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Lung carcinomas with a basaloid pattern: a study of 90 cases focusing on their poor prognosis

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ABSTRACT

Lung carcinomas with a basaloid pattern (BC) are classified as either basaloid variant of squamous cell carcinomas (SCC) or as variant of large cell carcinomas (LCC) depending on the presence of a squamous component. In a previous study of 37 cases, we showed that BC presented a shorter median and overall survival.

In order to confirm its clinical significance in a larger series, 90 BC, including 46 basaloid variants of LCC and 44 basaloid variants of SCC, were compared with 1328 other Non-Small cell Lung Carcinoma (NSCLC) with regard to clinical features and survival.

The survival of basaloid variants of large cell carcinomas and SCC was comparable. Median and overall survival were significantly lower for BC than for NSCLC in stage I-II patients, with a median survival of 29 and 49 months respectively, and 5-year survival rates of 27 % and 44% for BC and NSCLC (p=0.01). When disease-specific survival was considered, BC had a shorter survival than NSCLC (p=0.014) and SCC (p=0.005).

Basaloid pattern confers a poor prognosis in NSCLC, especially in stage I-II patients, suggesting that BC is not only a variant of SCC or large cell carcinoma but is a unique entity with a significantly poor prognosis.

KEYWORDS

Lung cancer • basaloid carcinoma • diagnosis and staging • pathology

INTRODUCTION

In the last two decades basaloid carcinomas have been identified in organs other than the lungs as aggressive tumors with a poor prognosis [1-7]. In 1992, we first reported this entity in the lung, and described its clinicopathological features in a founding paper based on the observation of 37 basaloid carcinomas. Carcinoma with basaloid pattern is now recorded in the WHO classification either as a variant of large cell carcinoma (LCC) in its pure form, or as a basaloid variant of SCC when associated with areas of squamous differentiation. Interestingly, these two histological subtypes, which both belong to the Non-Small Cell Lung Carcinoma (NSCLC) group, share a poor prognosis when compared to other NSCLCs, with a median survival of 20 months in the operable stages [1, 7, 8, 9]. This finding led to their recent inclusion in the revised WHO classification besides other prognostic entities, such as large cell neuroendocrine carcinomas or sarcomatoid carcinomas [10-15]. their prognostic significance has recently been questioned in a report based on a series of 35 basaloid carcinomas [16], which prompted us to carry out a new analysis on a larger series of 90 cases with a longer follow-up. We confirm herein our previous observations, and demonstrate that the basaloid pattern confers in itself a poor prognosis irrespective to the variant it belongs to, justifying the inclusion of the two variants with BC pattern within the same clinicopathological entity.

Materials and methods

Patients

Between January 1st, 1979 and December 31st, 2003, 90 out of 1418 cases of NSCLCs were classified according to the revised WHO classification criteria [10, 11] as basaloid variant of large cell carcinomas (n= 46), or as variant of SCC (n= 44) by two expert thoracic pathologists (EB, SL). Among them, 37 cases have already been described in the founding

paper in 1992. In the current study we have decided to analyze all carcinomas with basaloid pattern within the same group. The non BC group of 1328 patients included other histological subtypes without basaloid features (i.e. SCC; n= 884, adenocarcinomas; n= 387, Large cell carcinomas; n= 57). LCNEC were not included in the control group because of previously established unfavorable prognosis. All cases were resected in the same institution. The post-operative stage distribution was as follows: Stage I; 582 patients (BC 38, non BC 544), stage II; 459 patients (BC 28, non BC 431), stage IIIA; 369 patients (BC 16, non BC 353), and stage IIIB/IV; 8 patients (BC 8, non BC 0). The main clinical and surgical characteristics are detailed in Table 1.

