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Course and prognosis of basaloid squamous cell carcinoma of the head and neck: A case–control study of 62 patients

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ARTICLE INFO

Article history:
Received 11 September 2007
Received in revised form
29 October 2007
Accepted 2 November 2007

Keywords:
Basaloid squamous cell carcinoma
Head and neck cancer
Histo-prognosis

ABSTRACT

Objective: To describe the natural history and evaluate the prognosis of basaloid squamous cell carcinoma (BSCC) of the upper aero-digestive tract as compared to the usual squamous cell carcinoma (SCC).

Materials and methods: Sixty-two patients with BSCC and 62 patients with SCC were matched with regards to TNM classification, localisation and therapeutic modalities. Histological criteria, follow-up and 5-year survival were compared among the two groups.

Results: Survival rates were significantly higher in patients with SCC as compared to patients with BSCC. The rate of distant metastasis was six times higher in cases of BSCC, which was the major cause of mortality.

Conclusion: This study reveals that BSCC has distinct histo-pathologic features and an aggressive clinical course, justifying its consideration as a separate entity with poor prognosis. The authors propose to systematically perform a chest CT-scan and FDG-PET to rule out early distant metastasis and to include adjuvant chemotherapy in treatment protocols.

1. Introduction

Basaloid squamous cell carcinoma (BSCC) of the upper aero-digestive tract (UADT) was described for the first time in 1986 when Wain and colleagues[1] reported an atypical histological subtype of squamous cell carcinoma. This entity represents 2% of head and neck cancers as only 200 cases are reported in the literature so far.

As defined by the recent WHO classification of head and neck tumours,[2] BSCC is a variant of squamous cell carcinoma (SCC) with basaloid and squamous components associated in varying proportions.

Several case reports and small-sample-size studies have attempted to depict the clinical characteristics of BSCC; however, controversies over the progression and prognosis of this tumour in the UADT still exist. Whilst some authors consider this tumour as more aggressive than the usual SCC, and characterised by a less favourable outcome or an unpredictably short post-operative survival,[1–7] for others BSCC and SCC do not constitute separate histo-prognostic entities, and manifest similar paths of progression and prognosis.[8–13] Because no complete histo-prognostic analysis of this rare tumour has been performed on a large scale previously, we propose herein to evaluate the natural history of

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doi:10.1016/j.ejca.2007.11.008

BSCC and to determine its distinctive histo-prognostic criteria in a comparative study of 124 patients including 62 BSCC and 62 SCC matched patients.

2. Materials and methods

Over a period of 17 years (1988–2005), 81 patients were treated for BSCC (case group) of the pharynx, larynx or oral cavity at the University Medical Centre of Grenoble, France. Data related to pre-treatment diagnosis, anatomical location and staging of the disease, and treatment were collected, in addition to a detailed post-therapeutic follow-up. Moreover, a matched group of patients diagnosed with poorly-to-well differentiated SCC (control group) was selected from a large pool of patients ($n = 1800$) with upper aero-digestive tract SCC treated at the same institution.

2.1. *Inclusion criteria*

Inclusion required a histological confirmation of the diagnosis of BSCC, in addition to a minimum post-therapeutic follow-up of 24 months.

According to the WHO classification,[2] BSCC includes variable proportions of basaloid and squamous components (Fig. 1). The basaloid component is composed of small monomorphic cells closely packed in a solid pattern with a lobular

