Recurrence and Survival Following Resection of Bronchioloalveolar Carcinoma of the Lung–The Lung Cancer Study Group Experience

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Bronchioloalveolar carcinoma (BAC) of the lung is a controversial form of adenocarcinoma with varying presentations. The 1977 to 1988 Lung Study Group experience with this tumor was reviewed to more precisely define the incidence of recurrence and survival of surgically resected and staged patients, to determine the incidence of BAC in the adenocarcinoma population, and to evaluate the impact of age, sex, smoking, and chronic lung-disease history on the incidence of BAC. Of 1635 patients reviewed, 235 patients had pure BAC. It was found that resectable BAC presents at an earlier disease stage than does adenocarcinoma; BAC occurs more frequently in older patients and in those without smoking history or chronic lung disease than adenocarcinoma;

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BAC patients have less weight loss, brain recurrences, and recurrences without second primaries than adenocarcinoma; survival and recurrence-free survival are better for BAC than for non-BAC adenocarcinoma and large-cell carcinoma; early BAC survival is better than squamous-cell survival but after 2 years is equivalent; T1-N0 BAC patients have recurrence and survival rates similar to squamous-cell survival rates and better than non-BAC adeno survival rates; T1-N1/T2-N0 and Stage 2 and 3 BAC recurs more frequently than either squamous-cell or non-BAC adenocarcinoma; stage 2 and 3 BAC has a higher mortality rate than does squamous-cell carcinoma or non-BAC adenocarcinoma; BAC is a favorable prognostic factor when adjusted for extent of disease and age; and BAC's better prognosis is a result of presenting at an earlier stage of disease and because it appears to be less aggressive than other adenocarcinomas even after adjustment for extent of disease and other known prognostic factors. It is concluded that early diagnosis and resection are particularly important for patients with BAC.

BRONCHIOLOALVEOLAR CARCINOMA IS A controversial form of bronchogenic carcinoma with varying presentations. It was reported first in 1876 by Malassez[1] who described the multinodular form of the disease. In 1904 Musser[2] described the diffuse or pneumonic type of presentation of the disease. Skorpil[3] reported a 5-year rate of survival in a patient on whom he performed a lobectomy in 1936. This was believed to be the first living patient in whom the diagnosis had been made. In 1960 Liebow[4] officially named these entities bronchioloalveolar carcinoma and defined them as "well-differentiated adenocarcinomas primary in the periphery of the lung beyond a grossly recognizable bronchus, with a tendency to spread chiefly within the confines of the lung by aerogenous and lymphatic routes, the walls of the distal air spaces often acting as supporting stroma for the neoplastic cells." There continues to be controversy, however, because of the varying clinical presentations, ranging from a well-localized single pulmonary nodule to diffuse bilateral pulmonary involvement and on the results of treatment.[5] In addition, there has been disagreement about whether bronchioloalveolar carcinoma is an entity distinct from adenocarcinoma of the lung.[6] The Lung Cancer Study Group experience from 1977 to 1988 was therefore reviewed to more precisely define the incidence of recurrence and survival of surgically resected and staged patients with bronchioloalveolar carcinoma, to compare this to the adenocarcinoma population, and to evaluate the impact of age, sex, smoking, and chronic lung-disease history on the incidence of bronchioloalveolar carcinoma.

Materials and Methods

The Lung Cancer Study Group experience from 1977 to 1988 was reviewed to identify patients who had been entered into protocols who met the strict pathologic criteria for bronchioloalveolar carcinoma. A total of 1618 patients in seven Lung Cancer Study Group protocols were reviewed. Of these patients, 235 had pure bronchioloalveolar carcinoma. To qualify the patients met the accepted diagnostic criteria of (1) no evidence of a primary adenocarcinoma elsewhere;(2) absence of a central bronchogenic origin;(3)tumor cells growing along the walls of the alveoli with frequent papillary projections into the alveolar spaces;(4) and the interstitial lung tissue was generally unaffected, i.e.,the pulmonary architecture was preserved. All patients were required to meet strict and vigorous eligibility criteria for each protocol into which they were enrolled.

All patients underwent thoracotomy with surgical resection at which time they underwent intraoperative primary tumor and nodal staging. The Lung Cancer Study Group requirement for nodal staging includes sampling of an ipsilateral paratracheal node, a hilar node, a lobar node, a subcarinal node, and either an inferior pulmonary ligament or parasophageal node. If a segmentectomy or wedge resection is performed, a segmental node also must be biopsied. In addition, intrapulmonary nodes are analyzed within the specimen. The primary tumors are carefully measured to determine size, distance from the main carina, and visceral or parietal pleural involvement. All pathologic specimens were sent to a central pathology review laboratory for verification for pathologic quality assurance and to enhance uniformity of diagnosis between member institutions.

Patients were included from both control and treatment arms of the various protocols. They were divided into T N categories, i.e., T1-N0, T2-N0, T3-N0, T1-N1, T2-N1, T3-N1, T1-N2, T2-N2, and T3-N2. In order to have adequate numbers in these T N classifications for some of the data analyses, they were grouped into T1-N0, T1-N1/T2-N0, and Stages 2 and 3. The 235 bronchioloalveolar carcinoma patients were compared to 947 adenocarcinoma, including the bronchioloalveolar-cell patients, 608 squamous-cell patients, and 80 large-cell carcinoma patients.

Two major statistical endpoints were analyzed. The first was survival (and recurrence) following randomization in Lung Cancer Study Group protocols. A second endpoint of interest was the probability of the bronchioloalveolar-cell type in the population of patients having adenocarcinoma.

Standard life table methods and survival models were used for the time-to-event analyses. Event times were measured from the date of randomization. Hazard rates were calculated by dividing the number of events by the total exposure time. Hazard ratios are expressed relative to a baseline reference category for individual prognostic factors. Event time distributions were estimated using the product-limit method.[7] Survival and recurrence-free survival distributions were compared using the logrank statistic.[8] The effect of bronchioloalveolar-cell type on event times was adjusted for known prognostic variables (e.g.,

TABLE 1. *Sex By Cell Type*

Frequency / Per cent / Row Pct / Col Pct	Female	Male	
large cell	24	56	80
	1.47	3.43	4.90
	30.00	70.00	
	5.10	4.82	
adeno (excludes mixed)	262	448	710
	16.04	27.43	43.48
	36.90	63.10	
	55.63	38.55	
squamous	86	522	608
	5.27	31.97	37.23
	14.14	85.86	
	18.26	44.92	
BAC	99	136	235
	6.06	8.33	14.39
	42.13	57.87	
	21.02	11.70	
Total	471	1162	1633

$p < 0.001$ (Chi square).

TABLE 2. *T-Status by N-Status All Patients*

T Status / Frequency / Per cent / Row Pct / Col Pct	N Status			
	N0	N1	N2	Total
T1	819	83	48	950
	50.09	5.08	2.94	58.10
	86.21	8.74	5.05	
	66.59	38.07	25.67	
T2	388	109	117	614
	23.73	6.67	7.16	37.55
	63.19	17.75	19.06	
	31.54	50.00	62.57	
T3	23	26	22	71
	1.41	1.59	1.35	4.34
	32.39	36.62	30.99	
	1.87	11.93	11.76	
Total	1230	218	187	1635
	75.23	13.33	11.44	100.00

TN category) using the proportional hazards model of Cox.[9] Candidate prognostic factors were entered into the model and nonsignificant effects were removed in a stepwise fashion.

