LARGE CELL CARCINOMA OF THE LUNG: RESULTS OF RESECTION FOR A CURE

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Objective: The effectiveness of surgical resection of large cell undifferentiated carcinoma of the lung remains poorly defined because of the histology's relatively low frequency, the tendency for presentation with high-stage disease, and the failure in most published series to separate large cell carcinomas from the other variants of non-small cell lung carcinoma. To define the effectiveness of surgical treatment of large cell carcinoma, we reviewed the Mayo Clinic experience over a 5-year period.

Methods: We have retrospectively reviewed the Mayo Clinic experience with 61 patients with large cell carcinoma and 17 patients with adenocarcinoma with focal mucin production who came to surgical resection during the 5-year period of January 1, 1982, through December 31, 1986.

Results: One-hundred percent 5-year follow-up was obtained. For the 61 patients with large cell carcinoma, the overall 5-year survival was 37%. Five-year survival for those with stage I tumors was 58% (n = 31), stage II 33% (n = 6), stage IIIA 15% (n = 20), stage IIIB 0% (n = 2), and stage IV 0% (n = 2). No significant differences in survival were detected between the 61 patients with large cell carcinoma and the 17 patients with solid adenocarcinoma with mucin production. **Conclusions:** Our results suggest that there is a subset of patients with large cell carcinoma of the lung who can undergo resection with a reasonable expectation of long-term survival and that this survival is, stage for stage, comparable to or only slightly less than that achieved with other non-small cell lung carcinomas. (J Thorac Cardiovasc Surg 1999; 117:599-604)

Large cell carcinoma is the least common subtype of the 4 major histologic subtypes of carcinoma of the lung, comprising 10% or fewer of cases.¹ Large cell carcinoma has traditionally been classified as a non-small cell lung carcinoma along with squamous carcinoma and adenocarcinoma. The histologic diagnosis of large cell carcinoma is based on an absence of glandular or squamous differentiation in tumor cells that do not show features of small cell carcinoma.² Some studies have suggested a dismal prognosis even with apparently curative resection,³⁻⁵ but the prognosis

remains poorly defined. We have reviewed the Mayo Clinic experience for all cases of large cell carcinoma managed by resection with curative intent over a 5-year period and compared and contrasted our findings with those in the literature for large cell carcinoma as well as non-small cell carcinoma of the lung in general.

Patients and methods

A review of the records of the Mayo Clinic Rochester Division of Thoracic Surgery for the period of January 1, 1982, through December 31, 1986, revealed 98 patients who underwent surgical exploration for potentially resectable carcinomas for which a diagnosis of large cell carcinoma was rendered on initial pathologic review of only sections stained with hematoxylin and eosin. These patients comprised the initial study group, and their clinical records were retrospectively reviewed, histologic sections re-evaluated, and 5-year follow-up obtained.

After re-review of the original sections stained with hematoxylin and eosin, 20 cases were excluded from the study: 6 because there was insufficient histologic material for additional studies and 14 because of reclassification of the carcinoma as one of the following: squamous cell, combined small/large cell, adenosquamous, or adenocarcinoma.

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Table I. *Clinical features and follow-up data*

	Large cell carcinoma	Solid adenocarcinoma with mucin production	P value
No. of cases	61	17	
Sex			.74
Male	49	13	
Female	12	4	
Age (y)			.84
Mean	62	61	
Range	35-85	38-75	
Positive smoking history	98%	82%	.03
Pack-years			.10
Mean	60	50	
Range	13-120	20-132	
Symptoms			
Cough	38%	12%	.04
Hemoptysis	21%	12%	.50
Pain	15%	12%	1.00
Weight loss	10%	0%	.33
Pneumonia	8%	6%	1.00
Generalized weakness	13%	0%	.19
Tumor location			
Right upper lobe	41%	47%	
Right middle lobe	7%	6%	
Right lower lobe	13%	0%	
Left upper lobe	30%	24%	
Left lower lobe	10%	24%	
Complete resection	85%	82%	.72
Surgical staging			.97
Stage I	51% (31/61)	47% (8/17)	
Stage II	10% (6/61)	12% (2/17)	
Stage IIIA	33% (20/61)	41% (2/17)	
Stage IIIB	3% (2/61)	0%	
Stage IV	3% (2/61)	0%	

Seventy-eight cases remained, and on all of these a battery of histochemical and immunohistochemical staining was performed. Digested periodic acid-Schiff and mucicarmine stains were performed to look for evidence of intracellular mucin production. In addition, the following immunohistochemical studies were performed: keratin (AE1/AE3), carcinoembryonic antigen (polyclonal and monoclonal), Leu-7, chromogranin, synaptophysin, and S-100. The immunohistochemical stains were graded semiquantitatively on a scale of 0 to 2+ for intensity of staining and on the basis of percentage of positive cells (25%, 50%, 75%, and 100%).

