid histologic features only, we provide clinically relevant data that can assist surgeons and oncologists faced with navigating the risks and benefits of resection in these patients.

In conclusion, >5% of patients with subcentimeter typical carcinoids have lymph node involvement, and the risk of node involvement increases with increasing tumor size. Node involvement is an independent predictor of worse survival, but interestingly, tumor size is not. Given that even small tumors can have nodal involvement, and nodal involvement predicts worse survival, these results support a management strategy of early resection with thorough node evaluation even in patients with small tumors, as opposed to observation, to avoid converting a curable cancer to an incurable chronic disease with decreased overall patient survival.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2023.07.016] on http://www.annalsthoracicsurgery.org.

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## DISCLOSURES

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## REFERENCES


1. Shah S, Gosain R, Groman A, et al. Incidence and survival outcomes in patients with lung neuroendocrine neoplasms in the United States. *Cancers (Basel)*. 2021;13:1753.

2. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10:1243-1260.

3. Yao JC, Hassan M, Phan A, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26:3063-3072.

4. Singh S, Bergsland EK, Card CM, et al. Commonwealth Neuroendocrine Tumour Research Collaboration and the North American Neuroendocrine Tumor Society guidelines for the diagnosis and management of patients with lung neuroendocrine tumors: an international collaborative endorsement and update of the 2015 European Neuroendocrine Tumor Society expert consensus guidelines. *J Thorac Oncol*. 2020;15:1577-1598.

5. Baudin E, Caplin M, Garcia-Carbonero R, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32:439-451.

6. Brown LM, Cooke DT, Jett JR, David EA. Extent of resection and lymph node assessment for clinical stage T1aN0M0 typical carcinoid tumors. *Ann Thorac Surg*. 2018;105:207-213.

7. Bachman KC, Worrell SG, Linden PA, Gray KE, Argote-Greene LM, Towe CW. Wedge resection offers similar survival to segmentectomy for typical carcinoid tumors. *Semin Thorac Cardiovasc Surg*. 2022;34:293-298.

8. Kneuertz PJ, Kamel MK, Stiles BM, et al. Incidence and prognostic significance of carcinoid lymph node metastases. *Ann Thorac Surg*. 2018;106:981-988.

9. Gosain R, Groman A, Yendamuri SS, Iyer R, Mukherjee S. Role of adjuvant chemotherapy in pulmonary carcinoids: an NCDB analysis. *Anticancer Res*. 2019;39:6835-6842.