Examination of Factors Associated with Lymph Node Metastases in Lung Carcinoids

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INTRODUCTION

- Pulmonary carcinoid tumors, including typical and atypical carcinoids, have a decreased incidence of lymph node (LN) and distant metastases compared to their high-grade counterparts.[1]
- LN metastases confer worse prognosis, especially for patients with atypical carcinoids.[2]
- For resectable lung carcinoids, complete anatomic surgical resection and systematic nodal dissection are the standard of care.[3]
- There is limited data to guide the postoperative management of patients with lung carcinoids found to have LN metastases at the time of definitive surgical resection.
- This study aimed to (i) characterize the clinical, radiographic, surgical and pathologic factors associated with LN metastases in typical and atypical lung carcinoids at surgical resection and (ii) describe the postoperative management of patients with LN metastases.

METHODS

- In this retrospective study, 101 patients were identified who underwent surgical resection for lung carcinoids at Stanford University from 1998-2017.
- Histology was classified according to 2015 WHO Classification.[4]

2015 WHO Criteria	Typical Carcinoid, ≥5 mm	Atypical Carcinoid
Necrosis	No	Focal or Multifocal
Mitoses per 2 mm²	<2	2–10

- All cases (except 8 for which the specimen was not available) underwent re-review by a single pathologist (G.B.). A minimum of 1 slide per case was reviewed; for tumors near the mitoses count cutoffs, 2-3 slides were reviewed and the mean was used for determining the mitotic rate, rather than the single highest rate.
- LN map and staging was assessed using AJCC TNM staging version 7 (Figure 1).[5]
- Data was abstracted from the electronic medical record (Table 1). These features were examined between patients with and without LN metastases using the Wilcoxon test (continuous variables) and Fisher's exact test (categorical variables). A multivariate logistic regression model was used to examine association of LN metastases and pre-determined factors of clinical interest (Table 2) .

RESULTS

83% N0* Nodal Status (N=84)

17% N1/N2⁺ Nodal Status (N=17)

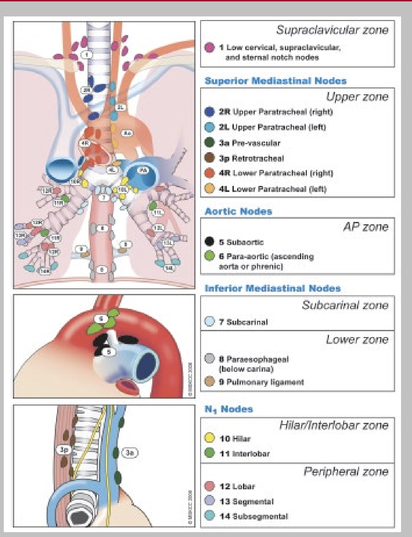

Figure 1 (ABOVE) Lymph node metastases in cohort. Image from American Cancer Society Pamphlet (© Memorial Sloan-Kettering Cancer Center, 2009.) *If no LNs sampled during surgical resection, considered N0 (n=3). ⁺AJCC version 7 nodal definitions: N1 = metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension; N2 = metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes. There were no patients with N3 LN metastases.

DEMOGRAPHICS	N0	N1/N2	P-value
Age, median-years (range)	58	56	0.65
Race (White/Non-White)[1]	56/28	13/4	0.57
Sex (M/F)	20/64	4/13	1.0
Smoking Status (Current/Former/Never)	**3/24/57**	**0/5/12**	**<0.001**
Prior Malignancy (Y/N)	18/66	7/10	0.12
Second Primary Cancer (Y/N)	4/80	0/17	1.0
Functional Syndrome (Y/N/UNK)[2]	9/46/29	2/8/7	0.55
IMAGING			
Preoperative Imaging[3]			
CT	73	15	1.0
18FDGPET	52	11	1.0
SSTR	12	6	0.07
Suspicion of LN Mets (Y/N)	10/74	5/12	0.13
Tumor Site (Central/Peripheral)	49/35	8/9	0.43
Tumor Laterality (R/L)	56/28	9/8	0.40
SURGERY			
Approach (Thoracotomy/VATS/Robotic)	59/23/2	14/3/0	0.69
Extent (Lobectoy/Sublobar Resection)	73/11	16/1	0.68
Mediastinal Lymph Node Dissection (Y/N)[4]	**81/3**	**17/0**	**<0.001**
No. of LN Stations Sampled median (range)	4 (0-10)	4 (1-8)	0.91
No. of LNs Sampled median (range)	9 (0-30)	9 (1-32)	0.81
PATHOLOGIC FEATURES			
Lung Carcinoid (Typical/Atypical)	76/8	14/3	0.39
Tumor Size median cm (range)	2 (0.7-9)	2.5 (0.7-4.5)	0.85
Mitotic Index (Low/Int)[5]	80/4	14/3	0.09
Necrosis (Y/N)	7/77	2/15	0.65
Margin (Pos/Neg)	2/82	2/15	0.13
Recurrence (Y/N)	**5/79**	**5/12**	**0.01**

