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Surgical management of pulmonary carcinoid tumors: sublobar resection versus lobectomy

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Lobectomy;
Wedge

Abstract

BACKGROUND: Surgical resection of bronchopulmonary carcinoid tumors can be curative and remains the primary treatment modality. There are limited data to delineate the optimal extent of resection for this disease.

METHODS: A retrospective review of the 3,270 patients diagnosed with typical and atypical carcinoid tumors between 2000 and 2007 in the Surveillance Epidemiology and End Results registry was performed.

RESULTS: The mean follow-up period was 46 months (range, 1–95 mo). Overall survival (OS) and disease-specific survival at 5 years was 80% and 90%, respectively. The mean OS was slightly better in the lobectomy group compared with those undergoing sublobar resection (86 vs 83 mo; $P = .008$). After adjusting for age, this finding was no longer present ($P = .513$). By using multivariate analysis, sublobar resection was noninferior to lobectomy with regard to disease-specific survival and OS ($P <$ .05).

CONCLUSIONS: Compared with lobectomy, sublobar resection is associated with noninferior survival in patients with typical carcinoid of the lung.

Primary carcinoid tumors of the lung are relatively uncommon neuroendocrine neoplasms, accounting for .5 to 3% of resected lung cancers. They are classified into 2 distinct categories: typical carcinoid (TC) and atypical carcinoid (AC) tumors, which have a worse prognosis. The AC subgroup, accounting for 16% of all carcinoids, was first described in 1982,[1] and its definition, based on the presence of a mitotic index between 2 and 10, necrosis, or architectural disruption, was refined in 1998.[2]

Although both subtypes share the 7th edition American Joint Committee on Cancer staging system with non–small-cell lung cancer (NSCLC),[3] they show comparatively benign behavior with an overall survival of 92% to 97% for TC and 66% to 78% for AC.[4,5] Furthermore, nodal involvement and metastasis is rare with only 13% of all carcinoids being node positive.[3] Consequently, many investigators have advocated limited resection in these patients,[6–9] but many believe lobectomy is indicated.[10–12] In NSCLC, sublobar resection likely offers lower perioperative mortality relative to lobectomy,[13] but the comparative oncologic outcome between the two remains an area of controversy.[14–16]

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Table 1 Demographics and staging summary

	N	%
Age, y		
<60	1,446	44.2
60–75	1,177	36.0
>75	647	19.8
Race		
Black	209	6.4
Other	91	2.8
Unknown	17	.5
White	2,953	90.3
Sex		
Female	2,241	68.5
Male	1,029	31.5
Histology		
Typical carcinoid	3,084	94.3
Atypical carcinoid	186	5.7
Stage		
IA	1,675	56.7
IB	475	16.1
IIA	189	6.4
IIB	147	5.0
IIIA	185	6.3
IIIB	13	.4
IV	268	9.1
Surgery		
Extended resection	104	3.2
Lobectomy	1,669	51.2
Local ablation	18	.6
No surgery	521	16.0
Pneumonectomy	122	3.7
Sleeve	35	1.1
Sublobar	784	24.1