Pathological examination

The basaloid pattern was characterized according to the 1999 and 2004 WHO classifications by a proliferation of relatively small cells presenting a typical high mitotic rate, forming a lobular pattern with peripheral palisading and comedo-type necrosis [10, 11]. The basaloid variant of large cell carcinoma was considered when cells were devoid of intercellular bridges or individual cell keratinization. However, according to the first description of basaloid carcinoma by Brambilla et al, were have decided to include as an additional criteria the presence of foci of abrupt pearl formation in the absence of progressive squamous maturation. In contrast, the variant of SCC was retained when squamous differentiation was obvious, but representing less than 50% of the tumor in agreement with the 1999 classification. Because 30% of basaloid carcinomas can exhibit rosettes, the absence of immunohistochemical neuroendocrine markers was systematically provided to rule out Large Cell Neuroendocrine Carcinomas (LCNEC) or Small Cell Lung Carcinomas (SCLC). In addition, because the basaloid pattern, as any non small cell carcinoma, may display one or two neuroendocrine markers in a small proportion (<10%) of tumor cells, the diagnosis of carcinomas with a

basaloid pattern was maintained when less than 10% cells displayed one NE marker in the presence of expression of a specific set of cytokeratins CK 1, 5, 10, and 14, recognized by the 34βE12 monoclonal antibody was present, those cytokeratins being never expressed in the NE tumors (8) .The post surgical (pathological) stages were determined according to the international TNM AJCC UICC classification [17].

Data collection

All surgical resections have been prospectively registered since 1998 in a computerized database. Cases prior to 1988 were revisited before registration, and all cases were reclassified using the TNM AJCC UICC classification [17]. As the median age of all patients was 63, 2 age categories, ≤63 years and >63 years, were considered in univariate and multivariate analyses. The Charlson comorbidity index was computed for each patient [18].

Statistical Analysis

Descriptive analyses comparing categorical variables were carried out using Fisher exact tests. Descriptive analyses comparing continuous and two-level categorical variables were carried out using t tests. Median follow-up was calculated by the Schemper and Smith method [19]. Overall survival was calculated from the date of surgery to the last day of follow-up or death. Disease-specific survival was computed using only lung cancer deaths and censoring all other causes of death. All patients surviving more than 5 years were censored after this time in order to avoid bias due to late mortality associated with comorbidity. Deaths occurring during the first 30 days after surgery were considered as hospital mortalities. Univariate survival analyses were performed using the Kaplan-Meier method and the log-rank test. Multivariate analysis was performed using a Cox proportional hazard model. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. Statistics were performed using

Statview 4.1 software (Abacus Concept Inc, Ca). A p-value of less than 0.05 was considered statistically significant.

Survival analyses were performed on the entire cohort of patients. To avoid bias related to organ failure caused by tumor compression or involvement, survival analyses were performed for stage I patients and stages I and II patients. Moreover, to avoid all bias related to perioperative mortality, analyses were carried out on patients surviving 1 month after the surgical resection. In order to obtain a sufficient number of patients and to avoid underpowered analyses, the latter survival analyses were performed on stage I-II patients (BC 59 patients, others 913 patients).

Results

Among a cohort of 1418 patients, 90 BC were diagnosed (prevalence 6.3 %). In the group of 90 carcinomas with basaloid pattern, 46 basaloid variants of large cell carcinomas and 44 basaloid variants of SCC were identified and considered as a whole (Figure 1A and B). The clinical characteristics of BC and other NSCLCs without basaloid features (non BC) are shown in Tables 1 and 2.

Most of the clinical characteristics were well balanced between these two groups. Patients with BC had greater tobacco consumption than patients with non BC, The presence of a single or multiple synchronous CIS on the surgical specimen was more frequent in the BC group than in the non BC and SCC groups (Table 1).

The median duration of follow-up was 109 months. The median actuarial survival of the 1418 patients was 40 months. At the time of the current study, 972 patients died (BC: 70, non BC : 902), 471 of them with a relapse of lung cancer (BC: 46, non BC : 425). Stage I patients had comparable clinical and therapeutic characteristics within the BC, non BC and SCC groups (Table 2); however, patients with BC were slightly older than the non BC patients (Mean age

65.8 years versus 62.4 years; p: 0.03). The causes of death for stage I patients are detailed in an additional table (Online only).