The association between the bronchioloalveolar-cell type and categorical factors was tested using the chi-square statistic. The probability of having the bronchioloalveolar-cell type in the adenocarcinoma group was predicted from baseline explanatory variables using a multivariate logistic regression model.[10]

For all these analyses, some continously distributed outcome measures were categorized into discrete levels. For example, weight loss was dichotomized as greater than or equal to 10% *versus* less than 10%. Similarly, performance status was dichotomized as 9 to 10 *versus* all others. All p values reported are two sided.

Results

There were 136 male (58%) patients and 99 female (42%) patients in the bronchioloalveolar carcinoma group. This is similar to the nonbronchioloalveolar adenocarcinoma group, which had 448 male (63%) and 262 female (37%) patients, but is significantly different from the squamous cell group, which had 522 male (86%) and 86 (14%) female patients ($p < 0.001$). Table 1 depicts the relationship of sex to cell type.

As noted, patients with three cell types were studied: large-cell (80 patients), squamous-cell carcinoma (608) patients, and adenocarcinoma including bronchioloalveolar (947 patients), with the bronchioloalveolar carcinoma subgroup of adenocarcinoma consisting of 235 patients (25% of the adenocarcinomas). The presenting extent of disease categories for patients are shown in Tables 2, 3, and 4. Table 2 shows all patients; Table 3 shows adenocarcinoma-only patients; and Table 4 shows bronchioloalveolar carcinoma-only patients. It is noted that in this series of which all patients are surgically resected, the predominant T N status is T1-N0, with T2-N0 being the second most common status. As noted in Table 4, 64% of bronchioloalveolar carcinoma patients fell into the T1-N0 category as compared to 54% of the adenocarcinoma patients and 50% of all patients. Eighty-four per cent of bronchioloalveolar carcinoma patients fell into

TABLE 3. *T-Status by N-Status Adenocarcinoma Patients Only*

T Status / Frequency / Per cent / Row Pct / Col Pct	N Status			
	N0	N1	N2	Total
T1	507	36	38	581
	53.54	3.80	4.01	61.35
	87.26	6.20	6.54	
	72.12	30.51	30.16	
T2	182	70	76	328
	19.22	7.39	8.03	34.64
	55.49	21.34	23.17	
	25.89	59.32	60.32	
T3	14	12	12	38
	1.48	1.27	1.27	4.01
	36.84	31.58	31.58	
	1.99	10.17	9.52	
Total	703	118	126	947
	74.23	12.46	13.31	100.00

TABLE 4. *T-Status by N-Status BAC Patients Only*

T Status / Frequency / Per cent / Row Pct / Col Pct	N Status			
	N0	N1	N2	Total
T1	150	4	4	158
	63.83	1.70	1.70	67.23
	94.94	2.53	2.53	
	75.00	25.00	21.05	
T2	48	10	14	72
	20.43	4.26	5.96	30.64
	66.67	13.89	19.44	
	24.00	62.50	73.68	
T3	2	2	1	5
	0.85	0.85	0.43	2.13
	40.00	40.00	20.00	
	1.00	12.50	5.26	
Total	200	16	19	235
	85.11	6.81	8.09	100.00

TABLE 5. *Categorical Prognostic Factors and BAC Among Adenocarcinoma Patients*

	BAC				
	No		Yes		
Variable	N	(%)	N	(%)	P value
T status					0.050
T1	423	(44.7)	158	(16.7)	
T2	256	(27.0)	72	(7.5)	
T3	33	(3.5)	5	(0.5)	
N status					<.001
N0	503	(53.1)	200	(21.1)	
N1	102	(10.7)	16	(1.7)	
N2	107	(11.3)	19	(2.0)	
Male sex	448	(47.4)	136	(14.4)	.153
Smoking status					<.001
Current	407	(43.9)	115	(12.4)	
Former	248	(26.8)	82	(8.9)	
Never smoked	41	(4.4)	34	(3.7)	
Race					.177
White	632	(66.8)	210	(22.3)	
Black	57	(6.0)	13	(1.4)	
Other	22	(2.3)	12	(1.3)	
Extent of resection					.485
Pneumonectomy	142	(15.1)	39	(4.1)	
Lobectomy	515	(54.6)	177	(18.8)	
Other	51	(5.4)	19	(2.0)	
>10% weight loss	63	(6.6)	8	(0.9)	.006
Hx hepatitis	13	(1.6)	10	(1.2)	.025
Hx chronic lung	194	(20.6)	43	(4.6)	.005
Hx heart disease	114	(12.4)	35	(3.8)	.678
Recurrence					
Local recurrence	81	(8.6)	23	(2.4)	.499
Brain only recurrence	81	(8.6)	10	(1.1)	.001
Nonbrain recurrence	138	(14.6)	43	(4.5)	.714
Any brain recurrence	219	(23.1)	53	(5.6)	.016

either the T1-N0 or T2-N0 category, i.e., Stage 1. There is, therefore, a tendency for bronchioloalveolar carcinoma patients to have an earlier stage of disease at presentation.

Among the adenocarcinoma patients, univariate analysis revealed that bronchioloalveolar patients were more likely to have early stage disease (T-status, $p = 0.05$, N-status, $p < 0.001$), no history of smoking ($p < 0.001$), a weight loss of less than 10% ($p = 0.006$), no history of hepatitis ($p = 0.025$), and no history of chronic lung disease ($p = 0.005$). In addition, brain recurrences are less likely to occur in bronchiolalveolar carcinoma as compared to adenocarcinoma ($p < 0.001$), as are recurrences without second primaries ($p < 0.008$). These results are presented in Table 5.

The survival of all patients by cell type is shown in Figure 1. The familiar worsening of survival from squamous-cell carcinoma to adenocarcinoma to large-cell carcinoma is illustrated. However, the survival curves also show that initially bronchioloalveolar carcinoma patients have a more favorable survival than even squamous-cell patients and that after approximately 2 years, the survival of bronchioloalveolar carcinoma patients and squamous-cell patients is approximately equivalent. The survival of bronchioloalveolar carcinoma patients is more favorable than that for nonbronchioloalveolar adenocarcinoma patients, as illustrated in Figure 2. Similar analysis for recurrence are shown in Figures 3 and 4. Tables 6 and7 list the mortality rate per patient-year of exposure and the recurrence rate per patient-year of exposure comparing bronchioloalveolar carcinoma, adenocarcinoma, and squamous-cell carcinoma by T N status. It is noted the T1-N0 patients with bronchioloalveolar carcinoma have recurrence and survival rates similar to squamous-cell carcinoma and significantly better than nonbronchioloalveolar adenocarcinoma. In T1-N1/T2-N0 and Stage 2 and 3, however, the incidence of recurrence in the bronchioloalveolar group is slightly higher than the adenocarcinoma group and significantly higher than squamous-cell carcinoma group, and the mortality in T1-N1 and T2-N0 status is similar to squamous-cell carcinoma and slightly less than adenocarcinoma, but in Stage 2 and 3 the mortality rate is somewhat higher than either group, although not significantly so. Overall mortality rates for both bronchioloalveolar carcinoma and squamous-cell carcinoma are less than that for nonbronchioloalveolar adenocarcinoma.

