

## Cardiothoracic Transplantation

# Pulmonary transplantation for advanced bronchioloalveolar carcinoma

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**Background:** No effective therapy is currently available for the diffuse stage of bronchioloalveolar carcinoma.

**Objective:** We tested the hypothesis that total lung replacement with standard lung transplantation techniques would provide curative therapy.

**Methods:** Nine patients aged 31 to 58 years with bronchioloalveolar carcinoma were entered in the study. Five patients initially had bilateral diffuse tumor. Four patients had recurrence in the contralateral lung after pulmonary resection.

**Results:** Between 1993 and 1998, all 9 patients underwent transplantation (2 single-lung and 7 bilateral transplants, 1 reoperative single-lung transplant, and 1 reoperative bilateral transplant). Two patients had mediastinal node metastasis (level 7) at the time of transplantation, and 1 of these had a frankly invasive adenocarcinoma. Of the 8 patients with pure bronchioloalveolar carcinoma, 6 had recurrent pulmonary tumor after transplantation. In 2 of these patients the tumor was localized and could be resected with left lower lobectomy in one case and left pneumonectomy in the other. One is alive 89 months after transplantation; the other died 82 months after transplantation. Four other patients had a diffuse pattern of pulmonary recurrence. Two died of progressive pulmonary failure; 1 of these had retransplantation with recurrence. A third patient died of cerebral edema shortly after bilateral retransplantation. The other patient is alive with recurrence 39 months after transplantation and has bronchiolitis obliterans. Two patients without recurrence are well with unrestricted performance levels 87 and 76 months after transplantation.

**Conclusions:** Transplantation produces a powerful palliative outcome in patients with advanced bronchioloalveolar carcinoma, but the recurrence rate is high. Transplantation for this indication remains controversial.

**B**ronchioloalveolar carcinoma (BAC) comprises about 3% of the malignant tumors of the lung. It is characterized as a subset of pulmonary adenocarcinoma in which well-differentiated tumor cells grow along the walls of alveoli with preservation of the underlying lung architecture. The more malignant histologic features of adenocarcinoma (severe cytologic pleomorphism, solid tumors that destroy the lung architecture, and invasive fibroblastic stroma) are

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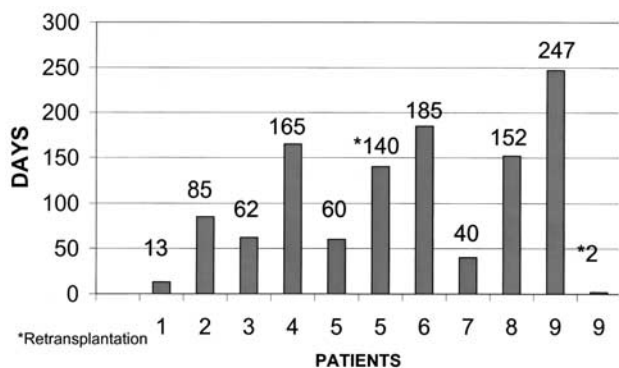
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**TABLE 1. Lung transplantation for BAC**

Case	Age (y)	Sex	Previous therapy	Transplant procedure
1	41	F	Right lower lobectomy	Bilateral with CPB
2	34	F	Left pneumonectomy	Right single with CPB
3	50	M	Right upper and right lower lobectomies, chemotherapy	Bilateral with CPB
4	53	M	None	Bilateral with CPB
5	48	F	Right pneumonectomy, radiation therapy	Left single with CPB
6	41	F	None	Bilateral with CPB
7*	50	M	Chemotherapy	Bilateral
8	58	F	None	Bilateral with CPB
9	31	F	Chemotherapy	Bilateral

CPB, Cardiopulmonary bypass.

\*Stage IV adenocarcinoma.



**Figure 1. Waiting time for transplantation in days. Cases 5 and 9 underwent retransplantation.**

absent. BAC usually is seen as a localized lesion, and surgical resection yields good long-term survival.<sup>1,2</sup> When the disease is diffuse and bilateral, however, survival beyond 2 years from the time of diagnosis is uncommon.<sup>3-5</sup> Disability and death are caused by pulmonary failure from tumor replacement of functioning lung, usually before regional or distant metastases occur. Effective treatment programs with radiotherapy and chemotherapy have not been established. We tested the hypothesis that total lung removal and replacement with standard single- and double-lung transplantation techniques could be curative for the diffuse form of BAC when confined to the lung.