Among the original 78 patients, there were 17 in whom significant amounts of intracellular mucin were identified (arbitrarily as more than 3 cells in a single 100× high-power field); these cases were reclassified as solid adenocarcinoma with mucin production according to World Health Organization (WHO) definition.²

Sixty-one cases of large cell carcinoma remained and these comprised the final study group. The 17 patients with solid

adenocarcinoma with mucin production were also studied as a comparison group.

Survival probabilities were calculated with the use of the Kaplan-Meier method from the day of surgery and included patients dying in the postoperative period (defined as 30 days or less from the day of operation or within the same hospitalization). Survival to first evidence of recurrent disease was also calculated from the day of surgery. Ninety-five percent confidence intervals were calculated for all survival estimates. Survival curves were compared with log-rank tests.

Comparisons of findings between the large cell carcinoma group and the solid adenocarcinoma with mucin production group were carried out with Wilcoxon rank-sum tests for continuous variables, Fisher's exact tests for nominal variables, and exact Wilcoxon rank-sum tests for ordered variables.

Results

Information regarding gender, age, smoking history, symptoms at diagnosis, anatomic location of disease, complete resection rates, and surgical staging are summarized in Table I. Recurrence and survival data are summarized in Table II. Immunohistochemical findings are summarized in Table III.

Large cell carcinoma. One patient had a history of silo filler disease, 1 was receiving steroids for rheumatoid arthritis, and 2 had received thoracic irradiation for reasons unrelated to their large cell carcinomas.

One patient had had a previous bilobectomy (right upper lobe and right middle lobe) for a stage I squamous cell carcinoma (T2 N0 M0). This patient's large cell carcinoma was identified 33 months after this resection.

Twelve patients (19%) had undergone resection of 12 extrapulmonary malignant tumors (2 bladder carcinomas, 2 breast adenocarcinomas, 2 prostate carcinomas, 1 neurofibrosarcoma, 1 melanoma, 3 basal cell carcinomas, and 1 colorectal adenocarcinoma). No patient had a history of chemotherapy before the diagnosis of large cell lung carcinoma.

Sputum cytologic examination was performed in 31 patients (50%) and the results were positive in 4 (6%). Bronchoscopic examination was performed in 42 patients (68%); brushings were positive for malignancy in 13 patients (22%), washings were positive in 11 (18%), and biopsy specimens were positive in 23 (39%). Mediastinoscopic examination was performed in 15 patients (24%) and the results were positive for malignancy in 1. Thoracentesis was performed once (1%) and did not disclose malignancy. Transthoracic needle biopsy was performed 8 times (13%) and was positive for malignancy in 7 patients (11%).

One patient had received preoperative chemotherapy and 2 preoperative radiotherapy for their large cell carcinomas.

Table II. Follow-up

	Percent free from recurrence*				
	Large cell (n = 52)		Solid adenocarcinoma with mucin production (n = 14)		
	Three years (95% CI); N	Five years (95% CI); N	Three years (95% CI); N	Five years (95% CI); N	P value
Overall	59% (46-75); 23	56% (44-73); 21	42% (21-84); 4	32% (13-77); 3	.17
Stage I	76% (46-75); 18	72% (57-91); 17	46% (18-100); 2	23% (4-100); 1	.06
Stage II	42% (15-100); 2	42% (12-100); 1	100%; 1	100%; 1	.39
Stage IIIA	27% (11-66); 3	27 (11-66); 3	20% (4-100); 1	20 (4-100); 1	.57
Stage IIIB	—	—	—	—	—
Stage IV	0%	0%	—	—	—
	Survival†				
	Large cell (n = 61)		Solid adenocarcinoma with mucin (n = 17)		
Overall	39% (29-54); 24	38% (27-52); 23	35% (19-67); 6	24% (10-55); 4	.19
Stage I	58% (43-78); 18	58% (43-78); 18	50% (25-100); 4	25% (8-83); 2	.07
Stage II	50% (23-100); 3	33% (11-100); 2	50% (13-100); 1	50%; (13-100); 1	.74
Stage IIIA	15% (5-43); 3	15% (5-43); 3	14% (2-88; 1	14% (2-88); 1	.60
Stage IIIB	0%	0%	—	—	—
Stage IV	0%	0%	—	—	—

*Deaths without recurrence censored.

