Do patients with adenosquamous carcinoma of the lung need a more aggressive approach?

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Tumors harboring both glandular and squamous differentiation form a rare subset of non–small cell lung carcinoma known as adenosquamous carcinoma (ASC). Few studies have reported on series of ASCs, but all have emphasized the aggressive behavior of these tumors.[1,2] ASCs are associated with a poor prognosis, despite relatively good differentiation and mostly peripheral location, because of a high rate of early metastatic spreading. Patients with ASC have been reported to have a poorer prognosis than that of patients with either adenocarcinomas or squamous cell carcinomas, even in stages I or II.[1,3] The aim of this study was to correlate the pathologic findings with prognosis and to generate a reflection on the management of this type of lung cancer.

Patients and Methods

From 1984 through 1999, 69 patients underwent surgical resection for ASC of the lung. Mediastinoscopy was not routinely used preoperatively, but it was used in patients with mediastinal lymph nodes of more than 1 cm on computed tomographic scan to rule out N3 disease. Specimens from each of these patients were reviewed critically by one of us (J.B.) and classified as ASC according to the new histologic classification of lung and pleural tumors.[4] There were 50 men and 19 women. Mean age was 59 ± 10 years (range 35-83 years). Twenty-three (33%) patients were in pathologic stage I, 17 (25%) in stage II, 23 (33%) in stage IIIA, 1 in stage IIIB, and 4 (6%) patients in stage IV.[5] In 1 patient who underwent wedge resection without nodal dissection, the disease was not staged. The tumor was classified as central when located in a main or segmental bronchus (25%) and as peripheral when located distally in areas in which bronchi or bronchioles could not be seen macroscopically (75%). Diameter of the resected ASCs was 5.1 ± 2.9 cm (range 1.3-14 cm). The operative procedure consisted in pneumonectomy in 31 (45%) patients, lobectomy in 31 (45%), bilobectomy in 3 (4%), segmentectomy in 1 (1.5%), wedge resection in 2 (3%), and exploratory thoracotomy for biopsy in 1 (1.5%) patient. Eighty-four percent of patients had complete tumor resection associated with radical lymph node dissection.

Prognosis was analyzed according to tumor location, completeness of resection, tumor differentiation, N involvement (N0, N1, and N2), pleural invasion (P_0: tumor with no pleural involvement; P_1: tumor that extends beyond the elastic layer of the visceral pleura but not on the pleural surface; P_2: tumor that extends to the pleural surface but does not involve the parietal pleura; P_3: tumor involving the parietal pleura),[6] and size of the tumor. For further evaluation of the prognosis and comparison with other histologic subtypes, the completely resected ASCs (n = 58) were compared with the completely resected squamous cell carcinomas (n = 906) and adenocarcinomas (n = 499) observed during the same period. Survival curves of each subgroup were drawn by means of the Kaplan-Meier method, and the statistical analysis was carried out by means of the log-rank test. Prognostic factors were analyzed by the Cox proportional hazards model.

TABLE 1. Clinicopathologic correlation in 52 patients with completely resected ASC and radical lymph node dissection (not including in-hospital mortality and patients lost to follow-up)

	n	Five-year survival (%)	Median (mo)	*P* value
Proximal tumor	5	60	80	.01
Peripheral tumor	47	12	21	
Differentiated	29	52	44	.03
Poorly differentiated	23	23	20	
N0	27	47	42	.17
N1 + N2	25	30.8	19	
P_0	20	48.9	32	.005
$P_{1\text{-}2}$	24	39.6	22	
P_3	8	0	10	
≤3 cm*	17	75.1	100	.0005
>3 ≤ 5 cm	20	29.3	24	
>5 cm	15	8.3	9	
TNM stage I†	16	64.3	38.5	.027
TNM stage II	17	28.5	20.2	
TNM stage III	19	15.4	13.8	

*Tumor size ≤3 cm was compared with >3 ≤ 5 cm and >5 cm.
†TNM stage I was compared with TNM stage II and stage III. *P* was not significant when comparing stage II versus stage III.

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Results

In-hospital mortality was 3%. Pathologic examination revealed differentiated ASCs in 39 patients and moderately or poorly differentiated ASCs in 30 patients. ASC was intrapulmonary in 36% of patients (P_0) and had invaded the visceral pleura in 42% (P_{1-2}) and the parietal pleura in 22% (P_3). Lymph node metastases were found in 36 of 68 patients (53%): 32 (47%) patients had N0 disease, 13 (19%) had N1 disease, and 23 (34%) had N2 disease. Thirty-one (45%) patients had adjuvant radiation therapy and 8 (12%) patients had adjuvant chemotherapy.

Five patients were lost to follow-up. Among the 64 remaining patients, follow-up ranged from 0.5 to 118 months (mean 23.5 months). Global 5-year survival was 33.1% (median 20.3 months). Five-year survival was 36.7% (median 25 months) in patients with complete resection and 11.1% (median 15 months) in patients with incomplete resection, a difference approaching statistical significance ($P = .07$). The most significant pathologic characteristics were cell type differentiation, tumor size, location of the tumor, and visceral pleura invasion (P_{1-2}) (Table 1). P_{1-2} involvement was the most common factor associated with size of the tumor (P_{1-2}, 86% in tumors ≥5 cm) and location of the tumor (P_{1-2}, 67% among peripheral tumors).

When comparing squamous cell carcinomas and adenocarcinomas to ASCs, we found P_{1-2} disease to be more frequent among ASCs: squamous cell carcinomas P_{1-2}, 13.5%; adenocarcinomas P_{1-2}, 25.5%; ASCs P_{1-2}, 42% ($P = .01$). Five-year survival was also significantly different among the 3 histologic subtypes of non–small cell lung carcinoma, whatever the N involvement: squamous cell carcinoma, 47.2% (median 51 months); adenocarcinoma, 43.3% (median 42 months); and ASC, 34.9% (median 26 months) ($P = .02$). Multivariate analysis indicated that ASC location and pleural invasion were factors associated with a poor prognosis ($P = .01$ and $P = .06$, respectively).

Discussion

This study confirms the aggressive biologic behavior of ASC, as already pointed out by others.[1,2] Our results reemphasize the fact that ASC is a single, significant, and independent factor associated with a poor prognosis.[3] Moreover, our data show that the pejorative characteristics of ASC are its peripheral location and its propensity to invade the visceral pleura. Because such characteristics may allow tumor cells to exfoliate within the pleural cavity, we postulate that exfoliated tumor cells may be absorbed by the pleural lymphatics. So doing, those cells may reach the bloodstream, contributing to cancer dissemination. Further studies are needed to confirm our results. Should our hypothesis be verified, a more aggressive approach including radical lymph node dissection and adjuvant chemotherapy with or without radiation therapy might be considered in all patients with ASC, whatever the stage.

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