**Methods**

Before lung transplantation, the histologic data from previous pulmonary resections and biopsy specimens of the original tumor were reviewed. Open lung biopsies were repeated as needed. At the time of open lung biopsy, a substantial pulmonary resection was required to ensure sampling of the central portion of the tumor. Mediastinal lymph nodes not accessible to mediastinoscopy were sampled at the time of open lung biopsy. All patients underwent bone scan, brain scan, computed tomographic scans of the thorax and upper abdomen, liver ultrasonography, and mediastinoscopy to exclude evidence of distant or regional metastasis. All

patients underwent a standard pulmonary transplant evaluation in addition to these studies. All study patients underwent transplantation between 1993 and 1998.

The study patients and their previous therapies are summarized in Table 1. Five patients were first seen with bilateral diffuse tumors that were unsuitable for localized pulmonary resection. Four patients had recurrence in the contralateral lung after pulmonary resection. The 2 patients with previous pneumonectomy underwent contralateral single-lung transplantation with cardiopulmonary bypass. The other 7 patients underwent bilateral sequential lung transplantation. Five of the 7 required cardiopulmonary bypass because of the inability to tolerate single-lung ventilation. The waiting times for lung transplantation are indicated in Figure 1. Immunosuppression consisted of cyclosporine (INN ciclosporin), azathioprine, and prednisone. No induction cytolytic therapy was used. Our standard follow-up care was given, including surveillance transbronchial biopsies at 3-month intervals during the first year, followed thereafter at 6-month intervals. Annual computed tomographic scans of the thorax and upper abdomen were added for tumor surveillance.

Survival curves were performed with the method of Kaplan and Meier.<sup>6</sup> Follow-up was through May 31, 2001. This study protocol was approved by the institutional review board, and study patients gave informed consent.

**Results**

The outcomes after transplantation are summarized in Table 2. After pathologic examination of the surgical specimens, 8 of the 9 patients were found to have true BAC. Three had the mucinous subtype (cases 4, 5, and 9) and the other 5 had the nonmucinous subtype. The tumor extensively involved the lung parenchyma, but all margins were free of tumor. All hilar and mediastinal lymph nodes were free of tumor except in 2 patients (cases 7 and 9), who had metastasis to level 7 lymph nodes. Case 9 had early diffuse recurrence at 9 months and died of cerebral edema 10 days after retransplantation. The second patient (case 7) had an invasive adenocarcinoma with a prominent bronchioalveolar pattern and metastasis to subcarinal lymph nodes (level 7). This patient is not included in the survival analysis in Figure 2.

Tumor recurrences in the transplanted lungs have occurred in 6 of the 8 patients with true BAC. Two patterns of

TABLE 2. Results of lung transplantation for BAC

Case	Rejection and treatment	Infection	Survival* (mo)	Status	Recurrence	
					Time† (mo)	Treatment
1	A3 and A2, bolus steroids (×2)	None	89	Unrestricted	39 75	Left lower lobectomy Wedge resection of right middle and right lower lobes
2	A2 ×2, bolus steroids (×2)	None	87	Unrestricted		None
3	None	None	82	Dead	49 68	Left lung, pneumonectomy Right lung, no treatment
4	None	None	76	Unrestricted		None
5	None	Pneumonia, <i>Staphylococcus aureus</i> and <i>Klebsiella pneumoniae</i>	33	Dead	12 32	Retransplantation None
6	A2 ×3, bolus steroids (×2), bronchiolitis obliterans, photophoresis	Cytomegalovirus	53	Severely restricted	27	None
7‡	None	None	38	Dead		Cerebral metastasis, chemotherapy, gamma knife Right rib metastasis, local radiation
8	A2 ×2, bolus steroids (×2)	Herpes zoster	15	Dead	10	None
9	A2 ×4, bolus steroids (×4)	CMV	21	Dead	9 21	Gene therapy Retransplantation

\*From date of transplantation; latest follow-up in cases of living patients.