The prognostic effect of individual factors on survival and recurrence is shown in Table 8. The bronchioloalveolar carcinoma cell type has a significant prognostic benefit on survival with a hazard ratio of 0.729 ($p = 0.008$) and recurrence with a hazard ratio of 0.701 ($p = 0.002$).

We attempted to determine if the bronchioloalveolar carcinoma cell type was a favorable prognostic factor for survival when it was adjusted for extent of disease and

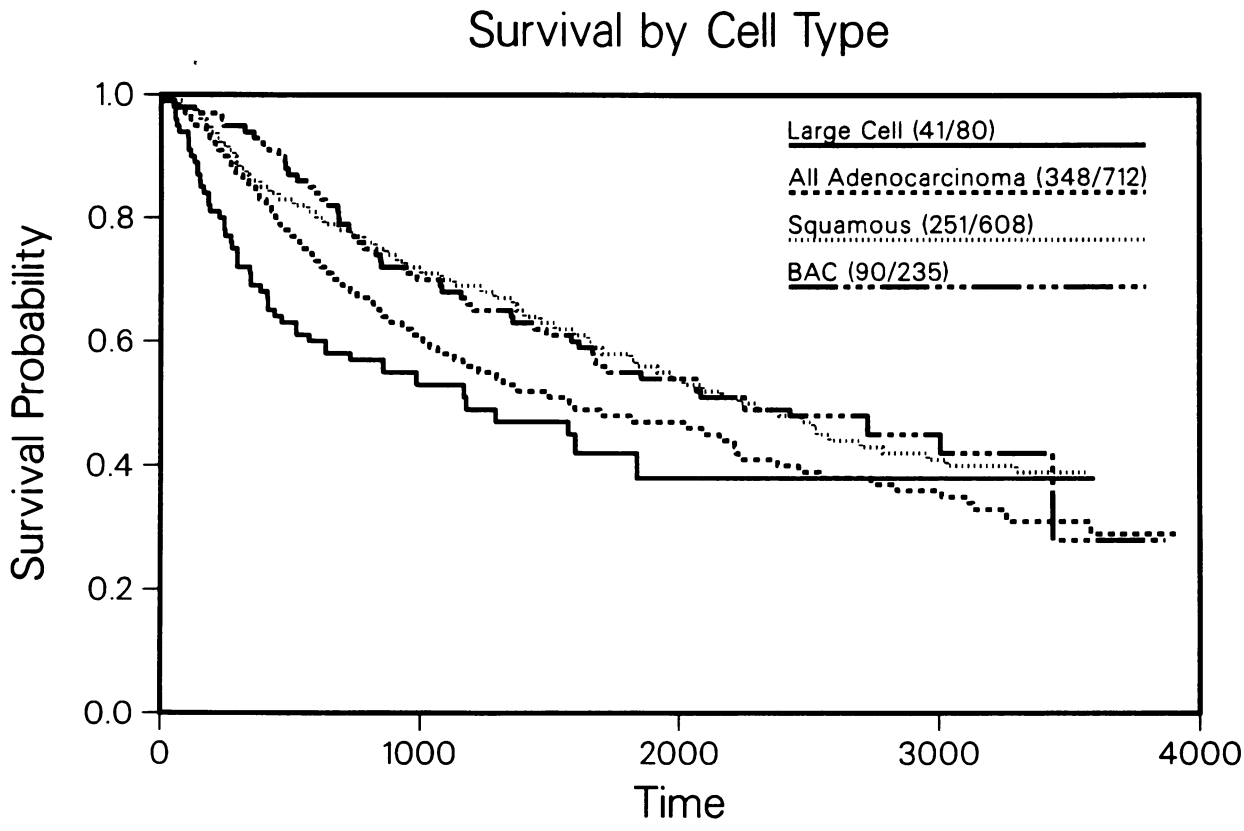


FIG. 1. This graph demonstrates survival by the four cell types. Note that the bronchioloalveolar carcinoma survival is superior to even squamous-cell carcinoma during the first 2 years following surgical resection and thereafter coincides with squamous-cell carcinoma. Both of these cell types have significantly better survival rates than do adenocarcinoma and large-cell carcinoma.

other known factors. Using the Cox proportional hazards model, the bronchioloalveolar carcinoma cell type was seen as a favorable prognostic factor when it was adjusted for T-status, N-status, and the age of the patient ($p = 0.03$; Table 9). However, when one further adjusts for sex and percentage of weight loss, the effect of the bronchioloalveolar carcinoma cell type is only marginally statistically significant ($p = 0.09$; lower portion of Table 9). These results are consistent with a modest independent variable effect on survival for the bronchioloalveolar carcinoma cell type when compared to adenocarcinoma (hazard ratio 0.814). This effect is associated with female patients and a lesser tendency toward weight loss, both of which also have independent prognostic importance. Consequently, when all variables are placed in the model, the effect of the bronchioloalveolar cell carcinoma is reduced.

In a similar way, we adjusted the effect of the bronchioloalveolar carcinoma cell type on recurrence-free survival for known prognostic factors. The results are shown in Table 10. Bronchioloalveolar carcinoma is marginally significant when adjusted for age, T-status, and N-status and is not significant when also adjusted for weight loss (lower portion of Table 10). Although the recurrence hazard ratio for bronchioloalveolar carcinoma *versus* nonbronchioloalveolar carcinoma is 0.834 and is comparable to that for survival, the result is not statistically significant.

The results of predicting the occurrence of the bronchioloalveolar carcinoma cell type among adenocarcinoma patients is shown in Table 11. When only demo-

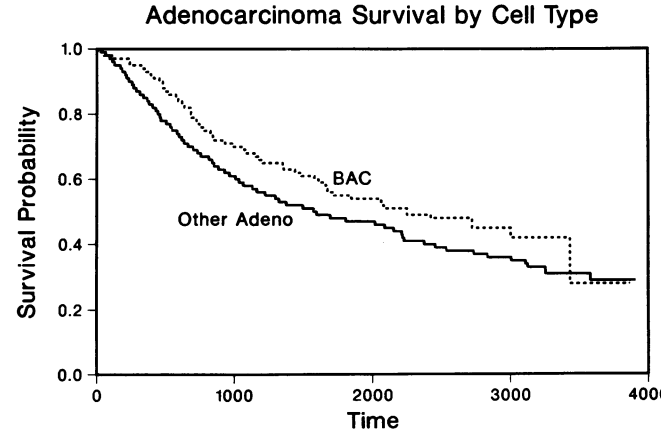


FIG. 2. This figure depicts survival in bronchioloalveolar carcinoma as compared to nonbronchioloalveolar adenocarcinoma. Note better survival throughout the follow-up period in the bronchioloaveolar carcinoma group ($p = 0.008$).