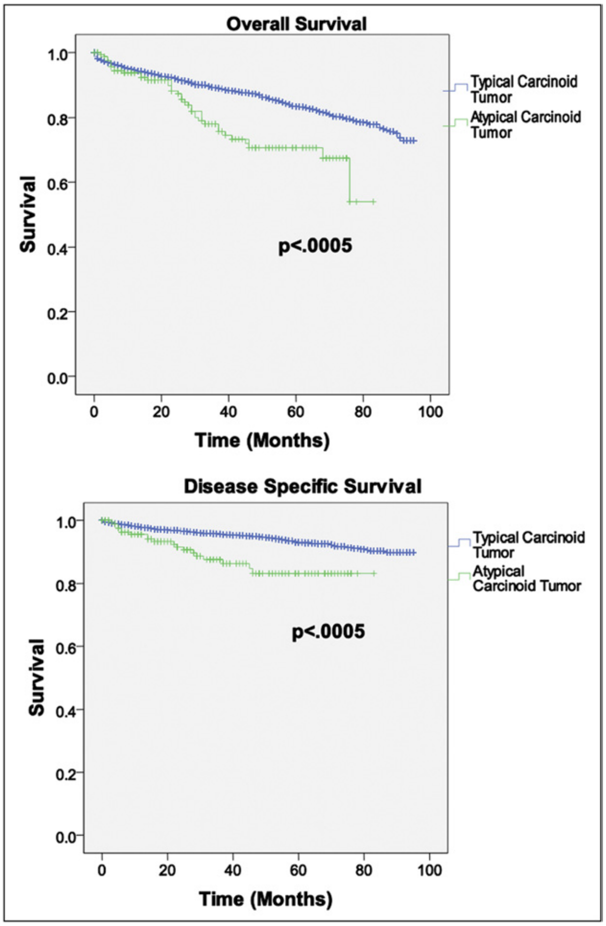

Figure 1 Comparison of disease-specific and overall survival in typical and atypical carcinoid patients.

Table 2 Effect of histology on stage

	Typical carcinoid		Atypical carcinoid		Mann–Whitney U P value
	N	%	N	%	
T-stage					
1a	1,327	49.5	53	32.9	<.0005
1b	446	16.6	39	24.2	
2a	557	20.8	36	22.4	
2b	88	3.3	8	5.0	
3	194	7.2	16	9.9	
4	68	2.5	9	5.6	
N-stage					
0	2,584	88.5	111	62.4	<.0005
1	165	5.7	25	14.0	
2	165	5.7	37	20.8	
3	6	.2	5	2.8	
M-stage					
0	2,842	92.2	160	86.0	.002
1a	140	4.5	10	5.4	
1b	102	3.3	16	8.6	
Overall stage					
IA	1,605	57.8	70	39.8	<.0005
IB	455	16.4	20	11.4	
IIA	168	6.1	21	11.9	
IIB	139	5.0	8	4.5	
IIIA	159	5.7	26	14.8	
IIIB	8	.3	5	2.8	
IV	242	8.7	26	14.8	

With regard to carcinoid tumors, few large case series exist to delineate the optimal extent of resection. Here, we use a large, multicenter database to compare disease-specific and overall survival in patients undergoing lobar and sublobar resection. Subgroup analysis was conducted to determine if certain situations (eg, nodal positivity or atypical histology), dictated a lobectomy.

Methods

With University of Louisville Institutional Review Board approval, the Surveillance Epidemiology and End Results (SEER) 17 database was reviewed, searching for typical and atypical carcinoid tumors in the lung (SEER histology codes 8240/3 and 8240/9) diagnosed between 2000 and 2007. This time frame was chosen because the classification of atypical carcinoid tumors was standardized in 1998.[2]

Typical carcinoids with a grade listed as greater than 1 and atypical carcinoids with a grade greater than 2 were excluded to reduce the chance of incorporating misclassified high-grade neuroendocrine tumors into the data. Patients with carinal tumors, unclear tumor extent, and an unknown m-stage also were excluded (extent of disease codes 25 and 99; collaborative staging scheme extent codes 11, 23, 25, 98, and 99, and metastatic codes 98 and 99). A total of 3,270 patients were identified for survival analysis. It was possible to completely stage 2,952 patients from the available data. Of the patients incompletely staged, 209 had an unknown tumor size, and 82 had an unknown nodal status. Both T and N stage were unavailable in an additional 27 patients. Statistical analysis was performed using SPSS 19.0 (New York, NY). Univariate and multivariate survival analyses were performed using the Kaplan method and Cox proportional hazards regression. Noninferiority survival analysis between lobectomy and sublobar resection was conducted using the methods outlined by Tunes da Silva et al.[17] A cumulative survival margin of 5% was assumed to be the minimum for clinical relevance. No error allocation was performed to account for multiple measurements.