†From date of transplantation.

‡Stage IV adenocarcinoma.

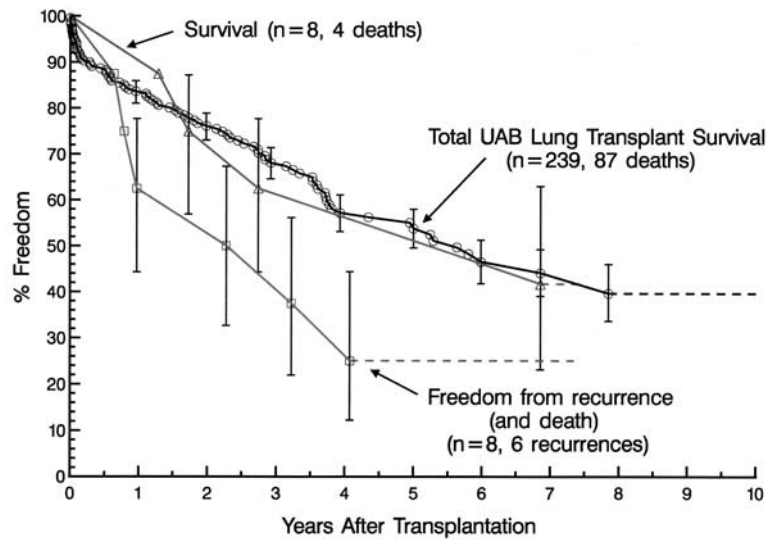
recurrence were noted: (1) one or more isolated lesions and (2) many small nodular lesions throughout the lung parenchyma. In 2 patients, secondary pulmonary resections for localized recurrent tumor were accomplished at 39 and 49 months after transplantation, but tumor has recurred again subsequently in both of these patients.

All patients achieved full rehabilitation and initial good quality of life after the transplant procedure. Pulmonary graft function has been good and stable (until the development of recurrent BAC) except in 1 patient who had bronchiolitis obliterans develop and has been treated with OKT3, tacrolimus, and photophoresis. Figure 2 shows the Kaplan-Meier depiction of overall survival and recurrence-free survival. Among the 8 patients with true BAC, 3 deaths were of pulmonary failure related to recurrent tumor in the transplanted lungs. The fourth death occurred after retransplantation for recurrent tu-

mor. Two patients had postmortem examinations, and no tumor was found in case 9. Case 5 had recurrent tumor in the lung parenchyma but no regional or distant metastasis.

### Discussion

Compared with the natural history of diffuse BAC,<sup>3-5</sup> complete pulmonary resection and transplantation resulted in improved survival and dramatic relief of severe dyspnea. Survival in these patients was comparable to that of patients undergoing lung transplantation for other types of end-stage lung disease. Twenty-five percent of our patients with true BAC had no apparent disease at 5 years. The main problem in pursuing this treatment method is the high rate of tumor recurrence. The mechanism of this is not understood, but the available evidence seems to indicate that the tumor is the same as the original lesions.<sup>7</sup> Effective treatment for recur-



**Figure 2. Survival and freedom from recurrence (Kaplan-Meier plot) after lung transplantation for 8 patients with pathologically confirmed BAC and survival for total lung transplantation population during same period. UAB, University of Alabama at Birmingham.**

rence has not been demonstrated. For those patients with localized lesions, resection may be a temporizing strategy, but its value is not established. No evidence of distant metastasis has been seen in the patients with true BAC, despite of long-term immunosuppression.

Our group stopped this study because of the high recurrence rate. A secondary reason was the increasing waiting time for transplantation. No patients died while waiting for transplantation, but several were desperately ill from pulmonary failure before transplantation. In our view, an argument can be made for using bilateral lung transplantation selectively for palliation in this disease if timely procurement of donor lungs is possible.

### Conclusions

In this small group of patients with BAC, 5-year survival after standard lung transplantation was 52%. The deaths were caused by pulmonary failure related to tumor recurrence in the lung allografts. The recurrence rate was 75% at 5 years. The mechanism of recurrence is not clear, and effective treatment for it is not available. Most patients had dramatic relief of their severe dyspnea and could return to

an active lifestyle. Transplantation for this indication remains controversial.

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