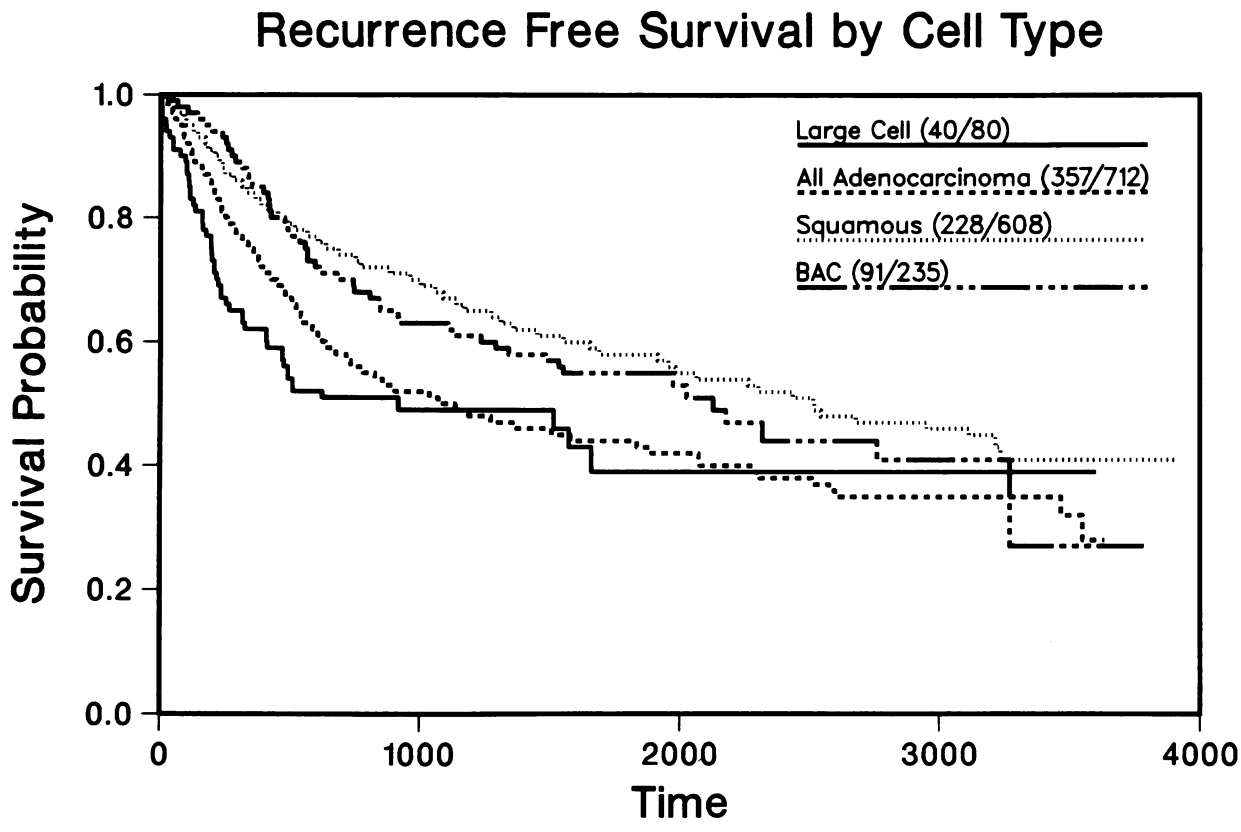


FIG. 3. This figure depicts the recurrence-free survival by the four cell types and is quite similar to overall survival. Again note that bronchioloalveolar carcinoma has the highest recurrence-free survival for the initial 2 years after resection but then is slightly less than squamous-cell carcinoma for the remainder of follow-up. Both cell types, however, have greater recurrence-free survival than do either adenocarcinoma or large-cell carcinoma.

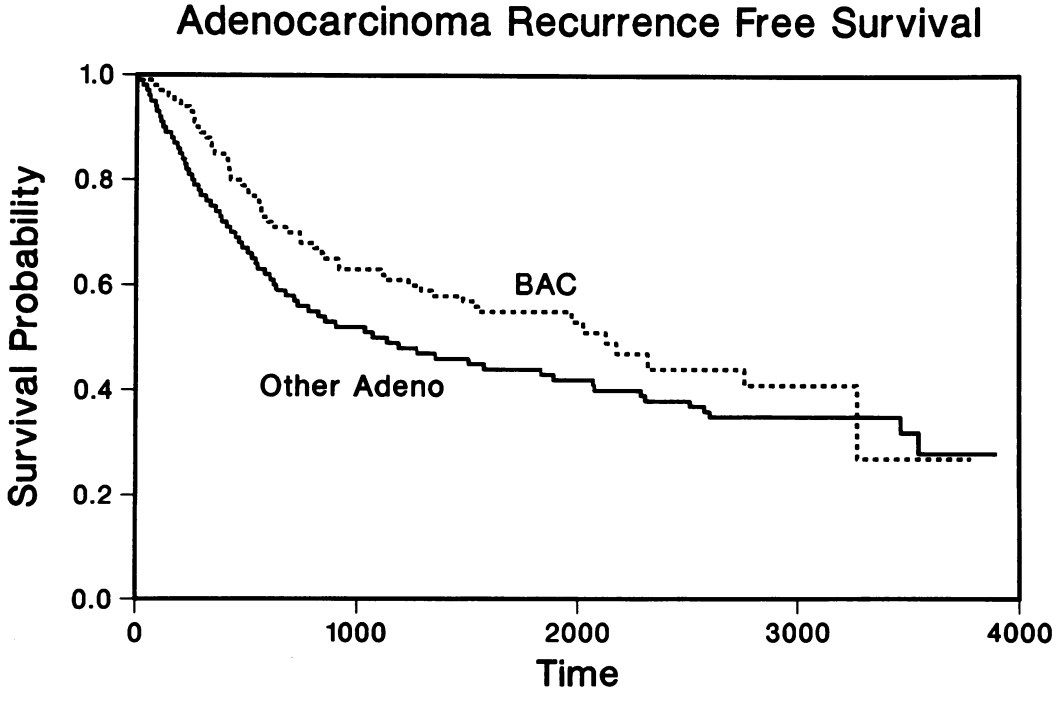


FIG. 4. This graph demonstrates recurrence-free survival in the adenocarcinoma group comparing bronchioloalveolar carcinoma to non-bronchioloalveolar adenocarcinoma. As was the case with overall survival, there is superior survival for the first 9 years following resection in the bronchioloalveolar carcinoma group ($p = 0.002$).

TABLE 6. *Overall Mortality (Rate per Patient-Year of Exposure)*

	T_1N_0	T_1N_1/T_2N_0	Stage II and III	Overall
BAC	.0737	.1219	.4057	.1170
Adeno	.1004	.1574	.3277	.1567
Squamous	.0741	.1227	.2744	.1156
	(p = .0542)	(p = .1688)	(p = .4182)	(p = <.00008)

BAC *vs.* Adeno (p = .1234); BAC *vs.* Sq (p = .6517); Adeno *vs.* Sq (p + .0026).
Pairwise comparison adjusted for TN status (Logrank statistic).

graphic and historical variables are candidate predictors (sex, age, smoking history, race, and history of hepatitis, lung disease, and heart disease), multivariate logistic regression reveals that only age and a history of chronic lung disease are predictive of the presence of the bronchioloalveolar carcinoma cell type. In particular, advancing age makes this cell type more likely and a history of chronic lung disease makes it less likely. A nonsmoking history can also be used as a predictor of bronchioloalveolar carcinoma in place of chronic lung disease probably because of the strong association of chronic lung disease and smoking (lower portion of Table 11).