†Deaths from any cause.

Complete resection was not possible in 9 patients (14%). In the remaining 52 patients, the procedure performed was wedge or segmental excision in 3 patients (4%), lobectomy in 36 (59%), bilobectomy in 1 (1%), and pneumonectomy in 12 (23%).

One patient had a second primary pulmonary malignant tumor identified at the time of resection for large cell carcinoma. A small bronchioloalveolar carcinoma was identified.

The mean hospital stay was 9.5 days (range 4-26 days; 10th percentile 5 days, 50th 8 days, 90th 19 days). There were 2 perioperative deaths (4%).

Recurrences occurred in 21 of the 52 patients who underwent complete resection (40%) and were detected a mean of 275 days (range 37-1543 days) after resection. Ninety percent of the recurrences were detected within 15.7 months of the day of surgery (10th percentile 1.9 months, 50th percentile 6.0 months, 90th percentile 15.7 months). The site of first recurrence (which could be simultaneous in more than 1 organ) was brain in 7 (33%), bone in 6 (28%), local or pulmonary in 4 (19%), lymph node in 1 (4%), liver in 1 (4%), and adrenal gland in 2 (9%).

Follow-up either to death or to December 31, 1991, was 100%. Seventeen patients (27%) are alive without evidence of disease. One patient (1%) is alive with

recurrent disease. In addition to the 2 postoperative deaths, 28 patients (45%) have died with recurrent disease, 11 (18%) have died without evidence of recurrence, and 2 (3%) have died of unknown causes.

Solid adenocarcinoma with mucous production.

No patient had any significant occupational exposure history of immunosuppression or prior thoracic irradiation.

Two patients had had prior pulmonary malignant tumors: 1 patient had a stage I (T1 N0 M0) adenocarcinoma of the right upper lobe 24 months before resection for solid adenocarcinoma with mucin production. Another patient had a stage I squamous cell carcinoma of the right upper lobe (T1 N0 M0) resected 37 months before resection of a solid adenocarcinoma with mucin.

Two patients (12%) had undergone resection of 3 extrapulmonary malignant tumors (1 breast adenocarcinoma, 1 prostate carcinoma, and 1 colorectal adenocarcinoma). No patient had a history of chemotherapy or radiation therapy before the diagnosis of malignant lung disease.

Cytologic examination of sputum cytology was performed in 8 patients (47%) and was positive in 1 (6%). Bronchoscopic study was performed in 13 patients (76%), brushings were positive for malignancy in 2 patients (12%), washings were positive in 2 (12%), and

Table III. Immunohistochemical findings

Antibody	Large cell carcinoma (n = 61)		Solid adenocarcinoma with mucin production (n = 17)	
	Positive	Strongly positive	Positive	Strongly positive
Keratin (AE1/AE3)	95%	79%	100%	100%
CEA (polyclonal)	48%	28%	63%	26%
CEA (monoclonal)	26%	11%	37%	16%
S-100 (tumor cells)	10%	0%	26%	0%
S-100 + stromal histiocytes†	—	46%	—	53%
Chromogranin	20%	0%	0%	0%
Leu-7	5%	2%	0%	0%
Synaptophysin	11%	0%	0%	0%

CEA, Carcinoembryonic antigen.

*Immunohistochemical findings shown were based on the following scoring system: Positive = at least 25% of the cells showing 1+ staining (scored 0 to 2+); strongly positive = at least 75% of the cells showing 2+ staining (scored 0 to 2+).

†These positive cells may represent Langerhans type histiocytes.

biopsy was positive in 3 (18%). Mediastinoscopy was performed in 2 patients and was negative in both. Neither thoracentesis nor transthoracic needle biopsy was performed in this group of patients.