No difference in survival between patients with a basaloid variant of large cell carcinomas and those with a basaloid variant of SCC was observed (Log rank p: 0.34), although a trend for shorter survival could be noted in the basaloid variant of the large cell carcinoma group (median survival 29 versus 36 months). Survival analyses performed in the different stages and histological groups are reported in table 3. Among these analyses the most significant differences were observed in the cohort of early stage I and II patients (figures 2 and 3).

When disease- specific survival was considered, BC had a shorter survival than non BC (Log rank p: 0.014) and SCC (Log rank p: 0.005). Basaloid variants of SCC were compared to SCC in stage I patients. Despite median and 5 years survival very similar to that observed in other analyses on stage I the log rank test was not significant (p : 0.19), this might be explained by the small number of patients in stage I basaloid variants of SCC group (19 patients).

Univariate analyses in stage I identified 3 other significant factors of prognosis: pathological T status (p: 0.01), age 63 or greater (p: 0.0007) and a Charlson comorbidity index of >2 (p: 0.0007) (Table 4). Cox proportional hazard models evaluating the independent hazard associated with baseline covariates were performed for stage I patients. Age, T status, presence of a basaloid pattern and a Charlson comorbidity index of >2 were associated with a prognostic significance (Table 4, model A). When excluding early post-operative deaths from the cohort of patients, age, T status, presence of a basaloid pattern, and a Charlson comorbidity index of >2 were still associated with a prognostic significance (Table 4, model B).

Discussion

Carcinoma with a basaloid pattern (BC) is a rare histological subtype of lung cancer with a prevalence of 6.3% in the current study based on 1418 NSCLC consecutive patients treated in the same institution. This type of tumor is well recognized in other locations such as the head and neck, esophagus and anal canal, where it is defined as "basaloid squamous cell carcinoma", irrespective of the amount of squamous differentiation and has a peculiarly aggressive behavior, characterized by a high frequency of lymph node and visceral metastases [1- 6]. However, because of the distinction in the WHO classification of lung tumors of two basaloid variants belonging either to the SCC group or to the large cell carcinoma group, diagnosis of lung carcinomas with a basaloid pattern remains a difficult area for pathologists. First, basaloid carcinoma pattern may represent diagnostic pitfalls, particularly on small or crushed tissue samples from bronchial or transthoracic fine needle biopsies [1, 11], or can be misdiagnosed either as adenoid cystic carcinoma, small cell lung carcinoma, large cell neuroendocrine carcinoma. Adenoid cystic carcinoma, typically lacks a high mitotic index and comedo-necrosis. With the help of a newly described panel of immunohistochemical markers, small cell lung carcinoma and large cell neuroendocrine carcinoma can be easily ruled out by the demonstration of cytokeratins 1, 5, 10, 14 and the lack of neuroendocrine markers [8]. However, the diagnosis of poorly differentiated SCC is possibly the most difficult to exclude, as it is only based on negative morphological criteria, i.e. the absence of a basaloid pattern, difficult to ascertain on a biopsy specimen. In addition, the 1999 and 2004 WHO classifications are too restrictive for the diagnosis of basaloid variant of large cell carcinoma; for instance, the presence of abrupt keratin pearl formation, mentioned in the very first description by Brambilla et al in addition to absence of intercellular bridges and individual cell keratinization, is no longer admitted in the WHO classification, leading probably to the rarity of this diagnosis. On the contrary, histological recommendations are too

vague for the diagnosis of basaloid variant of SCC, retained when squamous differentiation is prominent but not predominant; conversely, we could suspect that this variant is too frequently assimilated as a SCC.. As a first step, we therefore decided to include all our patients with basaloid features within the same histological class of BC in order to re-evaluate the prognostic significance of basaloid pattern in comparison with SCC and non BC .