Discussion

There has been considerable controversy regarding whether bronchioloalveolar carcinoma is a highly malignant multicentric entity or one of unicentric origin that can then be spread by the lymphatics, blood stream, and bronchi. At first, most felt that the disease was highly malignant and rather hopeless. It was not until 1953 when Story et al.,[11] reported successfully resecting two small peripheral lesions with success, which showed that when the bronchioloalveolar carcinoma was detected while still in a single, small nodular state, the prognosis could be quite good. Bronchioloalveolar carcinoma can present in many different ways. Radiographically, the tumors usually present as either a nodule (Fig. 5), mass consolidation (Fig.6), or a diffuse lesions.[12] Up to 45% of patients present with an asymptomatic peripheral lesion.[5] However, those with diffuse disease frequently have severe symptoms and

TABLE 7. *Recurrence (Rate per Patient-Year of Exposure)*

	T_1N_0	T_1N_1/T_2N_0	Stage II and III	Overall
BAC	.0723	.2166	.5576	.1455
Adeno	.1257	.1954	.4326	.1935
Squamous	.0799	.1262	.2883	.1157
	(p = .0007)	(p = .0102)	(p = .0228)	(p = <.0001)

* BAC *vs.* Adeno (p = .0824); BAC *vs.* Sq (p = .0554); Adeno *vs.* Sq (p = <.00001).

TABLE 8. *Univariate Time to Event Analyses for Survival and Recurrence Free Survival*

	Survival		Recurrence	
Term	Hazd. Ratio	P Value	Hazd. Ratio	P Value
T status				
T2	2.115	<.001	2.115	<.001
T3	3.587	<.001	4.054	<.001
N status				
N1	2.676	<.001	2.806	<.001
N2	3.110	<.001	3.207	<.001
Male sex	1.627	<.001	1.214	.051
Smoking status				
Former	1.217	.056	1.110	.313
Never	.8197	.305	.9258	.673
Race				
Non-White	1.218	.258	1.097	.611
Other	1.235	.395	1.342	.211
Extent of resection				
Lobectomy	.5123	<.001	.5724	<.001
Other	.5056	.002	.6177	.022
>10% weight loss	1.729	<.001	1.455	.024
Karnofsky > 8	.6789	.003	.7933	.091
Hx hepatitis	.9347	.818	.6001	.153
Hx chronic lung	1.216	.065	1.088	.428
Hx heart disease	1.346	.015	.9266	.570
BAC cell type	.7294	.008	.7006	.002
Age	1.018	<.001	1.008	.120
WBC	1.001	.052	1.001	.153
Calcium	.9334	.160	.9772	.671

can have massive intrapulmonary venoarterial shunting,[13] and some patients with advanced disease have a very productive bronchorrhea.[14,15] Shruffnagle[6] noted that bronchioloalveolar carcinoma accounted for approximately 6% of all primary lung cancers. It was associated with a higher frequency in women than other lung carcinomas and the

TABLE 9. *Multivariate Proportional Hazards Models for Survival*

Term	Coefficient	STD Error	P value	Hazd. Ratio
T2	.5698	(.103)	<.001	1.768
T3	.8939	(.205)	<.001	2.445
N1	.8299	(.133)	<.001	2.293
N2	.9976	(.130)	<.001	2.712
BAC Cell Type	−.2612	(.120)	.030	.7701
Age	.02801	(.0056)	<.001	1.028
T2	.5044	(.103)	<.001	1.656
T3	.8146	(.205)	<.001	2.258
N1	.8799	(.133)	<.001	2.411
N2	1.076	(.129)	<.001	2.932
Male Gender	.4269	(.106)	<.001	1.533
Age	.02696	(.0056)	<.001	1.027
>10% Wt Loss	.4805	(.158)	.002	1.617
BAC Cell Type	−.2060	(.121)	.089	.8138

TABLE 10. *Multivariate Proportional Hazards Models for Recurrence*

Term	Coefficient	STD Error	P Value	Hazd. Ratio
T2	.5461	(.103)	<.001	1.726
T3	.9916	(.208)	<.001	2.696
N1	.8277	(.132)	<.001	2.288
N2	.9703	(.131)	<.001	2.639
Age	.01598	(.0054)	.003	1.016
BAC Cell Type	−.2157	(.120)	.071	.8060
T2	.5299	(.103)	<.001	1.699
T3	.9975	(.208)	<.001	2.711
N1	.8548	(.133)	<.001	2.351
N2	.9875	(.131)	<.001	2.685
>10% Wt Loss	.3720	(.169)	.028	1.451
Age	.01563	(.0054)	.004	1.016
BAC Cell Type	−.1813	(.121)	.134	.8342

bronchioloalveolar group had fewer smokers. These authors noted that pulmonary scars were common and were associated with bronchioloalveolar carcinoma in 48% of the cases.

There has been debate over the years regarding the pathologic origin of bronchioloalveolar carcinoma. It was not until 1960 when Liebow[4] took the entities known as bronchiolo carcinoma, alveolar-cell tumors, and pulmonary adenomatosis and classified all of them as bronchioloalveolar carcinoma. The name bronchioloalveolar carcinoma suggests two origins—bronchiol and alveolar. Microscopically the tumor cells grow along the walls of the alveoli with frequent papillary projections into the alveolar spaces and the interstitial architecture of the lung is preserved (Figs. 7A and B). In addition, they often arise in or adjacent to scar tissue (Fig.8). Electronmicroscopy has identified clara cells or type 2 granular pneumocytes.[16] Immunohistochemistry and electron microscopy combined has revealed that some contain cellular subpopulations that produce mucosubstances and neuroendocrine products.[1] Tao et al.,[18] have further subclassified bronchioloalveolar carcinoma into three types, secretory, nonsecretory, and poorly differentiated. Edwards noted that the "bronchioloalveolar carcinoma is a heterogenous group of tumors which may be derived from either type

TABLE 11. *Multivariate Logistic Regressions Predicting BAC Cell Type Among Adenocarcinoma Patients*

Term	Coefficient	STD Error	P Value	Odds Ratio
Intercept	−10.48	(.466)	<.001	—
Age	.03468	(.00745)	<.001	1.035
Hx chronic lung	−.3741	(.169)	.027	.6879
Intercept	−10.42	(.469)	<.001	—
Age	.03058	(.00768)	<.001	1.031
Smoking status				
Former	.1880	(.146)	.199	1.207
Never	.4650	(.200)	.020	1.592