No patient received either chemotherapy or radiotherapy as treatment for their lung carcinoma before attempted resection.

Complete resection was not possible in 3 patients (18%). In the remaining 14 patients, the procedure performed was wedge or segmental excision in 2 patients (12%), lobectomy in 9 (53%), bilobectomy in 1 (6%), and pneumonectomy in 2 (12%).

Two patients had second primary pulmonary malignant tumors identified at the time of resection for solid adenocarcinoma with mucin, 1 showing an incidental bronchioloalveolar carcinoma and 1 showing a separate incidental adenocarcinoma.

The mean hospital stay was 8.6 days (range 4-15 days; 10th percentile 4 days, 50th percentile 7 days, 90th percentile 14 days). There was 1 perioperative death (6%).

Recurrences occurred in 8 of the 14 patients having complete resection (57%) and were detected a mean of 376 days (range 75-1171 days) after resection. Ninety percent of the recurrences were detected within 32.7 months of the day of surgery (10th percentile 2.5 months, 50th percentile 4.1 months). The site of first recurrence (which could be simultaneous in more than 1 organ) was brain in 3 (21%), bone in 2 (14%), local or pulmonary in 3 (21%), lymph node in 2 (14%), and liver or adrenal gland in none (0%).

Follow-up either to death or to December 31, 1991, was 100%. One patient (6%) is alive without evidence of disease, and 1 patient (6%) is alive with recurrent disease. In addition to 1 postoperative death, 10 patients (59%) have died with recurrent diseases, and 4 (23%) have died without evidence of recurrence.

Discussion

Large cell carcinoma of the lung, as defined by the WHO,² has traditionally represented a "wastebasket" category into which cases of lung carcinoma were placed when tissue did not show squamous or glandular differentiation (including mucin production) and did not show features of small cell carcinoma. This diagnosis is based on routine histologic findings, although cases diagnosed as large cell carcinoma may show features of differentiation (squamous, glandular, or neuroendocrine) when studied immunohistochemically or ultrastructurally,^{6,7} but these studies are not part of most routine pathology practices, and not part of the WHO classification of lung tumors.²

Large cell carcinoma of the lung is usually included among the other non-small cell carcinomas in clinical studies; thus it has been difficult to determine whether large cell carcinoma has significant clinical differences from squamous cell carcinoma and adenocarcinoma. Studies that both provide rigorous surgical staging and clear histologic criteria for the diagnosis of large cell carcinoma have characterized the prognosis for patients with the disease as dismal.³ Even for completely resected stage I or II disease, the 5-year survival has been estimated as between 0% and 21%.⁴ Our results for survival after resection of large cell carcinoma are more encouraging: the 5-year survival for stage I disease was 51%, for stage II 37%, and for stage IIIA 14%. We observed an overall recurrence rate of 40% at 5 years; 95% of these recurrences occurred within 2 years. This is similar to the recurrence rate of 41% reported by Immerman and coworkers.⁵ The anatomic pattern of recurrences seen in our series of large cell carcinomas was also similar to the pattern of recurrences seen after resection of squamous and adenocarcinomas.⁵ Ideally, our data for patients with large cell

carcinoma would be compared with series of patients with squamous cell carcinoma and adenocarcinoma from our institution during the same period, but these studies have not been performed. It is difficult to directly compare these results with previously published series of surgically treated squamous carcinoma and adenocarcinoma because patient characteristics, preoperative and postoperative therapies, and surgical techniques vary. However, it is likely that the overall survival, time to recurrence, and pattern of recurrence seen in our patients with large cell carcinoma are comparable with or only slightly worse at each stage than those previously published results for the resection of squamous and adenocarcinoma.