Table 1 (RIGHT): Comparing features across nodal status in lung carcinoids. **1.** Non-white race= 11 Asian (11%), 15 Not Reported (15%), 9 Other (10%); **2** Carcinoid Syndrome was detected in 10 patients and Cushing's Syndrome in 2 patients; **3.** 18FDGPET =Fludeoxyglucose Positron Emission Tomography; CT = Computed Tomography; SSTR imaging = Somatostatin Receptor imaging includes OctreoScan = Octreotide Scan and 68Ga-DOTATATE PET = 68 Gallium-DOTATATE Positron Emission Tomography. 8 had OctreoScan, 11 had 68Ga-DOTATATE PET scans, and 2 had both. **4.** At least one mediastinal lymph node station was sampled. **5**. Low= <2 mitoses/2mm²; Intermediate= 2-10 mitoses/2mm²

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RESULTS CONTINUED

- Of the 101 patients, 90 (89%) had typical carcinoids and 11 (11%) had atypical carcinoids.
- Seventeen (17%) patients had at least one positive LN, including 9 with N1 and 8 with N2 disease.
- None of the patients with LN metastases received adjuvant therapy.
- In a univariate analysis, smoking status and performance of mediastinal LN dissection was significantly associated with LN metastases.
- In a multivariate analysis, there was a trend towards performance of SSTR imaging and LN involvement (N0 14% vs. N1/N2 35%; Odds Ratio 3.18, p=0.06). Other variables in our multivariate regression, including lung carcinoid histotype, number of lymph node stations sampled, mitotic index, and presence of necrosis, did not reach significance .

Table 2. Factors of clinical interest associated with lymph node Involvement in multivariate logistic regression

Variables	Odds Ratio	95% Confidence Interval	P-value
Lung Carcinoid Histotype (Atypical Carcinoid)	0.46	0.018 – 11.75	0.64
Number of Lymph Node Stations Sampled	1.03	0.80 – 1.32	0.81
Performance of SSTR Imaging (OctreoScan or 68Ga-DOTATATE PET)	3.18	0.96 – 10.5	0.06
Mitotic Index	6.23	0.41 – 93.9	0.18
Presence of Necrosis	1.64	0.13 – 21.0	0.70

Definitions: SSTR = Somatostatin Receptor; OctreoScan = Octreotide Scan; 68Ga-DOTATATE PET = 68 Gallium-DOTATATE Positron Emission Tomography

CONCLUSIONS

- In the Stanford University dataset of 101 patients with typical and atypical lung carcinoids, smoking status and performance of mediastinal LN dissection was significantly associated with LN metastases at surgical resection. Recurrence was also associated with LN metastases; however, recurrence was not analyzed as a time-to-event category and some recurrences may not have been documented due to loss of follow-up.
- There was a trend towards an association between performance of preoperative somatostatin receptor (SSTR) imaging (i.e., OctreoScan and 68-Gallium DOTATATE PET) and LN metastases in both univariate and multivariate analyses. SSTR imaging is an emerging preoperative staging strategy[6] and may be more adept at identifying occult LN metastases and influence breadth of LN sampling at the time of surgery.
- Limitations of our study include its retrospective nature; the limited sample size, with only 17 patients with LN metastases; the assumption that patients who did not undergo LN sampling at time of surgery had no LN metastases; and the definition of mediastinal lymph node dissection including those patients that may have had less than the recommended optimal number of stations dissected.
- Further work is required to define the postoperative management for lung carcinoid tumors with LN metastases.

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