

Prognostic value of bronchioloalveolar carcinoma component in lung adenocarcinoma

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Summary. BAC is a common pattern in conventional lung adenocarcinoma. In the past, however, there were no well-defined criteria for BAC. As a result, it was difficult to evaluate the prognosis on this type of lung adenocarcinoma. Though the 1999 WHO classification of BAC provides a useful framework, it does not provide detailed enough information to predict prognosis in lung adenocarcinomas with BAC feature. The aim of this study was to address the prognostic value of bronchioloalveolar carcinoma (BAC) component in lung adenocarcinoma.

Ninety-one consecutive surgically treated patients with adenocarcinoma exhibiting various degrees of BAC features and complete follow-up records were retrospectively studied. According to the percentage of BAC component designed as less than 50%, 50%-79%, 80%-99%, and 100%, tumors were classified as type I, type II, type III, and type IV respectively. The overall 5-year survival rate was 64.84%. Multivariate analysis revealed that the four classified types are independent prognostic factors ($P=0.0008$), as is tumor stage ($P=0.0000$). The 5-year survival rates were 39.29%, 58.82%, 81.25%, 85.71% for the four classified types respectively, and were 88.89% for stage I, 46.15% for stage II, and 23.81% for stage III. However, the size of tumor (>2 cm) was significant only in the univariate analysis ($P=0.0275$). In the patients with tumor size exceeding 2 cm in diameter, the BAC component was also significant to predict prognosis ($p=0.0008$).

In lung adenocarcinoma, the BAC component may prove to be useful to predict the outcome of the patients, and the percentage of BAC pattern and pathological stage appear to be two independent prognostic factors.

Key words: Bronchioloalveolar component, Lung adenocarcinoma, Survival, Stage

Introduction

BAC is a common pattern in conventional lung adenocarcinoma. In the past, however, there were no well-defined criteria for BAC. As a result, it was difficult to evaluate the prognosis on this type of lung adenocarcinoma. In the 1999 WHO/IASLC classification (Travis et al., 1999), BAC is defined as an adenocarcinoma of the lung, which grows in a pure alveolar pattern, and the lack of invasive growth was added as an essential criterion. In fact, pure BAC is rare, accounting for only 2-14% of lung cancers (Travis et al., 1995; Bonomo et al., 1998). There have been a few studies recently on this issue in the literature. However, most of these studies focused on certain types of BAC, with some focusing on small size lung adenocarcinoma (Noguchi et al., 1995; Higashiyama et al., 1999), others on Stage I lung adenocarcinoma (Breathnach et al., 2001; Sakao et al., 2003), and still others comparing BAC with other types of lung adenocarcinoma (Goldstein et al., 1999; Rena et al., 2003). What is the critical value of percentage of BAC above which such components would have an effect on prognosis? And to what degree does the BAC component affect the prognosis? These important issues have not been fully analyzed in the literature.

The aim of this study was to address the above key issues. By examining a broad class of clinicopathologic factors (including gender, age, smoking history, size of tumor, mitoses, stage, and survival time, etc.), the result of this study showed the threshold level of BAC component to be 50% among cases in the sample. Furthermore, how different levels of the BAC component above the threshold level affect the prognosis

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Abbreviation: BAC: Bronchioloalveolar carcinoma; AJCC: American Joint Committee on Cancer.

of patients were analyzed.

Materials and methods

Clinical materials

All the cases of the lung adenocarcinoma patients at the Cancer Hospital/Institute of the Chinese Academy of Medical Sciences (CAMS) during 1993 to 1998 (a total of 781 cases) were retrospectively reviewed and analyzed. 1998 was chosen as the ending year in our study because we are interested in examining the factors affecting patients' five-year survival rate. Among the total 781 patients, 318 were found to be lung adenocarcinoma with BAC component. As a strictly implemented rule, our hospital conducts follow-up checks with all of our patients after they were discharged and for the rest of their life. The clinical follow-up record includes information about patients recovery and, more relevant to our study, their survival time.

Because of various factors, only 91 of the 318 patients of lung adenocarcinoma with BAC component had complete follow-up records. For the other cases, either the hospital had lost contact with them so we do not know whether or not they are still alive, or they had died of other diseases such as heart attack or cerebrovascular. Among the 91 cases with BAC component, 59 patients are still alive at the time of our study, and 32 patients had died of lung cancer.