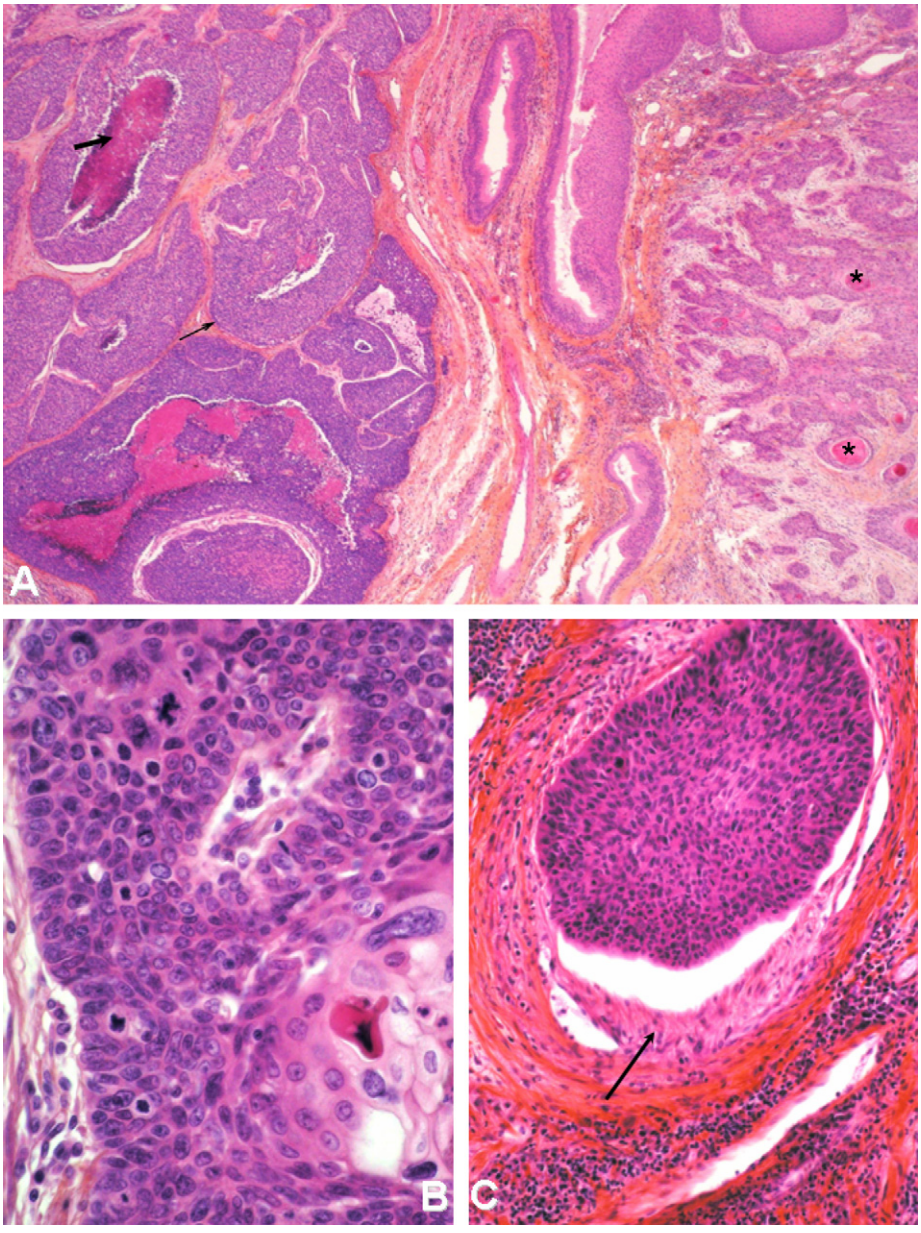

Fig. 1 – An example of basaloid squamous cell carcinoma histopathology (HES). (A) Basaloid squamous cell carcinoma: on the left, the basaloid component with lobules of small closely packed basaloid cells with typical peripheral palisading (sharp-arrow) and central comedonecrosis (thick-arrow). On the right, the well-differentiated squamous cell carcinoma component with 'pearl' keratinisation (*). (B) Basaloid cells arranged in solid lobules with focal squamous differentiation. Nucleo-cytoplasmic ratio and mitotic activity are typically high. (C) Vascular invasion by basaloid cells (→ = smooth-muscle wall vessel).