In our original publications in 1992 and 1994 [1,7], we had observed a the poorer prognosis of 37 lung carcinomas with a basaloid pattern of stage I-II as compared with 40 poorly differentiated squamous cell carcinomas of the lung. However, a recent study published by Kim *et al.* [16], based on 291 surgically resected lung tumors including 167 poorly differentiated SCC and 35 basaloid carcinomas compared in terms of clinical data and survival outcome, questioned their prognostic significance. Although the overall prevalence of basaloid carcinomas was 4.8%, consistent with our data even if slightly lower, but the authors found no difference in survival and behavior between BC and poorly differentiated SCC-However, as 14 of their 35 expressed at least one neuroendocrine marker, two cases stained two NE markers, and one expressed synaptophysin but no cytokeratin 1,5,10,14, we could suspect that their series included some large cell neuroendocrine carcinoma.. Our series remains the largest one reported with the longest median follow-up [7, 16]. Whereas the actuarial 5-year survival rate of our SCCgroup was equivalent to that observed by Kim *et al.* (38% vs 40.6%) [16], the BC group survival in our series was clearly poorer than that reported by Kim *et al.* (26 vs 36.5%). These authors did not observe any difference in stages I-II, in contrast with the our study, in which the actuarial 5-year survival rate was 44% in the NSCLC group and 27% in the BC group (Log rank p = 0.01). Interestingly, this difference was maintained when BC and SCC were compared as regards survival in stages I (33% vs 51%) (Log rank p: 0.02) and the median survival of 36 months for BC was not reached at 5 years for SCC. In addition, in order to avoid bias related to occult concomitant medical

conditions, comorbidities were scored and added to the analysis. Basaloid pattern confirmed its poor prognostic significance in uni- and multivariate analyses in the complete group of patients, and especially in earlier stage tumors such as resected stage I. In addition, patients with more advanced stages (IIIB and IV) were more frequent in the BC groupSince an excess of post-operative deaths, even if statistically non-significant, was observed in the BC group, we wondered whether our prognostic difference was biased by surgical mortality, a point raised by the peer review of our original publication. In the current analysis, we confirm the prognostic impact of basaloid histology either in the complete group of patients or in the group of patients alive after the 30 days following surgical resection. However, as carcinoma with a basaloid pattern was frequently associated with *in situ* carcinoma (CIS), which could be responsible for a more aggressive surgery, we have looked for the implication of CIS in this increase of peri-operative deaths. We found no differences between BC and NSCLC or SCC as regards the extend of surgical resection (lobectomy vs pneumonectomy). However we observed that BC patients were heavier smokers, which could explain the excess of concomitant CIS diagnosed in this population ($p< 0.0001$) and evokes its histogenesis from proliferative bronchial basal stem cells..

Surgical therapy might not be sufficient or curative for basaloid carcinomas as inferred by their poor prognosis after surgery at stage I.. Adjuvant chemotherapy is presently considered as a standard of care since beneficial effects have been demonstrated in stages IB to IIIA NSCLC [20]. However, some controversies still exist over the impact of adjuvant chemotherapy in stage IB [21, 22], which requires additional pathological and immunohistochemical criteria to identify those patients who could benefit most from adjuvant treatments. Since carcinoma with a basaloid pattern remains a rare tumor, patients should be included in prospective large scale and multicentric chemotherapy regimens. For instance,, stratification of patients could be based on the expression of biomarkers of drug-associated

resistance. Indeed, we recently demonstrated substantial survival benefits from cisplatin-based chemotherapy in patients with ERCC1 and P27 NSCLC negative tumors [23, 24]. Future studies will require a better definition of the basaloid carcinoma entity at histological level to adequatly include patients in randomized adjuvant trials.