The clinical data for the study included gender, age, smoking history, stage and follow-up records. Only those with a history of never-smoking were classified as non-smoker in our study. The follow-up records were considered from the date of operation. Each patient's disease was staged according to the AJCC (American Joint Committee on Cancer) criteria on TNM status in 1997, combined surgical resection and the pathologic examination results. For patients with two or more tumors in separate lobe or within the same lobe, we first tried to identify them to be synchronicity carcinogenesis or intra-lung satellite metastasis. Based on pathological-morphological analysis, the criterion used is as follows: When there is BAC component in the vicinity of cancer lesion with neighbor alveoli epithelium transitional changing, we may define it as primary lesion; otherwise it will be intra-lung metastasis (including the same lobe of lung metastasis, namely T4 and separate lobe lung metastasis, namely M1). In the current study, all the cases with BAC components were chosen and most of these multi-focal cases were thought to be multi-center carcinogenesis. The patients with multiple primary tumors were staged according to the most advanced TNM system.

Pathologic materials

The surgically resected tumors were routinely fixed in 10% neutral-formalin and embedded in paraffin. According to tumor sizes, three to six blocks were

obtained. Five micrometer sections were cut and stained with hematoxylin and eosin. The measurement of BAC percentage is as follows in this retrospective study. Each slide was observed under ocular field with grid (100 grids per field, supported by Olympus Company) and counted to get the ratio of BAC components. The average of BAC component of all slides was then taken for the tumor case. The process was repeated twice, and the final average was used as the percentage of BAC for a given tumor case. First, all cases were divided into two groups: those with BAC component below a given threshold level and those above it, and then each group compared with their five-year survival rate. The process was repeated for different threshold levels of 20%, 30%, 40%, 50%, ..., and 90%, respectively, and it was found that only when the threshold level reaches 50% did the BAC component affects the survival function significantly.

The sample tumors were then further classified into four types based on the percentage of BAC component within the whole tumor tissue. Those with less than 50% BAC component were classified as type I, those between 50% and 79% as type II, between 80% and 99% as type III, and 100% as type IV. Mitotic ratios were recorded in every 50HPF. The other pathologic factors included the size of the tumor and mitosis.

Statistical analyses

For the statistical study, all data were analyzed by SPSS (Version 10.0). The survival curve and survival analysis were constructed and conducted using the Kaplan-Meier method with log-rank analysis. The logistic-regression method was used for multivariate survival analysis in order to identify the independent prognosis factors. P value less than 0.05 was considered significant.

Results

The critical level of bac component and prognosis

The significance to predict prognoses occurred (with $P=0.0001$) when the percentage of BAC component reached 50%. Further studies were conducted to investigate the relationship between the four classified types and the 5-year-survival rate of patients. The results are showed in Figure 1. Among the 91 cases, 28 are type I (30.77%), 17 are type II (18.68%), 32 are type III (35.17%), and 14 are type IV (15.38%). The survival rates of type III and type IV patients were 81.25%, and 85.71%, respectively, which are significantly higher than those for type I and type II patients, whose 5-year-survival rates were 39.29%, and 58.82%, respectively, (with $P=0.0008$).

Other pathologic factors

Univariate analyses of other factors revealed that the

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effect on prognosis is significant if mitotic ratio exceeds 10/50HPF ($P=0.0001$), or if tumor size exceeds 2 cm ($P=0.0275$), (Fig. 2). In addition, among the patients with tumor size exceeding 2 cm, the four classified types were also significant to predict prognoses ($P=0.0008$), (Fig. 3).

Clinical factors and 5-year survival

Of the 91 patients, the mean age was 59.36 years old, and the median age was 63 with the range from 31-75. Among patients, forty-four cases were male, and forty-seven cases were female, with the male/female ratio being 1.017. Thirty patients had a history of smoking: fifty-seven patients did not, and four were unknown. Univariate analyses of sex and smoking history with survival significance were conducted. Neither of these exhibited significant prognostic value ($P=0.5347$ and $P=0.8979$, respectively).