Large cell carcinoma of the lung is separated from solid adenocarcinoma with mucin production based on the presence of mucin as demonstrated histochemically with mucin stains in the latter.² Since immunohistochemical and ultrastructural studies show that the majority of large cell carcinomas do show some differentiation (usually toward adenocarcinoma), it is not surprising that a significant portion of cases diagnosed as large cell carcinoma on routine hematoxylin-eosin sections would be reclassified as solid adenocarcinoma with mucin production based on the presence of intracellular mucin. Personal experience suggests that pathology laboratories do not routinely do mucin stains in this situation (T.V.C., unpublished data). In our review and histochemical study of 78 cases previously characterized as large cell carcinoma, we reclassified 17 cases (22%) as solid adenocarcinoma with mucin production on the basis of mucin stains. The clinical features, follow-up, and survival data for patients with large cell carcinoma and patients with solid adenocarcinoma with mucin production are summarized in Tables I and II. As shown in Table I, there is little difference between the 2 groups in terms of sex, age, smoking history, symptoms, tumor location, feasibility of complete resection, or surgical staging. The slight differences noted in smoking history and cough are probably not important. As shown in Table II, recurrence and overall survival data are also not significantly different between patients with large cell carcinoma and solid adenocarcinoma with mucin production, either overall or on a stage-for-stage basis. On the basis of these findings, we question the necessity of doing mucin stains to segregate a subgroup of solid adenocarcinoma with mucin production from "true" large cell carcinoma other than for research purposes.

Finally, a number of studies have suggested that the immunohistochemical demonstration of neuroendocrine markers in lung tumor tissue is associated with

a favorable prognosis, in terms of overall survival or response to chemotherapy.⁸⁻¹⁰ The findings, however, have not been uniform, and other studies suggest that these features are not prognostically significant.¹² Neuroendocrine differentiation generally has been demonstrated immunohistochemically with one or more of the following markers: neuron specific enolase, chromogranin A, synaptophysin, and Leu-7. We studied all 78 of our cases with 3 of these markers and did not find correlation between the presence or absence of positivity for these markers with either recurrence or survival.

In conclusion, prior reports have suggested that large cell carcinoma of the lung is a disease with an overwhelmingly poor prognosis. Our review of a consecutive series of patients seen and operated on at the Mayo Clinic suggests that reasonable survivals can be obtained for patients after complete resection of all known disease. Furthermore, our data suggest that the detailed characterization of pathologic tissue to allow segregation of subgroups of histologic types does not clearly define patient groups with such different outlooks as to alter therapy.

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REFERENCES

1. Travis WD, Travis LB, Devesa SS. Lung cancer. *Cancer* 1995; 75:191-202.
2. World Health Organization. The World Health Organization histological typing of lung tumors: second edition. *Am J Clin Pathol* 1982;77:123-36.
3. Downey RS, Sewell W, Mansour KA. Large cell carcinoma of the lung: a highly aggressive tumor with dismal prognosis. *Ann Thorac Surg* 1989;47:806-8.
4. Mitchel DM, Morgan PGM, Ball JB. Prognostic features of large cell anaplastic carcinoma of the bronchus. *Thorax* 1980;35:118-22.
5. Immerman SC, Vanecko RM, Fry WA, Head LR, Shields TW. Site of recurrence in patients with stage I and II carcinoma of the lung resected for cure. *Ann Thorac Surg* 1981;32:23-7.
6. Colby TV, Koss MN, Travis WD. Tumors of the lower respiratory tract. In: *Atlas of tumor pathology*, third series, fascicle 13, Washington [DC]: Armed Forces Institute of Pathology. 1995.
7. Ishida T, Kaneko S, Tateishi M, et al. Large cell carcinoma of the lung. *Am J Clin Pathol* 1990;93:176-82.
8. Graziano SL, Mazid R, Newman N, et al. The use of neuroendocrine immunoperoxidase markers to predict chemotherapy response in patients with non-small-cell lung cancer. *J Clin Oncol* 1989;7:1398-406.
9. Skov BG, Sorensen JB, Firsch FR, Larsson LI, Hansen HH. Prognostic impact of histologic demonstration of chromogranin

- A and neuron specific enolase in pulmonary adenocarcinoma. *Ann Oncol* 1991;2:355-60.
10. Carles J, Rosell R, Ariza A, Pellicer I, Sanchez JJ, FernandezVasalo G, et al. Neuroendocrine differentiation as a prognostic factor in non-small cell lung cancer. *Lung Cancer* 1993;10:209-19.
 11. Schleusener JT, Tazelaar HD, Jung S, et al. Neuroendocrine differentiation is an independent prognostic factor in chemotherapy-treated nonsmall cell lung carcinoma. *Cancer* 1996;77:1284-91.
 12. Linnoila RH, Piantadosi S, Ruckdeschel JC. Impact of neuroendocrine differentiation in non-small cell lung cancer: the Lung Cancer Study Group experience. *Chest* 1994;106:367S-71S.

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