Tumor fluoro-2-deoxy-D-glucose avidity on positron emission tomographic scan predicts mortality in patients with early-stage pure and mixed bronchioloalveolar carcinoma

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Objective: Bronchioloalveolar carcinoma is a clinically heterogeneous subtype of non-small cell lung carcinoma that frequently has low 2-[18F]fluoro-D-glucose (FDG) uptake on positron emission tomographic scanning. We investigated whether tumor FDG avidity was associated with worse survival among patients with completely resected node-negative pure and mixed bronchioloalveolar carcinoma.

Methods: We performed a cohort study of 36 patients who had completely resected pure and mixed bronchioloalveolar carcinoma between 1998 and 2004, who had no hilar or mediastinal lymph node metastases, and who had undergone a preoperative positron emission tomographic scan. Tumor FDG avidity was defined as a standardized uptake value of 2.5 or greater. Survival analysis was performed with a proportional hazards model.

Results: Of 36 patients studied, 26 patients (72%) were alive and 10 patients (28%) were dead after a median follow-up of 31 months (interquartile range 17-41 months). Seventeen patients (47%) had FDG-avid tumors, and 19 patients (53%) had non-avid tumors. Three-year survival was 49% in the FDG-avid group and 95% in the non-avid group ($P = .005$). FDG avidity had a hazard ratio of death of 8.6 (95% confidence interval 1.4-244.7, $P = .02$) after adjusting for tumor size, the presence of multifocal bronchioloalveolar carcinoma, and the presence of histologically mixed bronchioloalveolar carcinoma.

Conclusions: Preoperative tumor FDG standardized uptake value of 2.5 or greater on positron emission tomography is a powerful predictor of long-term mortality in patients with lymph node-negative pure and mixed bronchioloalveolar carcinoma who undergo complete surgical resection. Patients with a high level of FDG uptake (standardized uptake value ≥ 2.5) may benefit from adjuvant chemotherapy or more frequent clinical follow-up.

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Bronchioloalveolar carcinoma (BAC) is classified as a subset of lung adenocarcinoma but has a distinct clinical presentation, tumor biology, response to therapy, and prognosis from other subtypes of non-small cell lung carcinoma (NSCLC).¹⁻⁴ BAC histology is most commonly found in small lesions identified incidentally on chest radiography or computed tomographic (CT) scan and may represent a precursor lesion to invasive adenocarcinoma.^{5,6} The 1999 World Health Organization criteria for diagnosis of BAC require the absence of stromal, vascular, and pleural invasion. Tumors with invasive features and BAC are categorized as adenocarcinoma with mixed features (mixed BAC). Whereas pure BAC accounts for about 4% of NSCLC, tumors with histologically mixed BAC and adenocarcinoma may account for 20% of all NSCLC, and the incidence of BAC

Abbreviations and Acronyms

BAC	= bronchioloalveolar carcinoma
CI	= confidence interval
CT	= computed tomography
FDG	= fluoro-2-deoxy-D-glucose
HR	= hazard ratio
IQR	= interquartile range
NSCLC	= non-small cell lung carcinoma
PET	= positron emission tomography
SUV	= standardized uptake value

may be rising.⁷⁻⁹ Stage for stage, patients with pure and mixed BAC have a higher rate of long-term survival than patients with pure adenocarcinoma.^{3,5,10}

Positron emission tomography (PET) with fluoro-2-deoxy-D-glucose (FDG) is a highly sensitive imaging modality to differentiate benign from malignant lung nodules and to detect the presence of mediastinal lymph node and distant metastases.¹¹ A standardized uptake value (SUV) above 10 has been associated with more advanced stage and increased mortality among patients with NSCLC.¹²⁻¹⁶ While approximately 85% of NSCLCs are FDG avid, only 50% to 60% of tumors with BAC histology are FDG avid, when FDG avidity is defined as an SUV of 2.5 or greater.^{17,18} Another study found that pure BAC was more likely to be undetectable with PET and multifocal BAC was more likely to be detectable with PET.¹⁹ Lower metabolic activity in tumors with BAC histology is presumed to be secondary to the slower rate of proliferation of BAC compared to other lung cancers. If a higher metabolic activity is associated with more aggressive tumor biology, FDG avidity might identify a group of patients more likely to have a recurrence and die of disease. These patients might be more likely to benefit from adjuvant chemotherapy or closer clinical surveillance.