Results of postoperative survival analyses of all patients for the stage are shown in Figure 4. The number of these cases were 54 for stage I cancer (9 for Ia, 45 for Ib), 13 for stage II (0 for IIa, 13 for IIb), 24 for stage III (21 for IIIa, 3 for IIIb), and 0 for stage IV. The overall 5-year-survival rate was 64.84%, of which 88.89% was for stage I cancer (100% for Ia, 86.67% for Ib), 46.15% for stage II (IIb), and 23.81% for stage III cancer (23.81% for IIIa, 0 for IIIb), with $P=0.0000$. Thus, those patients with Ia stage cancer had the best prognosis (survival rate of 100%), and the survival rates of the patients with stage II and advanced stage were obviously

much lower.

Univariate and multivariate analysis for survival

Among the relationships presented above between gender, smoking history, tumor size, mitotic rate, classified type, and tumor stage with prognosis, only tumor size, mitotic rate, classified type, and tumor stage were significant prognostic factors in univariate analysis.

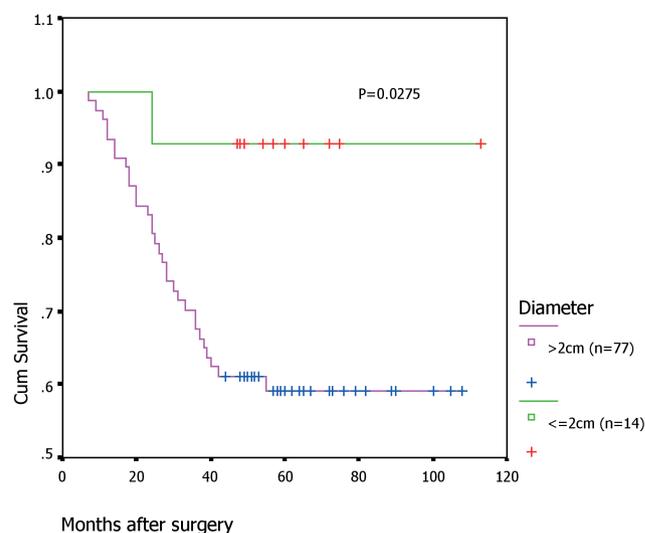


Fig. 2. Cumulative survival curves of tumors grouped by size at cut-off point of 2 cm in diameter.

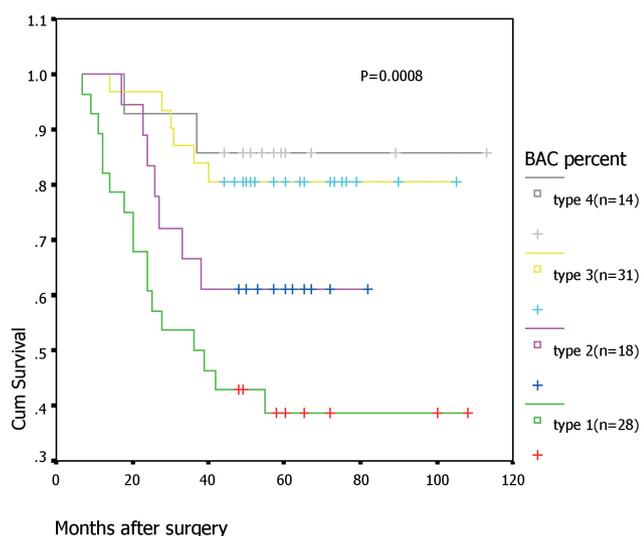


Fig. 1. Cumulative survival curves by the histologic subtypes (type I= adenocarcinoma with less than 50% BAC component; type II= adenocarcinoma with BAC component between 50% and 79% percentage; type III= adenocarcinoma with BAC component between 80% and 99% percentage; type IV=pure BAC).

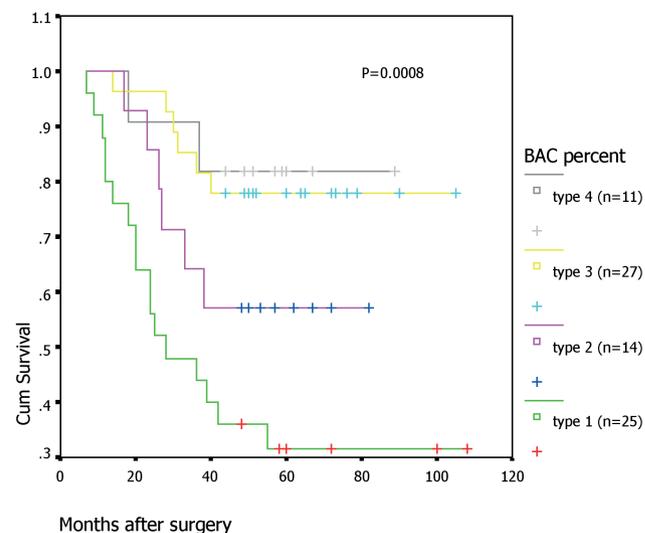


Fig. 3. Cumulative survival curves of the histologic subtypes grouped by tumor size exceeding 2 cm in diameter.