Table 3 Demographics and staging by surgery type

	No surgery		Pneumonectomy		Sublobar		Lobectomy		Sublobar vs lobectomy
	N	%	N	%	N	%	N	%	*P* value
Age, y									
<60	75	22	86	75	246	33	862	53	<.0005
60–75	114	33	25	22	329	44	557	34	
>75	157	45	4	3	168	23	212	13	
Sex									
Female	233	67	64	56	552	74	1,094	67	<.0005
Male	113	33	51	44	191	26	537	33	
Race									
Black	35	10	12	10	45	6	87	5	.41
Other	10	3	5	4	23	3	34	2	
Unknown	2	1	0	0	4	1	8	0	
White	299	86	98	85	670	90	1,502	92	
Histology									
Typical carcinoid	325	94	107	93	718	97	1,537	94	.013
Atypical carcinoid	21	6	8	7	25	3	94	6	
T-stage									
1a	103	40	14	13	492	73	704	45	<.0005
1b	50	20	11	10	63	9	334	21	
2a	42	16	52	47	54	8	385	25	
2b	13	5	12	11	8	1	53	3	
3	29	11	15	14	43	6	68	4	
4	19	7	7	6	16	2	19	1	
N-stage									
0	251	84	76	66	681	97	1,430	89	<.0005
1	7	2	21	18	7	1	122	8	
2	38	13	17	15	15	2	63	4	
3	2	1	1	1	0	0	0	0	
Overall stage									
IA	123	54	18	16	517	80	948	61	<.0005
IB	33	14	33	30	47	7	318	21	
IIA	8	3	24	22	11	2	136	9	
IIB	20	9	12	11	38	6	63	4	
IIIA	37	16	21	19	30	5	81	5	
IIIB	8	3	3	3	0	0	2	0	

Results

Demographics

Most patients were white (90.5%), female (68.7%), and had stage IA or IB disease (72.8%). Demographic and pathologic information is summarized in Table 1. The majority of patients 1,669 (51.2%) received a lobectomy with 784 (24.1%) undergoing wedge resection or segmentectomy. There were 521 patients (13%) who did not undergo curative resection. The remaining patients underwent local tumor ablation, pneumonectomy, bronchoplasty, or an extended resection. The median follow-up period was 45 months (range, 1–96 mo). Overall survival (OS) at 2, 5, and 7 years was 89.6%, 80.1%, and 73.5%, respectively. Disease specific survival (DSS) at 2, 5, and 7 years was 94.9%, 90.1%, and 87.3%, respectively.

Effect of histology on stage and prognosis

Only a small fraction of the tumors (5.7%) were characterized as AC. AC tumors on average had higher T, N, M, and overall stages ($P < .0005$), with 37.6% of AC patients having nodal metastases compared with just 11.4% in the TC cohort (Table 2). OS and DSS was significantly worse in the AC patients ($P < .0005$) (Fig. 1).

Effect of surgery type on survival

DSS and OS were evaluated in patients undergoing sublobar resection, lobectomy, pneumonectomy, and in those patients not undergoing surgery. Pneumonectomy patients were grouped separately because of the higher perioperative and long-term mortality associated with the procedure in NSCLC.[18–20] Patients with M1a and M1b disease and those undergoing local tumor destruction, bronchoplasty, or extended resection were excluded from this portion of the analysis. A comparison of the demographic and pathologic characteristics of the patients stratified by surgery type is shown in Table 3. Pairwise comparisons were made between the sublobar and lobectomy groups. Patients were older in the sublobar resection group ($P < .0005$) and had a lower T-stage, N-stage, and overall stage ($P < .0005$) compared with the lobectomy group.

Patients undergoing all 3 types of surgery possessed superior DSS and OS compared with patients not undergoing surgery (Fig. 2). Sublobar resection and lobectomy showed better DSS then pneumonectomy patients ($P = .008$ and $P = .002$, respectively). Compared with lobectomy, sublobar resection was statistically noninferior at 2 and 5 years ($P < .00001$). This comparison approached statistical noninferiority at 7 years (93.6% vs 91.9%; $P = .070$). Lobectomy patients had a statistically significantly better OS than sublobar resection patients (mean survival, 86 vs 83 mo; $P = .008$). However, when controlling for age, this difference in OS disappeared ($P = .513$). Tests for noninferiority between sublobar resection and lobectomy were only significant at 2 and 5 years for the younger than age 60 years strata ($P < .001$) and at 2 years for the age 60 to 75 years strata ($P = .002$) (Fig. 3).

The effect of extent of resection on DSS then was analyzed in patients stratified by histology, T-stage, and nodal status. Patients with TC undergoing sublobar resection had noninferior DSS compared with lobectomy at 2 and 5 years ($P < .00001$), and approached significance at 7 years ($P = .123$). In the AC group, no DS mortality occurred in patients undergoing sublobar resection (n = 25). Consequently, statistical comparisons could not be performed, but there did appear to be a trend toward noninferior survival compared with lobectomy (Fig. 4).