round or polycyclic configuration and typical peripheral palisading cellular disposition and frequent central comedonecrosis. In one-third of the cases, rosette or pseudo-rosette figures are observed. The basaloid cells present a high nuclear:cytoplasmic ratio, scant cytoplasm, an oval shaped hyperchromatic nuclei without nucleoli and a high mitotic rate. Occasionally, pseudo-cylindrical, micro-cystic spaces filled with basal material are encountered. The stromal reaction is polymorphic, but hyalinised collagen is usually observed with an occasional inflammatory infiltrate. The usual squamous component is made of larger cells, showing well-defined borders and linked by inter-cellular bridges, with occasionally keratinised cytoplasm. Superficially, carcinoma *in situ* may be seen.

The main histo-pathological differential diagnosis includes adenoid cyctic carcinoma, neuro-endocrine carcinoma and poorly differentiated squamous cell carcinoma.

For all specimens, histological diagnosis was asserted by two expert histopathologists. A minimum of 10% of basaloid component was required for the diagnosis of BSCC to be finally reported.

The tumours were deliberately classified into three groups depending on the percentage of basaloid component as follows:

- Group 1: 10–39% basaloid component.
- Group 2: 40–79% basaloid component.
- Group 3: >80% basaloid component.

Immunohistochemical analysis confirmed the absence of neuro-endocrine markers (N-CAM, synaptophysin or chromogranin A) in 96% of BSCC specimens, the remaining cases were positive for only one marker (N-CAM or chromogranin A) in less than 20% of the cells.

Each case of BSCC was paired with a case of poorly-to-well differentiated SCC (40 well differentiated, 16 moderately differentiated and 6 poorly differentiated) originating from the same anatomical site, presenting identical TNM classification, and subjected to similar therapeutic strategies within the same decade. In addition, recurrent cases of BSCC were paired with recurrent SCC cases that have received the same treatment before and after recurrence. Sex, age and alcohol and tobacco consumption were also matched in both groups. In the presence of several possible SCC matches for one case of BSCC, one SCC matching case was picked randomly to eliminate selection bias.

2.2. *Treatment modalities*

Forty-six (74%) matched pairs of patients did not receive any prior treatment, whilst 16 (26%) matched pairs of patients were previously treated with radiotherapy.

2.3. *Data analysis*

Overall survival rate, specific survival rate and recurrence-free survival rate were calculated for both case and control groups. Survival period was calculated from the resolution of treatment to the last follow-up (or death).

Statistical analysis system Stat-view 5.0 software was used (SAS Institute Inc, Cary, NC, USA, http://www.statiew.com). Survival curves were obtained by the non-parametric method of Kaplan–Meyer, and comparison among different group survival curves was conducted through a univariate analysis following the log-rank test. In addition, multivariate analysis was performed using logistic regression tests. *p*-values less than 0.05 were considered as statistically significant.

3. Results

One hundred and twenty-four patients were included, 62 cases (59 men) of BSCC and 62 with usual SCC. Mean age was comparable in both groups, 61 years (44–83) and 58 years (34–78), respectively.

There was no difference between alcohol (>30 g/day) and tobacco consumption (>120 g/day) in both groups.

The most frequent BSCC and SCC primary sites were the hypopharynx and oropharynx. In each group, 31 tumours were localised to the hypopharynx, 19 to the oropharynx and oral cavity, 8 to the larynx, 3 to cervical lymph nodes and 1 to the cavum.

BSCC patient distribution according to percentage basaloid component was as follows: 15 patients in group 1, 19 patients in group 2 and 28 patients in group 3.

BSCC and SCC patients presented with an advanced stage tumour (T3 or T4) in 51% of the cases, and 52% had clinical or radiological lymphadenopathy (Table 1).

Different therapeutic modalities employed for each group are summarised in Fig. 2.

Post-operative adjuvant radiotherapy was performed in the presence of specific histo-pathologic criteria: namely inadequate margins of resection, angio or perineural invasion, more than three invaded cervical lymph nodes or lymph node capsular rupture.