However, multivariate analysis of the same parameters revealed that only the effects of classified type and patients' stage were statistically significant. So, the classified type and stage were two independent prognostic factors with statistical significance, both with $P=0.0001$. The OR ratios were 0.585, and 3.011, respectively, whereas the PE values were -0.53 and 1.10 , respectively.

Percentage of bac component and other parameters

Our study also tested the association between BAC component classification (type I-IV) and other clinicopathological factors in lung adenocarcinoma. The results are shown in Table 1. Of these factors, mitotic ratio and stage had significant difference with classified types (with $P=0.001$ in both cases). Among these patients with less than 10/50HPF mitotic ratios, 62.26% (33 out of 53) were type III or type IV patients. Type I cases were dominant among the patients with more than 10/50HPF mitotic ratios, accounting for 52.63% (20 out of 38). In addition, the association between stage and classified types showed that type III or type IV patients accounted for 64.82% (35 out of 54) in patients with stage I, while in the patients with stage II and III, type I patients were dominant, accounting for 61.54% (8 out of 13) and 50% (12 out of 24), respectively.

Discussion

When analyzing the follow-up data, our analyses of 91 patients show that in lung adenocarcinoma the percentage of BAC component had a prognostic factor when it was more than 50% of the tumor. This finding coincides with the approach used the literature. For instance, Koga (Koga et al., 2001) proposed that BAC

with invasion (less than 50% of the invasion area) should be classified as an independent histological subtype. Based on this, tumors in our data were divided into three types of: Type II: adenocarcinoma with predominant bronchioloalveolar component (BAC content between 50% and 79%); Type III: mixed bronchioloalveolar subtypes with focal invasion (BAC content between 80% and 99%) and Type IV: pure BAC. (Those cases with BAC content lower than 50% are called Type I.)

The prognostic results within the four types showed that type I is the worst subtype in terms of 5-year survival rate. Type III or Type IV together is better than Type I or Type II, while Type III and Type IV have similar survival rates. The latter property implies that there are no prognostic differences between pure BAC and mixed BAC with small area invasion (less than 20% of the invasion area) in predicting the outcomes. Taken together, the classification based on the degree of BAC involvement in lung adenocarcinoma, as found in this study, may better reflect the prognostic characteristics: A higher percentage of BAC favorably influences survival rate of the patient.

Our classification is confirmed by univariate and multivariate statistical analyses and are consistent with the results of other studies (Breathnach et al., 1999; Suzuki et al., 2000; Yokose et al., 2000; Castro et al., 2001). It is worth noting that in the study by Ebright (Ebright et al., 2002), the subtype of PBAC (pure bronchioloalveolar carcinoma) and BWFI (bronchioloalveolar carcinoma with focal invasion) were similar to type IV and III mentioned in our study, but neither PBAC or BWFI had prognostic difference with AWBF (adenocarcinoma with bronchioloalveolar feature). A possible reason for the different findings is

Table 1. Correlation between the clinicopathologic features and histologic subtypes Based on BAC Component.

	Type I (n=28)	Type II (n=17)	Type III/IV (n=32/14)	Total (n=91)	P Value
Sex(M/F)	13/15	9/8	22/24	44/47	NS
Age(yrs, mean)	57.16	58.47	60.76	59.36	NS
Smoking					
-	16	12	29	57	NS
+	11	5	14	30	
Unknown	1	1	2	4	
Size					
≤ 2cm	3	4	7	21	NS
> 2cm	25	14	38	70	
Mitotic rate					
< 10/50HPF	8	12	33	53	0.001
≥ 10/50HPF	20	5	13	38	
Stage					
I	8	11	35	54	0.001
II	8	1	4	13	
III	12	5	7	24	