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Figure legends

Figure 1A: Basaloid variant of large cell carcinoma, composed of small-size cells, arranged in a typical lobular pattern with peripheral palisading; no squamous differentiation (Hematoxylin-Eosin-Saffron, original magnification x 200)

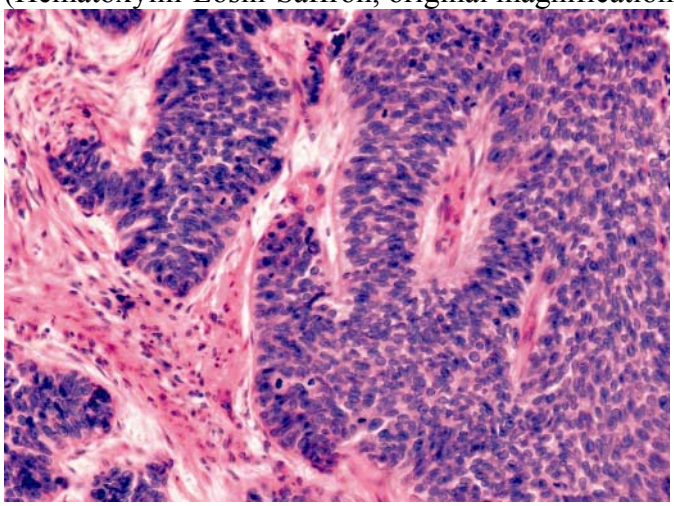


Figure 1B: Basaloid variant of squamous cell carcinoma. On the left side, a lobule with basaloid features (star); on the right side, a lobule exhibiting obvious squamous differentiation (arrow) (Hematoxylin-Eosin-Saffron, x 200).

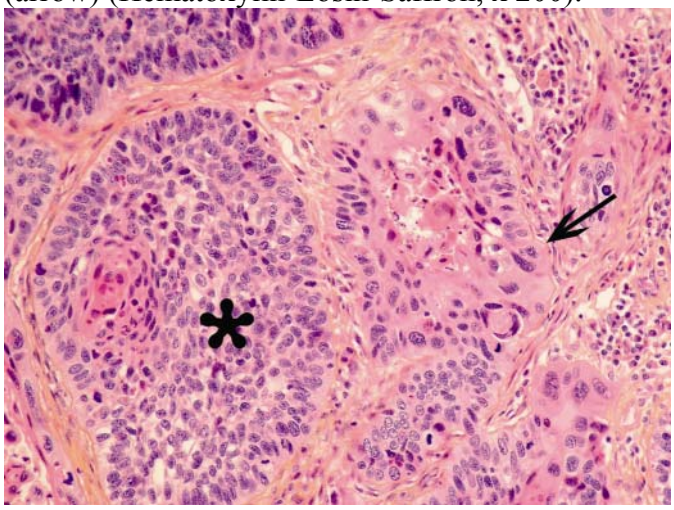


Figure 2: Overall survival curves for stage I patients (BC vs non BC) (Log rank p: 0.01)