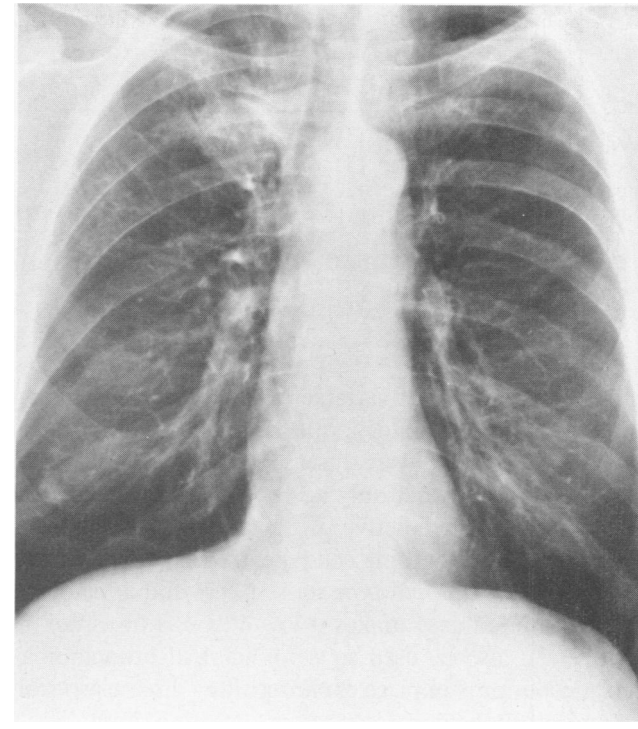


FIG. 5. This PA roentgenogram reveals a small T-1 lesion in the right uppper lobe and is typical of the many T-1 N-0 bronchioloalveolar carcinomas that were entered on the study.

II cells, clara cells, or bronchial mucous cells."[5] He also noted that many of them arose from bronchiomucous cells and were very similar to mucous-secreting adenocarcinomas, and further added that a substantial proportion of bronchioloalveolar carcinomas may arise from a bronchiol or stem cell that can differentiate into Type 2 cells, clara cells, ciliated cells, and goblet cells.

There are a number of reports of the surgical treatment and results for bronchioloalveolar carcinoma. In 1953 Storey and his colleagues[11] reported on three of their own cases and reviewed 205 other cases. They noted that of 112 cases of diffuse disease only 9 were resected with 3 patients living at the time of their report. However, in those with localized disease, 39 of 45 patients were resected, and 66% were long-term survivors. McNamara, et al.,[19] reported on 57 cases with bronchioloalveolar carcinoma, 41 of whom had resection of their tumors. There were 2 pneumonectomies, 35 lobectomies, and 4 segmental resections. Five-year survival rate by the life table method was 48%. Ludington[20] in 1972 reported operating on 10 patients with diffuse but operable lesions with 2 survivors, 1 of them living for more than 4 years. In 10 cases with localized disease, 7 patients were still living at the time of the report, 6 of whom reached the 2-year survival mark. In 1976 James et al.[21] reported on 48 patients with bronchioloalveolar carcinoma. Twenty-seven per cent survived 5 years or longer, but 13 of 32 who had

isolated peripheral nodules survived for 5 years (40.6%). Munnell,[22] in 1978, reported on 12 patients with bronchioloalveolar carcinoma who had lobectomy and noted that the overall 5-year survival rate was 75%. Greco et al.[23] in 1976 reviewed 122 patients with bronchioloalveolar carcinoma with an overall 5-year survival rate of 42% that ranged from 75% for those with Stage 1 disease to 66% for Stage 2, 12% for Stage 3, and 8.7% for Stage 3 M1. However, only 53% of Stage 1 patients were free of disease at 5 years. These authors caution that several patients who had segmentectomy for localized lesions had tumor recurrence along the plane of segmentectomy and suggested that an anatomical lobectomy is the procedure of choice.

Our study is the largest reported series of surgically resected bronchioloalveolar carcinoma of the lung. In addition, this series is the only series that had compulsive uniform operative staging performed so that the patients could be placed in an accurate TNM status. The study is weighted toward those patients with more localized disease because all patients were resected. This is reflected by the high number of T1-N0 and T2-N0 patients. In addition, all patients met strict and rigorous eligibility criteria for the protocols in which they were entered. They were followed as part of a treatment protocol minimizing differential follow-up and reporting bias. All specimens underwent an independent pathologic review and standard statistical methods were used to screen for and adjust for prognostic factors.

Our study noted a higher incidence of female involvement with the bronchioloalveolar cell type as compared to squamous-cell carcinoma, although there was no increase when compared to adenocarcinoma. When compared to adenocarcinoma, the bronchioloalveolar carcinoma patients in our study tended to have an earlier stage of disease. There were more nonsmokers and less of them had a weight loss of 10% or more. In addition, less had a history of hepatitis or chronic lung disease. Our study did not identify those patients with pulmonary scars but only those who had chronic obstructive pulmonary disease. Therefore, we were not able to make a correlation between pulmonary scars and associated bronchioloalveolar carcinoma.

The long-term mortality rate in our series for bronchioloalveolar carcinoma in the T1-N0 subgroup was 7% per year, which reflects a relatively favorable prognosis. However, the mortality rate of 12% per year for T1-N1 and T2-N0 disease and 40% per year for Stage 2 and 3 disease reflects the more dismal prognosis associated with advanced disease with this cell type. Again, this is similar data to the above papers, but because of the intraoperative staging it is more precise. As mentioned, the bronchioloalveolar carcinoma occurred more frequently in our series in female patients and those without a significant