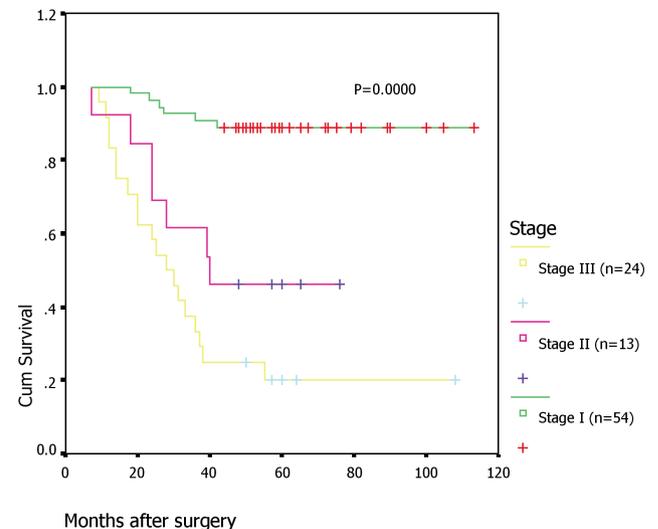


Fig. 4. Cumulative survival curves of tumors grouped by stage.

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that many lung adenocarcinomas with BAC component were not included in the sample of Ebright's data, and the association between histological subtype based on BAC component with clinical stage was not evaluated as well in their study.

Consistent with findings in the literature (Iisu et al., 1995; Regnard et al., 1998), our study also showed that patient stages (stage I, II, III) have significant impacts on 5-year survival rate. In particular, as in Noguchi (Noguchi et al., 1995) reported that stage Ia patients had a survival rate of 100%. In contrast, Stage II or Stage III patients showed a worse clinical outcome than did stage I patients. This conclusion was also demonstrated by Volpino (Volpino et al., 2001). This is clearly suggestive of oncobiological characteristics of the tumors.

The component of BAC in lung adenocarcinoma may predict clinical course. This was reflected in our study when stages (I, II, and III) were compared with histological subtypes (type I, type II, type III/IV). Our data suggest that the classified type is closely related with stage. In particular, type III/IV was dominant in stage I, whereas type I was dominant in stage II or stage III. This indicated that higher BAC component is associated with better biological characteristic. This is similar to findings in other studies. For example, Brethnach's work (Brethnach et al., 2001) showed that BAC in stage I had a favorable prognosis, with a 5-year-survival of 83%, whereas other mixed type lung adenocarcinoma in that study had a 5-year-survival of only 63%.

Furthermore, univariate analysis of the sample data demonstrated that the tumor size and mitotic ratio both have significant impacts on 5-year-survival rate. Specifically, tumor size of 2 cm is a useful cut-off point, consistent with some other reports (Goldstein et al., 1999; Sakao et al., 2003). In addition, of the patients with the tumor size exceeding 2 cm, the four classified types may be also significant to predict prognoses. This hasn't been reported before. Mitotic ratio may predict a worse prognosis when it is over 10/50HPF. (Noguchi et al., 1995, mentioned that mitoses higher than 5/10HPF would predict worse prognosis in their study of tumors smaller than 2 cm.) However, the above relationships were not significant in our multivariate analysis.

In the analyses of other clinical factors with prognosis, other reports had found that BAC appears to be higher in incidence in female patients (Liu et al., 2000; Ebright et al., 2002). They also found that female patients have a significantly longer survival rate than male patients. On 5-year-survival rate and smoking history, Koga (Koga et al., 2001) predicted a significantly negative relationship. In our study, however, there was no significant relationship between gender and incidence or outcome. Similarly to what was reported in the literature, 1/3 of all patients in our sample (30 cases) had a history of smoking. Among the 30 patients, only 5 were female. There was no significant difference between 5-year-survival rate and smoking history.

To sum up, while the 1999 WHO classification of BAC provides a useful framework, it does not provide detailed enough information to predict prognosis (Laskin et al., 2005). In the present study, the classification is based on the BAC component area in lung adenocarcinoma. First, this study indicated the threshold level of BAC component to be 50% among cases in our samples, as confirmed in many existing studies. Based on this, lung adenocarcinomas with BAC component were further divided into three types: adenocarcinoma with BAC feature (less than 50% BAC), adenocarcinoma with predominant bronchioloalveolar component (BAC content between 50% and 79%); mixed bronchioloalveolar subtypes with focal invasion (BAC content between 80% and 99%) or pure BAC. This more detailed classification may prove that the percentage of BAC component and patient stages are two independent prognostic factors. Additionally, these results were supported by both univariate and multivariate analyses.

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