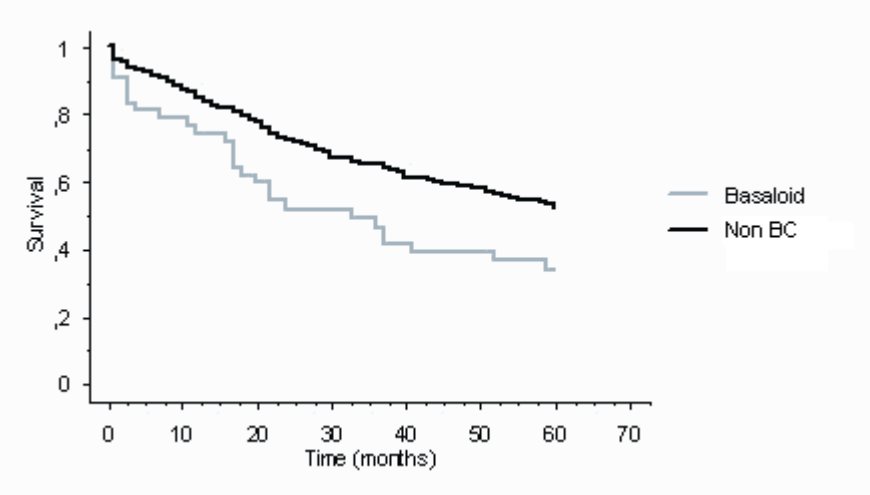


Figure 3: Overall survival curves for stage I patients (BC vs SCC) (Log rank p: 0.02)

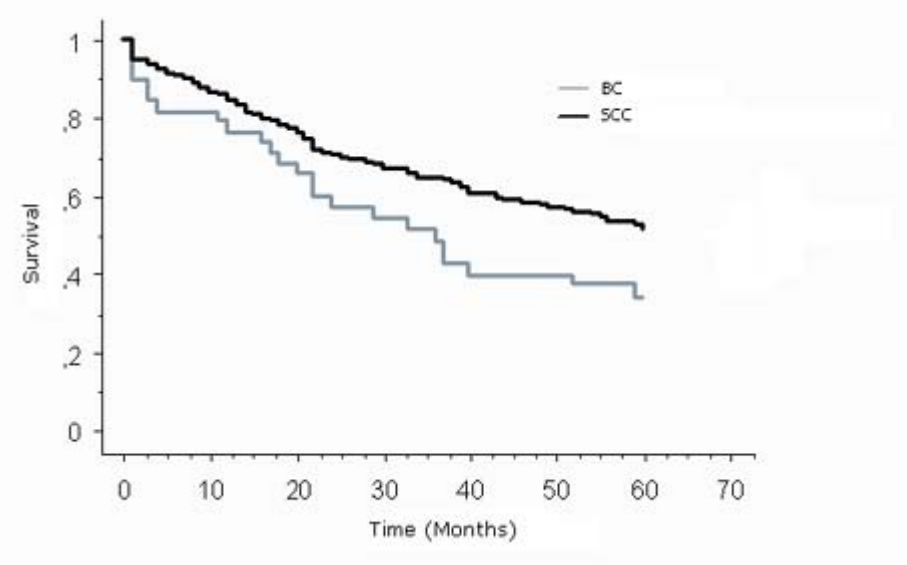


Table 1: Clinical and demographic characteristics of the different groups of patients

Variables	BC (n=90)	non BC (n=1328)	p value BC/ non BC	SCC (n=884)	p value BC/SCC
Mean age (min-max)	63.6 (37-82)	62.4 (31-86)	NS	62.9 (31-86)	NS
Males/ Females	87/3	1196 / 132	NS	847/87	NS
Tobacco (Packs year: mean)	46.0	32	<0.0001	33,5	0.0002
Stage I	38	544	<0.0001	323	<0,0001
Stage II	28	431		337	
Stage IIIA	16	353		224	
Stage IIIB, IV	8	0		0	
N0	42	658	0.03	407	NS
N1	40	444		350	
N2	8	226		127	
Pneumonectomy	22	320	NS	587	NS
Lobectomy	64	944		264	
Segmentectomy	4	64		33	
Associated CIS	28	109	<0.0001	98	<0.0001

BC: Lung carcinomas with a basaloid pattern, NS: Not significant, SCC : squamous cell carcinoma, non BC: non basaloid carcinoma

Table 2: Clinical, demographic and survival characteristics of the 2 groups of stage I patients.

Variables	BC (n=38)	non BC (n=544)	p
Mean age (min-max)	65.8 (37-79)	62.4 (33-86)	0.03
Males/ Females	38/0	488/56	NS
Right sided tumor	19	305	NS
Pneumonectomy	4	47	NS
Lobectomy	30	459	
Segmentectomy	4	38	
Post operative deaths	4	26	NS
T1	22	230	NS
T2	16	314	
Charlson index ≤ 2	32	497	NS
Median survival	36 months	Not reached at 5 years	0.01
5 years survival	33%	51%	

BC: Lung carcinomas with a basaloid pattern, non BC: non basaloid carcinoma, NS: Not significant.