We investigated whether preoperative tumor FDG avidity predicted long-term mortality in patients with early-stage lung cancer with pure BAC and mixed BAC adenocarcinoma. Since lymph node involvement is a powerful predictor of poor survival in patients with lung cancer, we restricted our study to patients without evidence of hilar and mediastinal lymph node metastases.

Patients and Methods

From 1998 to 2004, 76 patients who underwent lung cancer resection at our institution had BAC features on final pathologic examination. Specimens without stromal, pleural, or vascular invasion were classified as pure BAC, while specimens with BAC histology and any invasive features were classified as adenocarcinoma with mixed features (mixed BAC). All specimens were reviewed by surgical pathologists at the University of California, San Francisco, after resection; however, specimens were not reviewed for this study. One patient died within 30 days of the

operation and was excluded. Of the 75 remaining patients (Figure 1), we excluded from the study 4 patients with N1 only disease, 5 with N2 disease, 1 with T3 disease, 4 with unresectable or metastatic disease, and 1 patient who underwent wedge resection and did not have hilar or mediastinal nodal sampling. Patients with mediastinal FDG uptake who underwent neoadjuvant chemotherapy were considered to have N2 disease regardless of final pathologic stage and were excluded from the study. Of the 61 eligible patients, 40 (66%) underwent a preoperative PET scan. Five patients did not undergo preoperative PET scanning because mediastinoscopy alone was used for staging, and 3 patients did not undergo PET scanning because of subcentimeter tumors unlikely to be detected by PET scan. PET scanning only became routinely integrated into our clinical practice in 2001. Eleven of 13 patients with BAC who were operated on before 2001 did not undergo preoperative PET scanning.

Patients were administered an average of 14 mCi of FDG and imaged 60 minutes later with a CTI HR+ PET scanner (CTI PET Systems, Inc, Knoxville, Tenn.). Images were reconstructed with ordered subjects expectation maximization algorithm in two subsets with eight iterations. PET scanning was performed either at our institution or at satellite facilities. Maximum tumor SUV was recorded for each of the patients. Elevated FDG uptake was considered to be an SUV of 2.5 or more. This threshold is used at our institution for differentiating malignant from benign lung nodules when NSCLC is suspected and is a common threshold used in the literature.^{14,17,18,20} Four patients who underwent PET scanning at satellite facilities were excluded because maximum tumor SUV was not reported.

Four patients with completely resected multifocal BAC were included in this study. Three patients had more than one tumor in the same lobe of the lung and underwent lobectomy. One patient had two wedge resections, one from each lung, including hilar and mediastinal node sampling. In patients with multifocal BAC the largest SUV was used in the analysis. Thirty patients (83%) underwent lobectomy, 1 (3%) underwent pneumonectomy, and 5 (14%) underwent wedge resection or segmentectomy alone. Three patients (8%) were treated with neoadjuvant chemotherapy. Two patients were treated as part of a clinical trial of neoadjuvant chemotherapy for stage I and II lung cancer, and 1 patient with multifocal BAC (one in each lung) was treated with chemotherapy between resections. Prechemotherapy PET scan results were used in 2 of these patients. In 1 patient only a postchemotherapy PET scan was documented. As previously mentioned, patients with FDG-avid mediastinal nodes who received neoadjuvant chemotherapy were considered to have N2 disease and were excluded from the study. Two patients (5%) were treated with adjuvant chemotherapy for stage Ib disease.

All patients included in this study underwent preoperative chest CT scan with either 3- or 5-mm sections. The presence of ground-glass opacity and focal consolidation in or surrounding the tumor was recorded.

The Social Security Death Index was used to determine vital status and date of death. Follow-up time was defined as the number of months between the date of operation and the date of death or the date of data analysis for living patients.

Figure 1. Flow diagram of patient selection for this study. *BAC*, bronchioloalveolar carcinoma; *PET*, positron emission tomography.