Eight patients (13%) of each group were subjected to neo-adjuvant chemotherapy as part of a laryngeal preservation protocol. Amongst them, five patients responded favourably (tumour lysis $\geqslant$80%), and were treated with radiotherapy (one patient underwent neck dissection followed by

Table 1 – TNM repartition in both groups

Primary disease	T1	T2	T3	T4	Tx	Total
N0	3	7	4	3	0	17
N1	1	3	4	1	0	9
N2	2	8	2	1	1	14
N3	1	1	2	0	2	6
Total	7	19	12	5	3	**46**
Recurrent disease	T1	T2	T3	T4		Total
N0	0	2	7	0		9
N1	0	0	4	0		4
N2	0	1	2	0		3
N3	0	0	0	0		0
Total	0	3	13	0		16

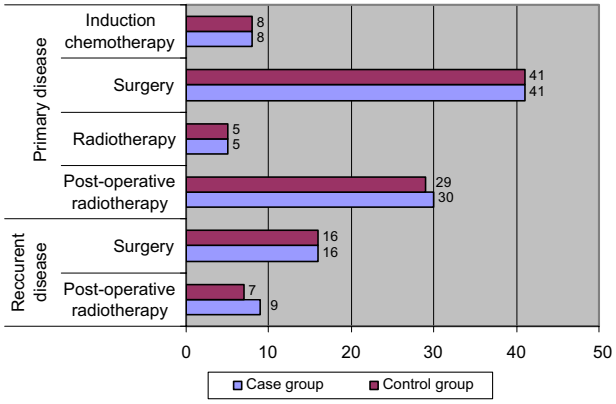

Fig. 2 – Therapeutic modalities. The number of case and control patients in different classes of treatment was similar.

radiotherapy); three patients only had a partial response (tumour lysis = 50–80%) and underwent surgical resection followed by radiotherapy. Forty-one patients (62%) underwent primary surgical resection with or without adjuvant radiotherapy. Exclusive radiotherapy was performed in 5 patients (16%). Sixteen patients (26%) underwent salvage surgery, of which 9 patients were re-irradiated post-operatively.

Mean follow-up for the BSCC and the usual SCC cases was 28 and 57 months, respectively. Three patients among the SCC group were lost to follow-up beyond 34 months.

The post-therapeutic survival and death circumstances varied significantly between the two groups. Loco-regional recurrence caused death in only 15% of the BSCC patients, and in 51% of the SCC patients. Distant metastasis occurred in 45% ($n = 28$) of the BSCC group as opposed to only 7% ($n = 4$) of the usual SCC group (Fig. 3). The sites of distant metastasis in BSCC cases, in the decreasing order of occurrence, were as follows: lung (71%), liver (39%), bone (11%), skin and brain (4%). Fifty percent of BSCC with metastatic disease had multiple sites of metastasis. In addition, distant metastasis was considered as the cause of death in 70% and 13% of the BSCC and SCC, respectively. The difference of overall survival rates at 3 and 5 years was statistically significant between the two groups ($p < 0.01$). In addition, the specific survival rates and disease-free survival rates were also statistically different ($p < 0.01$) (Table 2, Fig. 4).

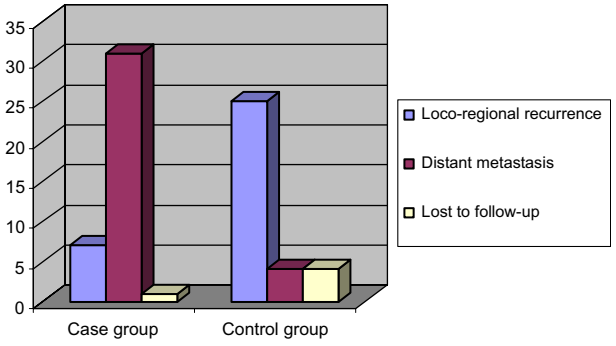

Fig. 3 – Comparison of death circumstances.