With regard to T-stage, sublobar resection was significantly noninferior at 2 and 5 years in the T1 and T2 groups, respectively ($P < .05$), and at 2 years in the T3 group ($P = .027$). At 5 and 7 years in the T3 patients, and at 2, 5, and 7 years in the T4 patients, DSS in sublobar resection and lobectomy patients was neither significantly different nor

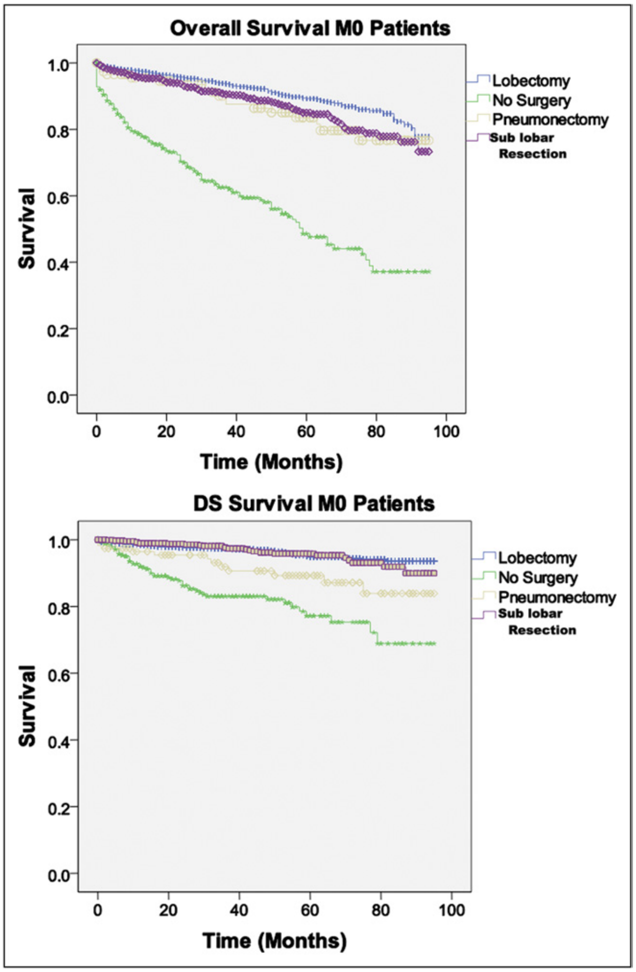

Figure 2 Sublobar resection patients have statistically noninferior DS survival compared with patients undergoing lobectomy. Overall survival was slightly worse in the sublobar resection patients. Patients undergoing any type of surgery had better DSS and OS compared with the nonsurgical patients.