Statistical Analysis

Clinical characteristics of patients with an SUV of 2.5 or more and an SUV of less than 2.5 were compared. All statistical analysis was performed with STATA release 9.1. Categorical variables were compared by the Pearson χ^2 test or the Fisher exact test. Continuous variables were compared by the Student *t* test or the Mann-Whitney rank sum test. Survival between FDG-avid and non-avid groups was compared by a proportional hazards model. *P* values and confidence intervals (CIs) for variables in the model were calculated by likelihood ratio testing. Each variable in the model was sequentially dropped to assess for confounding by noting changes in the hazard coefficient and *P* value with exclusion of a variable. The presence of multifocal BAC and mixed BAC were included in the model for face validity. Interactions were tested for by adding variable cross-product terms to the model.

Ethical Considerations

This research study involved analysis of existing data from the University of California, San Francisco, Thoracic Oncology clinical database with no subject intervention. This study was approved by the University of California San Francisco Institutional Review Board (approval number H8714-11647-10).

Results

Of the 36 patients studied, 26 patients (72%) were alive and 10 patients (28%) were dead after a median follow-up of 31 months (interquartile ratio [IQR] 17-41 months). The median tumor SUV was 2.2 (IQR 1.4-4.5). The distribution of tumor SUV and tumor size in patients alive and dead at last follow-up are graphically displayed in Figure 2. Seventeen patients (47%) had FDG-avid tumors, and 19 patients (53%) had non-avid tumors. Clinical characteristics of both groups of patients are summarized in Table 1. Mean age, proportion of women and Asians, and smoking status were similar in both groups. There was also no significant difference in the percentage of patients in either group who had ground-glass opacities or focal consolidation on CT scan. Patients with ground-glass opacities had a lower mean tumor SUV than patients without such opacities (1.8 vs 3.2), but this difference did not reach statistical significance (*P* = .16). No patient in this study had complete ground-glass opacities.

Operative procedure and histopathologic characteristics are summarized in Table 2. Of note, tumor size was significantly larger in the FDG-avid group (3.4 vs 2.8 cm), *P* =

Figure 2. Distribution of maximum tumor standardized uptake value (SUV) among patients with early-stage bronchioloalveolar carcinoma (BAC). Points represent patients who are labeled as either alive or dead at follow-up. Length of follow-up time was variable among patients. PET, positron emission tomography.

.05. The percentage of patients with adenocarcinoma with BAC features (mixed BAC) was not significantly different between groups, with 71% among patients with an SUV of 2.5 or larger compared with 53% among patients with an SUV less than 2.5, $P = .27$. The number of patients with multifocal BAC was also similar between groups, with 2 patients (12%) among patients with an SUV of 2.5 or larger compared with 1 patient (5%) among patients with an SUV of less than 2.5, $P = .59$.

TABLE 1. Patient characteristics stratified by FDG avidity

	SUV < 2.5 (n = 19)	SUV ≥ 2.5 (n = 17)	P value*
Age, y (mean ± SD)	70.0 ± 8.3	71.8 ± 9.0	.53
Female, n (%)	11 (58%)	11 (65%)	.68
Ethnicity			
Non-Asian	16 (76%)	18 (95%)	
Asian	5 (26%)	1 (6%)	.18
Smoking status			
Current	1 (5%)	0	
Past	12 (63%)	14 (82%)	
Never	6 (32%)	3 (18%)	.35
CT scan findings†			
Ground-glass opacity	4 (21%)	3 (18%)	.57
Consolidation	1 (5%)	4 (24%)	.14

FDG, Fluoro-2-deoxy-D-glucose; SUV, standardized uptake value; SD, standard deviation; CT, computed tomographic. *P value is for *t* test for age and Fisher exact test for all other comparisons. †Partial ground glass opacity or focal lung consolidation on CT scan.