3.1. *Anatomical site related survival*

There was no statistically significant difference in specific survival rates amongst patient with BSCC in the oropharynx, hypopharynx or larynx. On the other hand, SSC of the larynx was associated with higher specific survival rates as compared to SCC of the oropharynx and hypopharynx ($p = 0.03$).

3.2. *Tumour T stage related survival*

Survival rates were found to be significantly different between the case and control groups. The survival rates of T1 and T2 tumours for BSCC and SCC cases were 64% and 86% ($p = 0.04$), respectively. Similarly, survival rates of T3 and T4 tumours were 57% and 85% ($p = 0.04$), for the case and control groups, respectively.

3.3. *Tumour N stage related survival*

Whilst N0 BSCC and classical SCC patients had similar survival rates, N1–N3 BSCC and the usual SCC patients had a statistically different overall survival ($p < 0.001$), specific survival ($p < 0.01$) and disease-free survival ($p < 0.01$), with BSCC histology being always associated with poorer survival rates.

3.4. *Evolution and survival of patients treated following relapse ($n = 16$)*

There was no statistically significant difference in survival rates between the case and control groups in this category of patients. However, there was a significantly higher rate of 5-year loco-regional recurrence in the control group (50% for SCC and 33% for BSCC, $p < 0.01$), and a higher rate of 5-year distant metastasis in the case group (56% for BSCC and 6% for SCC, $p < 0.001$).

3.5. *Primary treatment related survival rates ($n = 46$)*

Specific survival rates were significantly higher ($p < 0.01$) in patients with usual SCC as compared to patients with BSCC in the case of primary treatment. In addition, the rate of distant metastasis was markedly higher in the BSCC group (41%) than in the usual SCC group (6%).

Table 2 – Case and control group survival

Survival		1 year	3 years	5 years	Median[a]
Overall ($p < 0.01$)	Case (%)	85	44	35	26
	Control (%)	94	69	57	76
Specific ($p < 0.01$)	Case (%)	91	48	36	36
	Control (%)	95	75	69	>120
Disease-free ($p < 0.01$)	Case (%)	61	39	29	24
	Control (%)	87	69	46	54

a Median survival in months. The percentages corresponding to the number of living patients in relation to the follow-up period in both case and control groups.