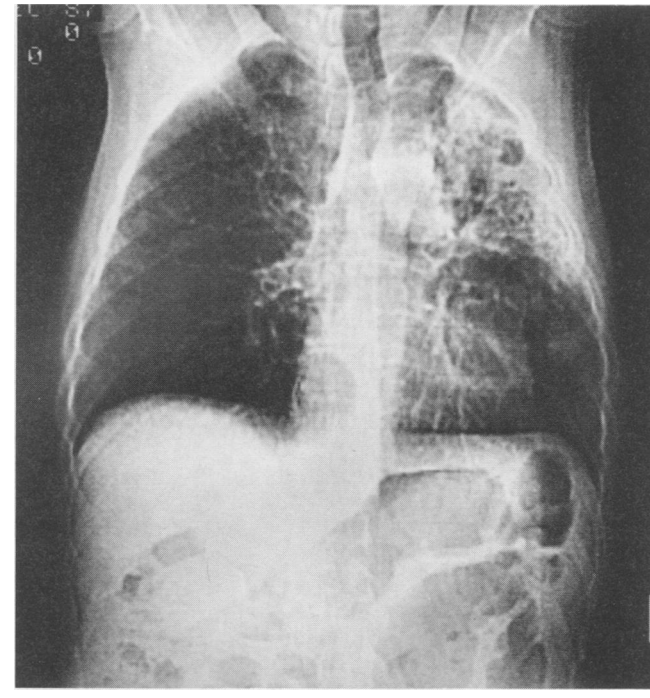
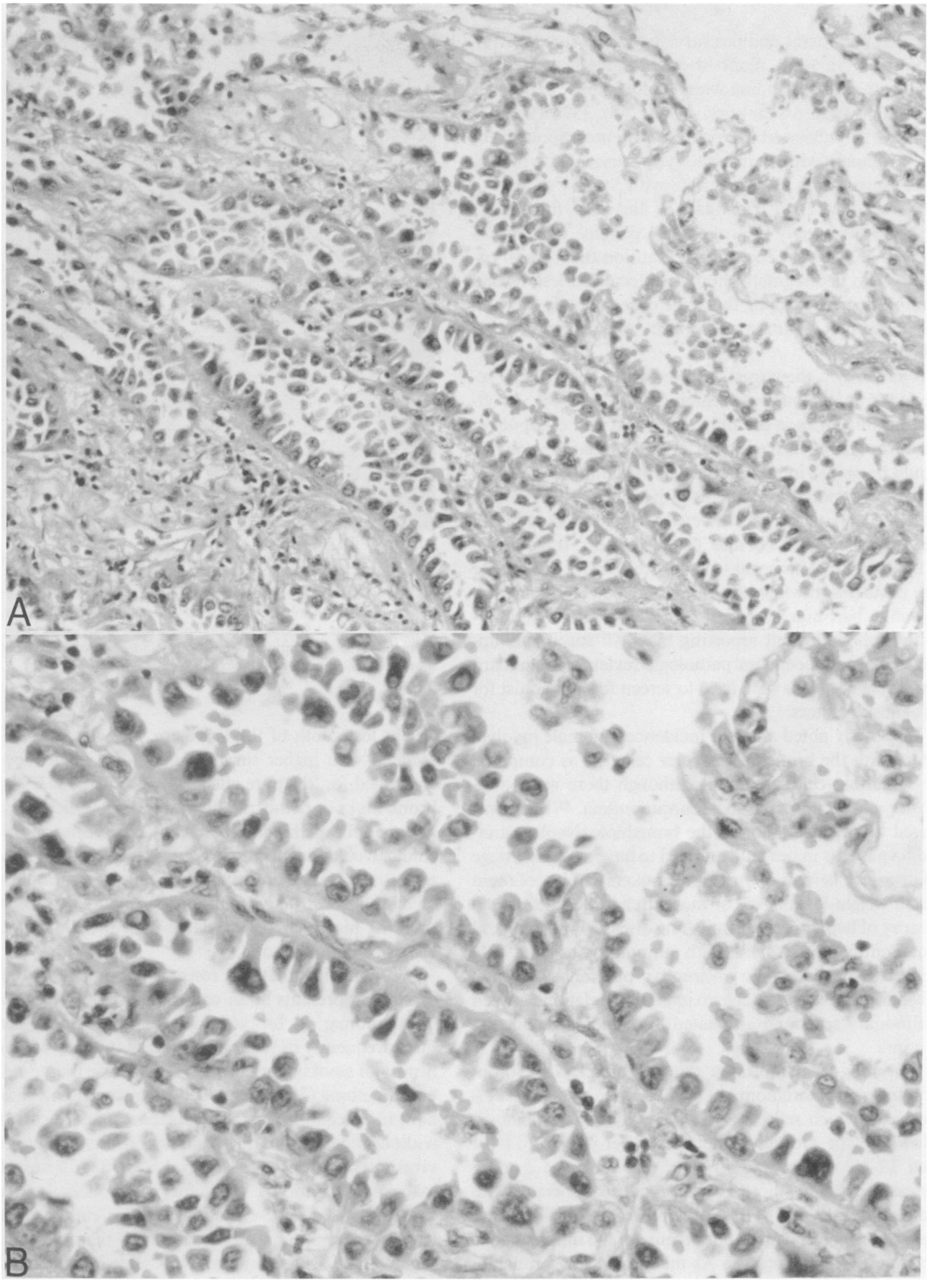


FIG. 6. This PA roentgenogram demonstrates a large consolidative lesion of the left lung that is a T-2 lesion but still resectable and represents one of the less favorable lesions that were included in this study. At operation this involved both lobes, was T2-N2, and required pneumonectomy. Patients with the diffuse bilateral infiltrative process sometimes seen with broncioloalveolar carcinoma were not included in this study because they are not surgically resectable patients.

weight loss. Both of the latter are variables that are associated with higher survival; therefore, when they are controlled for, the pure effect of the cell type is lessened. If one looks at demographic and historic differences between nonbronchioloalveolar adenocarcinoma and bronchioloalveolar adenocarcinoma, the multivariate logistic regression revealed only that advancing age, lack of history of chronic obstructive pulmonary disease, and a nonsmoking history were correlated with the bronchioloalveolar carcinoma group.

We conclude that (1) resectable bronchioloalveolar carcinoma presents at an earlier disease stage than adenocarcinoma; (2) bronchioloalveolar carcinoma occurs more frequently in older patients and in those without a history of smoking or chronic lung disease than does adenocarcinoma;(3) bronchioloalveolar carcinoma patients have less weight loss, brain recurrences, and recurrences without second primaries than adenocarcinoma;(4) survival and recurrence-free survival are better for bronchioloalveolar carcinoma than for nonbronchioloalveolar carcinoma and large-cell carcinoma;(5) early bronchioloalveolar carcinoma survival is better than the survival for squamous-cell carcinoma, but after 2 years the rates are equivalent;(6) T1-N0 bronchioloalveolar carcninoma patients have recurrence and survival rates similar to



FIGS. 7A and B. (A)This low power photomicrograph with H & E stain demonstrates the thickened alveoli with the dark hyperchromic nuclei of the abnormal malignant cells lining the alveoli. Adjacent are some thinner, more normal alveoli. The pulmonary architecture is preserved. (B) This is a higher-power photomicrograph of the same lesion revealing the malignant tumor cells lining the alveolar space with thickened septae.