Table 3 : Univariate survival analyses performed in the different groups and different histological subtypes.

Histological subtypes	Stages	Type of analysis	Median survival	5 years survival	p
BC vs non BC	All patients	Overal survival	29 vs 34 months	26% vs 38%	0.05
BC vs non BC	All patients	Disease specific	45 months vs NR	41% vs 59%	0.014
BC vs non BC	Stages I and II	Overal survival	29 vs 49 months	27% vs 44%	0.01
BC vs non BC	Stages I and II *	Overal survival	37 months vs NR	30% vs 47%	0.03
BC vs non BC	Stages I and II	Disease specific	49 months vs NR	45% vs 65%	0.008
BC vs non BC	Stage I †	Overal survival	36 months vs NR	33% vs 51%	0.01
BC vs SCC	All patients	Overal survival	29 vs 33 months	26% vs 37%	0.15
BC vs SCC	All patients	Disease specific	45 months vs NR	41% vs 61%	0.005
BC vs SCC	Stage I ‡	Overal survival	36 months vs NR	33 % vs 51%	0.02
Basaloid variants of SCC vs SCC	Stage I	Overal survival	37 months vs NR	36 % vs 51%	0.19

* patients who died within 30 days after surgery are excluded, † : figure 2, ‡ : figure 3, NR : not reached, vs : versus, BC : Lung carcinomas with a basaloid pattern, SCC : squamous cell carcinoma, non BC: non basaloid carcinoma

Table 4: Hazard Ratios (95% Confidence Interval, p values) for variables in multivariate Cox model in stage I patients.

variables	Model A : Stage I patients Hazard ratio (CI, p value)	Model B : Stage I patients alive 1 month after surgery Hazard ratio (CI, p value)
Age > 63 years	1.42 (1.1-1.84, p : 0.006)	1.39 (1.06-1.83, p : 0.015)
T2 versus T1	1.37 (1.06-1.78, p : 0.015)	1.37 (1.04-1.80, p : 0.023)
Comorbidity index >2	1.79 (1.23-2.61, p : 0.002)	1.93 (1.3-2.85, p : 0.0008)
BC vs non BC	1.68 (1.18-2.53, p : 0.012)	1.6 (1.03-2.5, p : 0.03)

BC: Lung carcinomas with a basaloid pattern, CI: confidence intervals, non BC: non basaloid carcinoma.