TABLE 2. Procedure, pathology, and outcome stratified by FDG avidity

	SUV < 2.5 (n = 19)	SUV ≥ 2.5 (n = 17)	P value*
Surgical procedure			
Lobectomy or pneumonectomy	17 (89%)	14 (82%)	.65
Wedge resection or segmentectomy	2 (11%)	3 (18%)	
Chemotherapy			
Neoadjuvant	2 (11%)	1 (6%)	.8
Adjuvant	1 (5%)	1 (6%)	
Histology			
Pure BAC	9 (47%)	5 (29%)	.27
Mixed BAC	10 (53%)	12 (71%)	
Mucin-producing BAC	2 (11%)	1 (6%)	.54
Tumor size, cm (median, IQR)	2.8 (1.8-3.5)	3.4 (2.6-4)	.05
>3 cm	9 (47%)	11 (65%)	
<3 cm	10 (53%)	6 (35%)	.3
Multifocal tumor	1 (5%)	3 (18%)	.33
Median follow-up time, mo (IQR)	33 (22-41)	20 (16-39)	.57

FDG, Fluoro-2-deoxy-D-glucose; SUV, standardized uptake value; BAC, bronchioloalveolar carcinoma; IQR, interquartile range. *P value is for Mann-Whitney rank sum test for follow-up time and tumor size, and Fisher exact test for histology, multifocal procedure, chemotherapy, and multifocal tumor comparisons.

Overall, patients with FDG-avid and non-avid tumors received similar treatment for their lung cancer (Table 2). The proportion of patients treated with wedge resection was similar in both groups ($P = .65$). The proportion of patients treated with neoadjuvant or adjuvant chemotherapy was similar in both groups ($P = .80$). Median follow-up time was 33 months (IQR 22-41) among patients with an SUV of less than 2.5 and 20 months (IQR 16-39) among patients with an SUV of more than 2.5 (Table 2). Three-year survival was 95% for the FDG non-avid group and 49% for the FDG-avid group, $P = .005$ (Figure 3). When FDG avidity and mortality were analyzed alone in a proportional hazards model, the hazard ratio for SUV of 2.5 or more was 9.9 (CI 1.2-79.4, $P = .005$).

When tumor size, multifocal BAC, and mixed BAC were added to the model, the adjusted hazard ratio was 8.6 (CI 1.4-244.7, $P = .02$). When the proportional hazards model was run excluding patients who received neoadjuvant or adjuvant chemotherapy, the hazard ratio for FDG-avid tumors was 7.6, $P = .04$. Tumor size, multifocal BAC, and mixed BAC histology were not significantly associated with increased hazard of mortality in the multivariate model (Table 3) but were included because of existing evidence that these variables may predict worse long-term survival. There were no significant interactions among variables when tested by adding variable cross-products into the model.

Figure 3. Kaplan-Meier curves of patients with early-stage bronchioloalveolar carcinoma (BAC), stratified by fluoro-2-deoxy-D-glucose (FDG) avidity. *P* value given is calculated by the log-rank test. *SUV*, standardized uptake value.

Discussion

Our results suggest that preoperative tumor FDG avidity is a powerful predictor of long-term survival among patients who undergo resection of early-stage lung cancers with BAC histology. Although our study was small, patients with BAC histology and FDG-avid tumors on PET scan were more likely to die than patients with non-avid tumors, even after adjusting for tumor size, the presence of invasive features, and multifocal disease. Patient characteristics, such as age, female gender, Asian ethnicity, and smoking status were similar among both groups, suggesting that these factors were unlikely to account for a significant amount of the effect seen. Moreover, patients in both groups were treated similarly. Both groups had similar proportions of wedge resections or segmentectomies, and both groups had similar proportions of patients treated with adjuvant or neoadjuvant chemotherapy. Excluding the small group of patients who were treated with neoadjuvant or adjuvant chemotherapy did not change the conclusions of the study.

Among patients undergoing surgical resection of early-stage lung cancer, mediastinal lymph node metastases and, to a lesser extent, hilar lymph node metastases are powerful predictors of long-term mortality. PET scanning is increasingly used to evaluate for mediastinal and distant metastatic disease as part of clinical lung cancer staging. High-intensity tumor SUV, varying between 7 and 10 depending on the study, has consistently been associated with advanced-stage lung cancer and poor prognosis among patients with surgically resected lung cancer.^{11-14,20}

Unlike other subsets of NSCLC, PET scanning is not a useful diagnostic test to differentiate between a benign

TABLE 3. Proportional hazards model of the association between FDG avidity and mortality

	HR	95% CI	<i>P</i> value*
SUV $\geq$ 2.5	8.6	(1.4-244.7)	.02
Tumor size in cm	1.2	(0.8-1.6)	.39
Multifocal tumor	0.4	(0.04-4.2)	.39
Pure BAC	1.3	(0.3-6.1)	.71

FDG, Fluoro-2-deoxy-D-glucose; *HR*, hazard ratio; *CI*, confidence interval; *SUV*, standardized uptake value; *BAC*, bronchioloalveolar carcinoma.