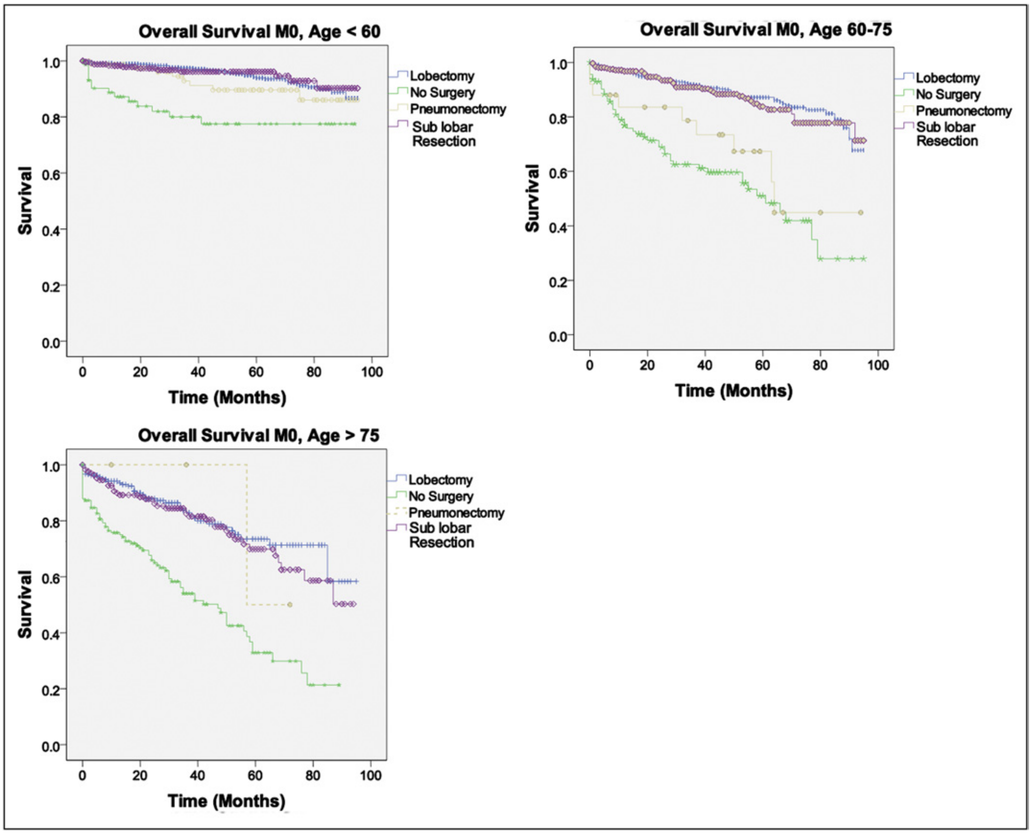

Figure 3 No overall survival advantage was found in lobectomy patients when the patients were stratified by age ($P = .513$).

noninferior (Fig. 5). In node-negative patients, sublobar resection was noninferior at 2 and 5 years, but not at 7 years ($P \geq .0005$ and $P = .212$). In node-positive patients, DSS after sublobar resection was neither statistically different nor noninferior compared with lobectomy (Fig. 6).

Multivariate analysis

Univariate analysis regarding the effects of demographics, stage, and treatment on DSS and OS was conducted using Cox proportional hazards regression. Multivariate models then were created using covariates significant under univariate analysis at the $P < .05$ level. Overall stage was used in lieu of T, N, and M stages to reduce colinearity and the effect of missing values. Stages IA, IB, IIA, IIB, IIIA, and IIIB were simplified to stages I, II, and III. Patients undergoing surgical procedures other than standard sublobar resection, lobectomy, or pneumonectomy were excluded. The results are summarized in Tables 4 and 5. Patients in the pneumonectomy and nonsurgical group had significantly higher disease-specific and overall mortality hazards and were excluded from the subsequent noninferiority analysis.

Noninferiority testing of the relative mortality hazard ratio between sublobar resection and lobectomy (r) patients was performed.[17] The value of the baseline DSS and OS functions at 5 years was determined by SPSS. The critical relative hazard ratio to declare noninferiority (γ_0), was calculated at the mean covariate values using an absolute survival margin (Δ) of .05 (2.48 for DSS and 1.52 for OS). The 90% ($1–2\alpha$) confidence interval of r was found to be .631 to 1.22 for DSS, and .922 to 1.36 for OS. Consequently, sublobar resection was declared statistically noninferior to lobectomy with regard to disease-specific and overall survival ($P < .05$).

Comments

As with any retrospective analysis, these results should be interpreted with caution. Our results show that with univariate analysis, the sublobar group had a slightly worse overall survival than the lobectomy group with a difference of 3 months. However, the patients chosen for limited resection were older, and it is likely that they had greater comorbidities and worse lung function, further confounding OS. Unfortunately, these data are not captured by SEER. However, disease-specific survival between the 2 groups was equivalent, the sublobar group was on average older, and the difference in overall survival was not apparent after controlling for age. When all confounders were factored using multivariate analysis, disease-specific and overall survival after sublobar resection was statistically noninferior.