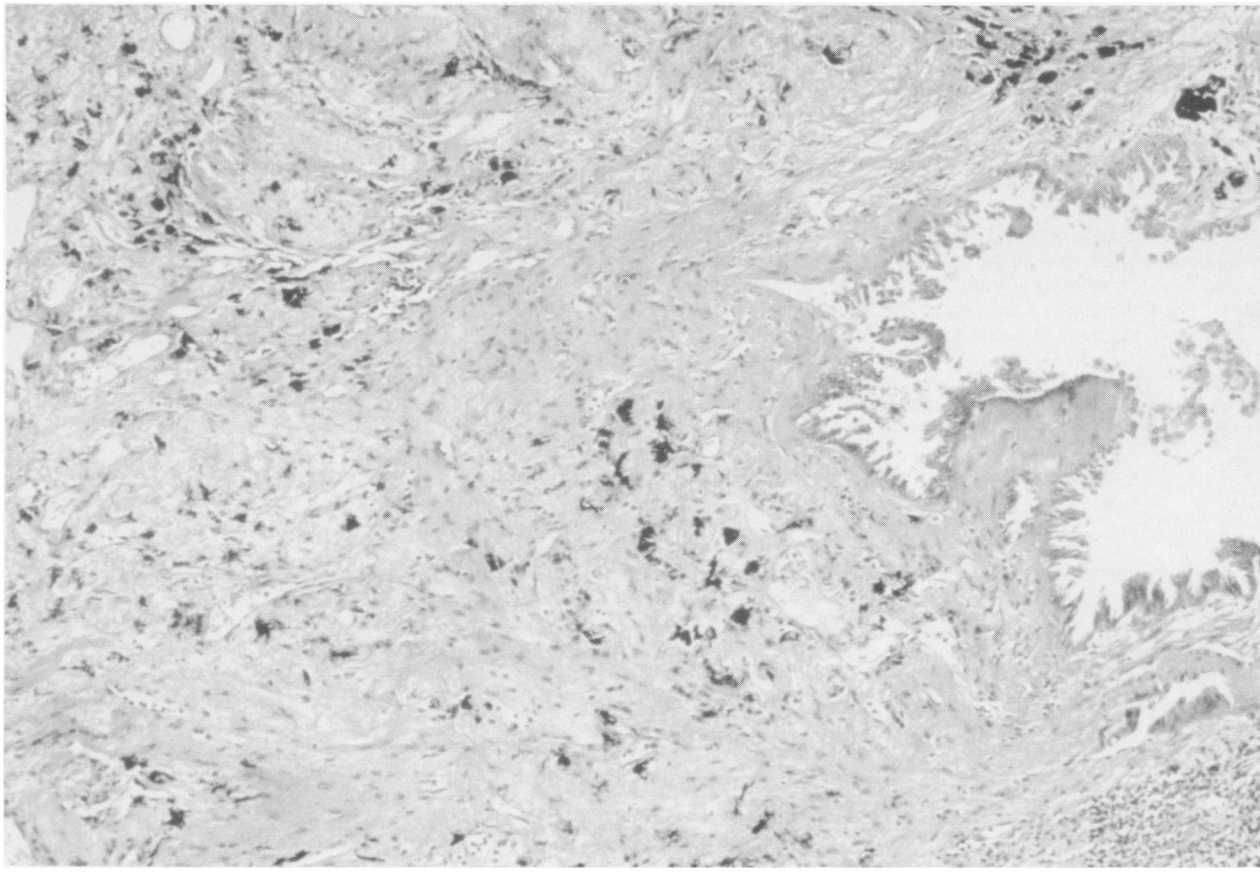


FIG. 8. This photomicrograph is from the same patient whose xray is shown in Figure 5. Note the scar adjacent to the alveolus which is lined with malignant cells. This tumor, therefore, represents the entity of a scar-bronchioloalveolar carcinoma. This has been reported to occur in more than 40% of bronchioloalveolar carcinomas.

squamous-cell carcinoma and better than nonbronchioloalveolar carcinoma;(7) T1-N1, T2-N0 and Stage 2 and 3 bronchioloalveolar carcinoma patients have recurrences more frequently than do either squamous-cell or nonbronchioloalveolar adenocarcinoma patients;(8) Stage 2 and 3 bronchioloalveolar carcinoma has a higher rate of mortality than do squamous or nonbronchioloalveolar adenocarcinoma;(9) bronchioloalveolar carcinoma is a favorable prognostic factor when adjusted for extent of disease and age;(10) the prognosis for patients with bronchioloalveolar carcinoma is at least as favorable as even that of squamous-cell carcinoma, both because bronchioloalveolar carcinoma seems to present at an earlier stage of disease (or equivalently progresses more slowly) and because this cell type appears to be less aggressive than other adenocarcinomas even after adjustment for extent of disease and other known prognostic factors. Early diagnosis and resection of bronchioloalveolar carcinoma while it is in an early stage is important.

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Discussion

Dr. Watts R. Webb (New Orleans, Louisiana): This has been a very beautiful presentation of a collected series from the Lung Cancer Study Group. I have had the opportunity to review this, and as you have the opportunity, you will see that this is a gold mine of information regarding this tumor that has not been very widely appreciated before, particularly the extent of it. The fact that one fourth of our adenocarcinomas really turn out to be bronchioloalveolar carcinomas was really much of a surprise, and I think perhaps the focusing of pathologic criteria has played a large part in this.

It was very interesting that about 40% of these bronchioloalveolar carcinomas proved to be scar carcinomas. In our series some years ago that looked at scar carcinomas, we were very much surprised to find that about 60% of these were the bronchioloalveolar carcinomas, which is a relatively small group over all.

The good news here, of course, is that if you get these early, the prognosis is quite good. If you get them late, the prognosis then becomes very bad.

It also emphasizes that if you are going to resect, you certainly should do more than a segmental resection because these tumors spread along the bronchi and the alveoli, and you must get completely around them.

We wonder if you noticed any evidence for aspirational metastases, not only lymphatic or hematogenous. We had some experimental data some years ago to indicate that the bilaterality and the multicentricity may be due to aspiration of tumor cells down the bronchi more than to conventional spread.

There is no denominator on this group because this is the resected group. I would like to know if you have, Fred, the number of total cases from which these resectable groups were taken. Also, we have occasionally seen some rather significant improvement in patients in response to radiation therapy and we wonder, while it is outside the scope of this study, if you have anything to indicate to us the role of chemotherapy and irradiation.

Dr. Frederick L. Grover (Closing discussion): Specifically, in answer to your question as to whether there is higher local recurrence if bronchioloalveolar carcinoma is resected by wedge or segmental resection rather than by lobectomy, it is true that there have been reports of local spread when one does less than a lobectomy because these tumors can be aggressive locally by both lymphatic and vascular invasion. At this point in our study we have found no evidence that there is a difference in recurrence or mortality with the degree of resection. I might add, however, that just two weeks ago we closed a protocol that compares lobectomy with segmentectomy or wedge resection in patients with T-1-N-O disease for all of the nonsmall cell types. This data will take about 3 to 4 years to mature, and at that point we may be able to answer this question because there were a significant number of patients in the bronchioloalveolar carcinoma subgroup entered into this study.

I don't have the information necessary to tell you whether we had any evidence of aspirated metastasis at this point, although I can say that on the basis of our analysis, there was no difference in local recurrence between the adenocarcinoma and the bronchioloalveolar carcinoma subgroups.

As for the denominator of the group, you rightfully pointed out and I want to emphasize again that patients who are entered into Lung Cancer Study Group protocols are patients who are operative candidates, so these were all surgically resected patients. I can tell you that from articles of individual institutions' experiences that approximately 45% to 60% of patients with bronchioloalveolar carcinoma present with resectable disease rather than with diffuse bilateral disease or with distant metastasis. Our series therefore is representative of the 45% to 60% of patients with bronchioloalveolar carcinoma who are surgically resectable.

In regard to the question of the efficiency of radiation therapy and chemotherapy, several of the protocols that these patients were entered into did involve these modalities. There was no difference in the rate of response of this tumor to those modalities compared to the other cell types. We did note in Stage II and III patients with completely resected adeno and large-cell carcinoma an increase in the disease-free interval of 6 months and a 7-month increase in survival in patients treated with CAP (Cytoxin, Adriamycin and Cisplatinum) in the postoperative period. In another protocol that studied patients who had incompletely resected nonsmall cell carcinoma, company postoperative CAP *versus* CAP and radiation therapy, we found a prolongation of median survival of 7 to 8 months in the group receiving both CAP and radiation therapy. The bronchioloalveolar carcinoma patients responded in a manner that was similar to the entire group.