**P* values and 95% confidence intervals were calculated with likelihood ratio testing.

pulmonary process and BAC since only approximately 50% of patients with BAC have FDG-avid tumors on PET scan. Our results demonstrate that among patients with lymph node-negative NSCLC with BAC features on histologic examination, the presence of tumor FDG uptake, defined as a maximum SUV of 2.5 or more, is useful in identifying a population at high risk for mortality. Patients at high risk for mortality might benefit from adjuvant cytotoxic chemotherapy or treatment with an epidermal growth factor receptor tyrosine kinase inhibitor. Conversely, patients with non-avid tumors, who in this study had a remarkable 95% 3-year survival, seem unlikely to benefit from adjuvant chemotherapy. Furthermore, this subset of patients might be adequately treated with a limited lung resection. The benefit of adjuvant chemotherapy in high-risk BAC group patients can only be determined by prospective trials or by analyzing the effect of adjuvant chemotherapy on mortality among existing adjuvant chemotherapy data in subsets of patients with BAC who have preoperative PET scan data.

In this study, we included patients with both pure and mixed BAC. Evidence strongly supports the prognostic value of any BAC features on histologic examination compared with pure adenocarcinoma. Although several Japanese investigators have described improved survival with pure BAC compared with mixed BAC, this finding has not been reproduced in Western institutions.^{10,21-25} In addition, the molecular biology of both pure and mixed BAC is distinct from pure adenocarcinoma, supporting the unique biological behavior of tumors with mixed BAC histology.²⁶ A limitation of this study, and any study including mixed BAC, is that a standardized classification scheme for mixed BAC that is reflective of prognosis does not exist. While only patients classified as having pure BAC meet the World Health Organization criteria for BAC, we included patients with mixed BAC in our study because they comprise a large proportion of patients with early-stage lung cancer and have similar PET characteristics to pure BAC. In this study, tumor FDG avidity remained a powerful predictor of mortality even after adjusting for the presence of invasive features in multivariate analysis.

Patients with BAC are a clinically heterogeneous group, and we used multivariate analysis to adjust for the presence of invasive features and the presence of multifocal lung cancer. Even after adjustment for these variables, FDG avidity remained a powerful predictor of mortality. Three patients with multifocal BAC were included in this study of early-stage lung cancer. At least one study demonstrated significantly greater detectability of multifocal disease on PET when compared with solitary BAC.¹⁹ We did not find that patients with multifocal BAC were more likely to have FDG-avid tumors, although we did not have enough patients with multifocal disease to detect a more subtle difference in FDG avidity. Although patients with multifocal BAC would be considered to have T4 or M1 disease by current American Joint Committee on Cancer TNM staging, patients with multifocal BAC who undergo complete surgical resection have long-term survival comparable with that of patients with stage I disease.^{27,28}

There are several limitations to this study. This is a single-institution study, and other institutions should confirm our findings. Also, although most patients were imaged at our institution, several patients had PET scans at satellite facilities that used a similar technique to perform the scans. Four patients were excluded because there was insufficient information on tumor SUV and technique. Finally, pathologic specimens were not re-reviewed for this study, although complete pathology reports were reviewed to ensure proper assignment of diagnosis. Although it would have been ideal to review the pathology of all our patients with BAC and adenocarcinoma, our results are arguably more generalizable to clinical practice.

The molecular basis for the unique biology of tumors with BAC histology is not well understood and more investigation is needed into the molecular predictors of survival in BAC. Until molecular markers of prognosis are identified and sufficiently validated for clinical use, tumor FDG avidity seems to be a reasonable surrogate marker of lung cancer aggressiveness. Among patients with BAC who undergo complete surgical resection, FDG-PET appears to be a powerful prognostic test to identify patients at high and low risk of mortality.

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