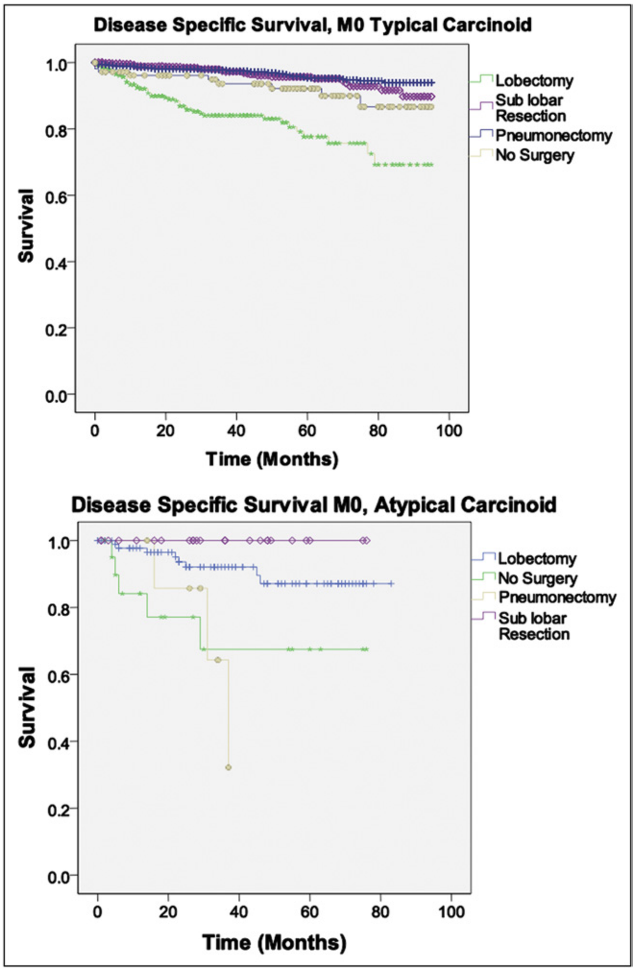

Figure 4 Disease-specific survival stratified by tumor histology. Survival after sublobar resection was statistically noninferior compared with lobectomy in the typical carcinoid patients ($P < .00001$). In patients with atypical carcinoid tumors, no disease-specific mortality was seen after sublobar resection. However, statistical comparisons could not be performed.

One weakness of this study was the differentiation between AC and TC tumors. Previous studies have reported that 16% of all carcinoids contain atypical histology compared with just 5% in this study. The multicenter nature of SEER reporting makes the standardization of pathologic review and reporting difficult. Consequently, it is likely that some AC tumors were misclassified as TC. This is supported by the slightly lower than expected overall survival in the TC subgroup. An unfortunate secondary effect of this misclassification was an insufficient sample size to properly conduct noninferiority testing in the AC subgroup. Other problems specifically related to the data collected by SEER include the lack of recurrence information and differentiation between segmentectomy and wedge resection in coding. Previous studies in NSCLC patients have shown higher local recurrence and worse survival after wedge resection compared with lobectomy,[21,22] whereas segmentectomy is thought to offer more oncologically acceptable outcomes.[23] These results are not necessarily applicable to the benign carcinoid tumors studied here, but the ability to compare wedge resection with segmentectomy would have been preferable.

We did not attempt to address lymphadenectomy in this study because less than half of patients had data regarding the extent of lymph node dissection. Furthermore, it was difficult to compare this between institutions. Because 12% of TC and 37.5% of AC patients are node positive[3] and both are prone to skip metastasis,[24] we believe that, at a minimum, systematic lymph node sampling is indicated. Although current data in NSCLC suggest no increased efficacy for complete mediastinal lymph node dissection over lymph node sampling in node-negative patients,[25] further trials are needed to determine the optimum approach for carcinoid tumors.

Finally, it is uncertain how many typical carcinoid tumors are amenable to limited resection. Approximately