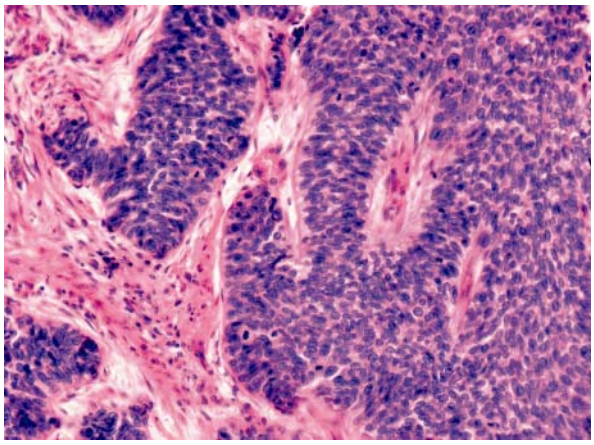


Figure 1A

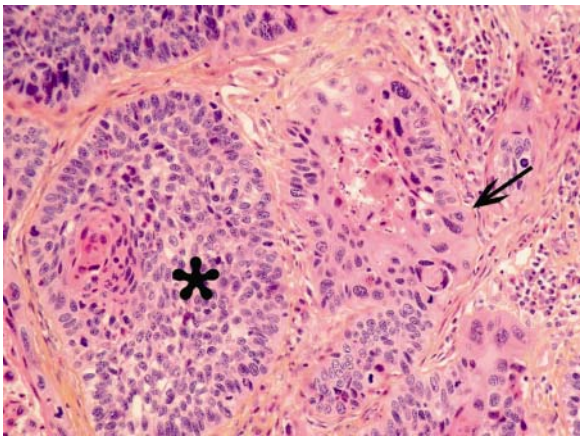
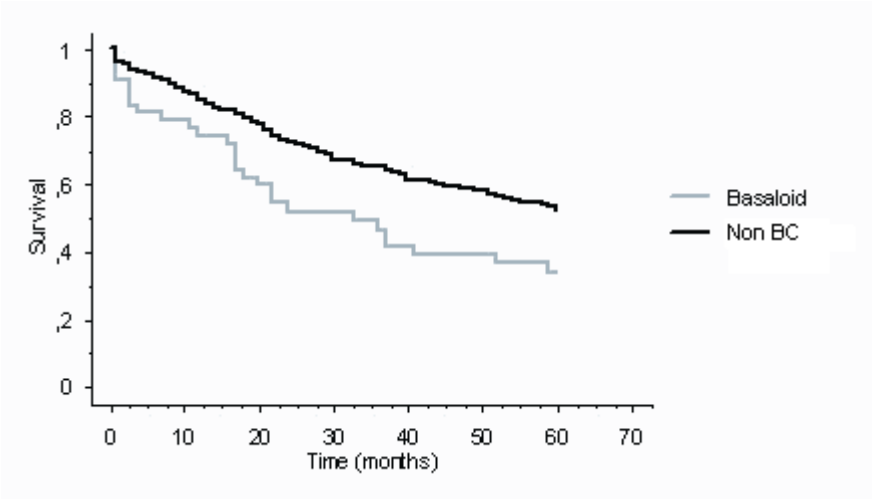


Figure 1B


1
,8
,6
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0
Survival
0
10
20
30
40
50
60
70
Time (months)
Basaloid
Non BC

Figure 2

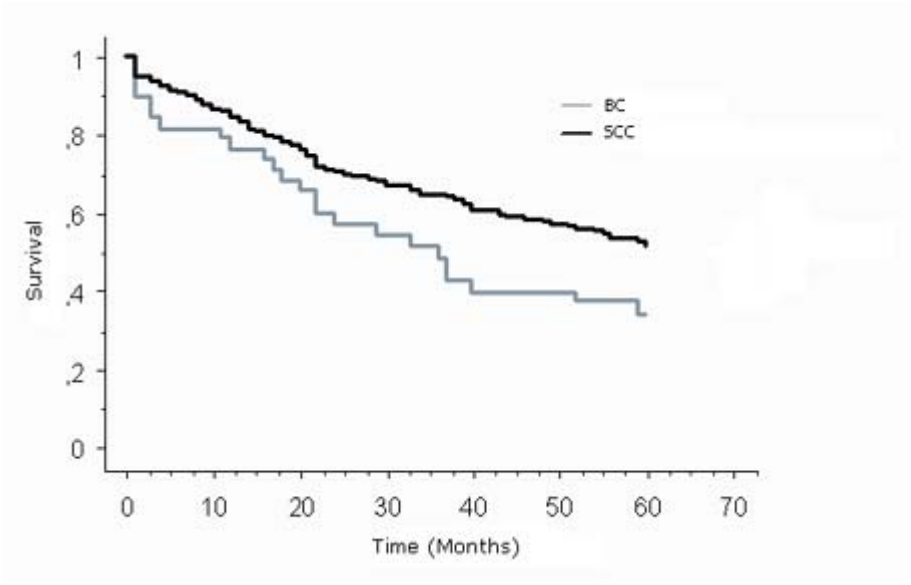

Figure 3