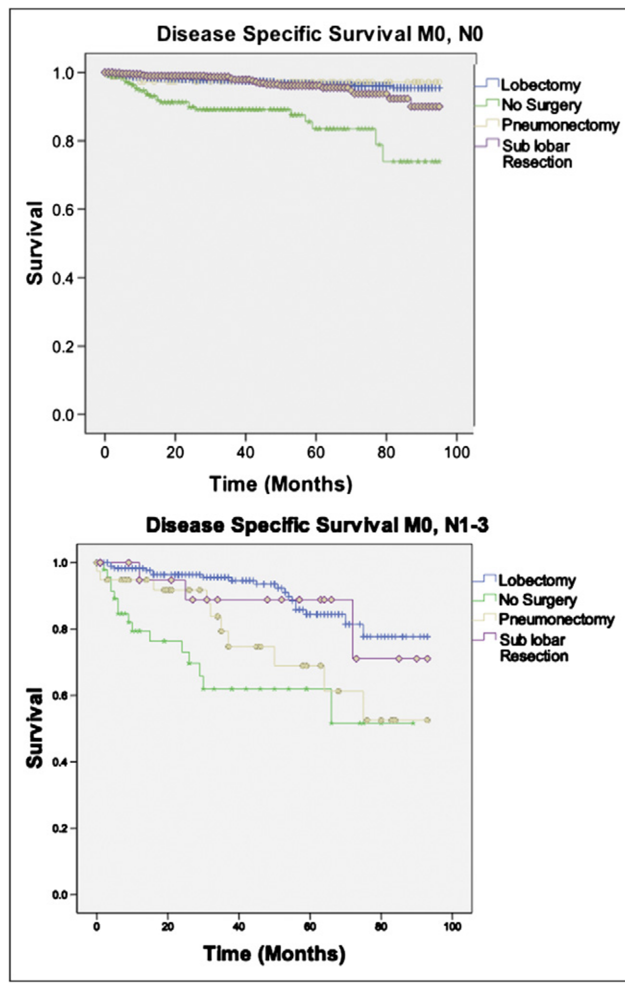

Figure 5 Disease-specific survival stratified by t-stage. Sublobar resection had statistically noninferior survival in T1 and T2 patients compared with lobectomy ($P < .05$). No difference in survival between sublobar resection and lobectomy patients was seen in T3 and T4 tumors ($P = .885$ and $P = .190$), but sublobar resection was not statistically noninferior ($P = .248$ and $P = .145$).

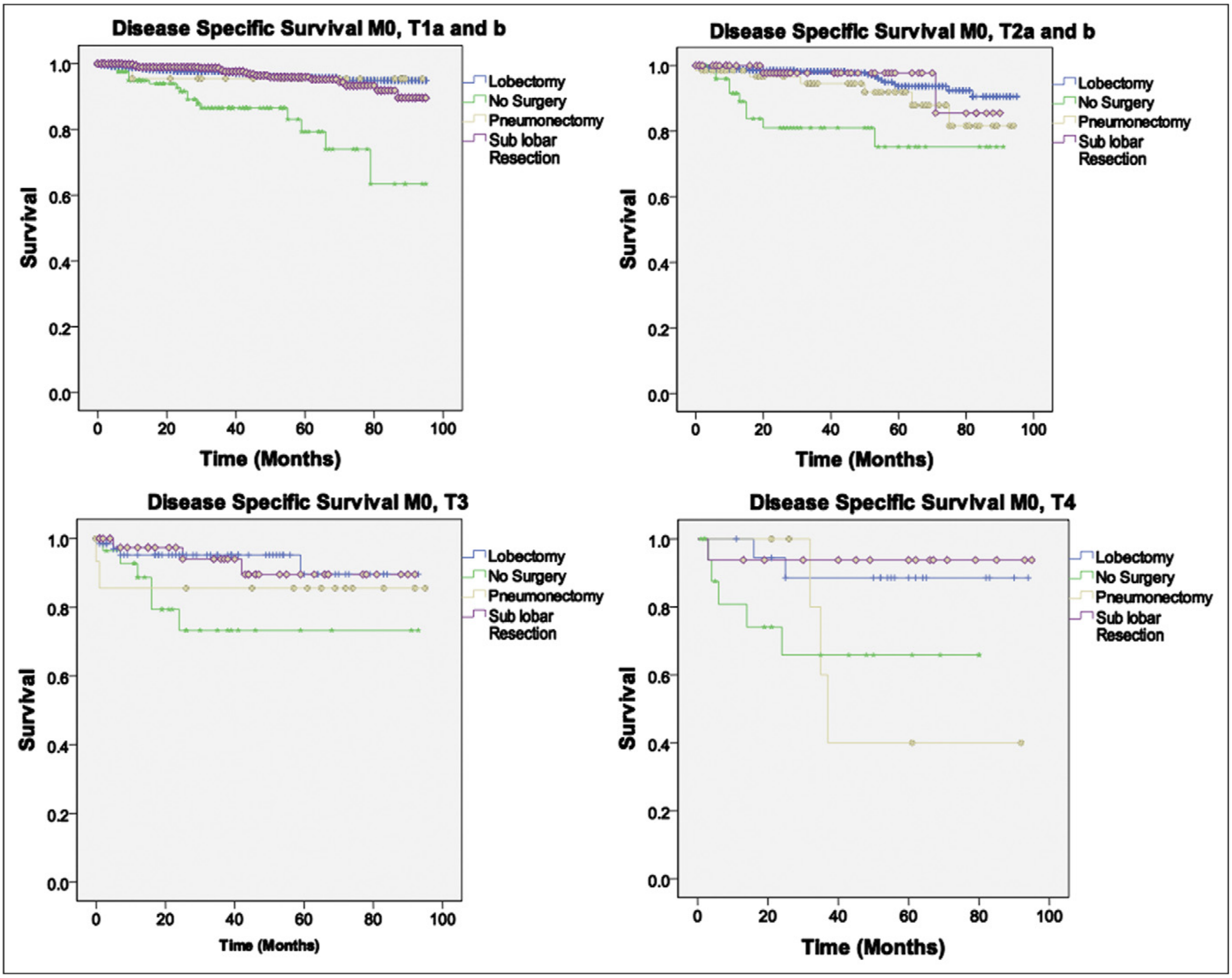

Figure 6 Disease-specific survival stratified by n-stage. In node-negative patients, survival after sublobar resection was noninferior at 5 years ($P \geq .0005$). In node-positive patients, lobectomy and sublobar resection were neither statistically different nor noninferior ($P = .725$ and $P = .535$, respectively).

80% to 90% are central tumors[26] potentially requiring lobectomy and possible bronchoplasty. Peripheral tumors, which are more likely amenable to sublobar resection, have higher rates of atypical histology than central lesions.[27] Furthermore, a preoperative diagnosis of carcinoid, not including subclassification into TC or AC, can be difficult to obtain. Intraoperative frozen section identifies carcinoid tumors with a relatively low error rate,[28] but its use in distinguishing AC from TC histology is unclear.[29] However, given that only 20% of peripheral N0 tumors are AC[27] and the lack evidence for worse survival after sublobar resection in AC patients, we recommend the following.

Limited resection should be performed, when possible, for known carcinoid tumors. Unknown lung lesions should undergo wedge excisional biopsy. If intraoperative frozen section is consistent with carcinoid and the margins are negative, mediastinal lymph node sampling should be performed. If the patient is node negative then completion lobectomy is not required. In node-positive patients with adequate pulmonary reserve, lobectomy should be performed regardless of histology. If atypical features are found during permanent pathologic evaluation then interval completion lobectomy may be considered in good-risk patients.

A randomized controlled trial is the ideal method to compare treatment efficacies. Unfortunately, the relative rarity of carcinoid tumors makes this impractical. This study used formal noninferiority testing to compare survival outcomes in lobar and sublobar resection, and an adequate sample size would not have been possible without a multicenter registry. The data clearly show that sublobar resection offers acceptable oncologic outcomes in patients with node-negative typical carcinoid tumors of the lung. Further studies with larger sample sizes are needed to make a definitive determination of the efficacy of limited resections in patients with atypical carcinoids or nodal disease. Until then, in good-risk patients, lobec-

Table 4 Cox proportional hazards analysis of overall survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Age, y				
<60	1	<.0005	1	<.0005
60–75	2.961		3.127	<.0005
>75	6.630		6.060	<.0005
Sex				
Female	.732	.003	.634	<.0005
Race				
White	1	<.0005	1	<.0005
Black	1.947		2.373	<.0005
Other	1.288		1.027	.942
Unknown	1.328		2.831	.145
Histology				
Atypical histology	1.956	<.0005	1.627	.018
Stage				
I	1	<.0005	1	<.0005
II	1.662		1.558	.005
III	2.391		1.366	.086
Radiation	3.919	<.0005	1.685	.023
Surgery				
Lobectomy	1	<.0005	1	<.0005
No surgery	6.426		3.236	<.0005
Pneumonectomy	1.550		1.808	.023
Sublobar	1.427		1.097	.540

Table 5 Cox proportional hazards analysis of disease-specific survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Age, y				
<60	1	<.0005	1	<.0005
60–75	3.569		4.006	<.0005
>75	5.333		5.941	<.0005
Sex				
Female	.709	.045	.697	.065
Race				
White	1	<.0005	1	<.0005
Black	2.997		3.538	<.0005
Other	2.217		1.393	.523
Unknown	1.898		5.093	.109
Histology				
Atypical histology	2.654	<.0005	1.685	.081
Stage				
I	1	<.0005	1	<.0005
II	3.155		2.561	<.0005
III	5.669		3.020	<.0005
Radiation	8.428	<.0005	2.533	.001
Surgery				
Lobectomy	1	<.0005	1	.001
No surgery	5.716		2.205	.002
Pneumonectomy	2.598		2.337	.012
Sublobar	1.020		.861	.569

tomy should remain the standard of care for these more aggressive tumors.

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