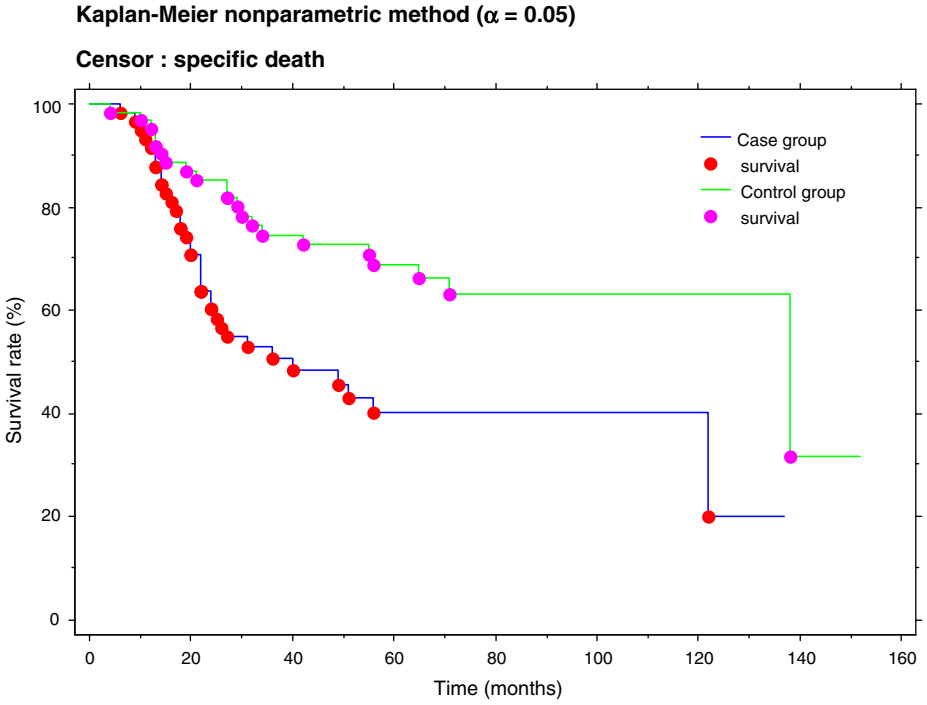

Fig. 4 – Comparison of specific survival rates related to the initial illness. Five-year specific survival rates in the BSCC and SCC groups (36% and 69%, respectively) were significantly different ($p < 0.01$, with exact binominal 95% confidence interval).

In fact, there was no significant difference in the rates of overall survival amongst patients with BSCC whether they were managed primarily or following recurrence, whereas primary management in cases of classical SCC was related to significantly higher rates of survival. In all cases of BSCC, poor prognosis was directly related to the frequency of metastasis.

3.6. *Histo-prognosis data related survival*

Lymphovascular invasion was observed in 20 surgical specimens of BSCC and 13 of classical SCC. These BSCCs were associated with higher rates of distant metastasis, and lower rates of 5-year survival (0% as compared to 46% in the matched control group, $p < 0.001$). Furthermore, the presence of lymphovascular invasion significantly affected the survival rate amongst the BSCC group, but not in the classical SCC group ($p < 0.01$). On the other hand, no correlation was statistically observed between basaloid component level and global survival rates, specific survival rates or recurrence rate.

3.7. *BSCC survivors*

Out of the 62 patients with BSCC, only 14 (23%) were alive 5 years after diagnosis. Remarkably, none of the 5-year survivors presented lymphovascular invasion in the surgical resection specimen.

3.8. *Multivariate analysis*

Amongst BSCC tumour-specific and treatment-related characteristics, only the presence of lymphovascular invasion in the resected specimen was strongly associated with the specific survival rate ($p < 0.001$).

4. Discussion

This study shows that BSCC is associated with a poor prognosis, characterised by rapid growth and a low survival rate, independently of tumour stage and other disease-related characteristics. This finding differentiates BSCC from SCC without basaloid component. Patients with usual SCC present a higher rate of loco-regional recurrence, whilst patients with BSCC develop a higher rate of distant metastases.

In a previous case–control study conducted on 49 pairs of patients diagnosed with BSCC and SCC of the UADT, we have demonstrated similar differences in the rates of global, specific and recurrence free survival between the two groups.[14] The present study confirms our previous findings with a higher degree of statistical significance, and compliments the analysis of these findings. In fact, the performance of multivariate analysis, made possible by a larger sample size, helped us prove that the higher mortality rate found in the BSCC group is actually related to the higher rate of metastasis and the presence of endo-vascular emboli in the primary tumour. The presence of tumour emboli was found to be associated with a potential for distant dissemination only in the BSCC group, and we were unable to explain the absence of this association in the SCC group.

Review of the literature reveals a number of BSCC case reports describing the tumour's histo-pathological features and characteristic behaviour.[1–8,10,12,13,15–21] ever, studies evaluating the influence of histological criteria on the clinical

behaviour are lacking. Banks and colleagues[9] published one of the largest series of BSCC (40 cases) analyzing the histo-pathological features, and provided new immuno-histochemical tools to differentiate BSCC from other pathological entities and their results are comparable to those reported in the present study. Winzenburg and colleagues[6] have conducted a 26 matched-pairs case–control study to evaluate the behaviour of BSCC as compared to poorly differentiated SCC. Their findings confirm the significant difference in survival between BSCC and SCC, regardless of the degree of differentiation, which is actually not related to survival rates.[19,20]

Controversies still exist about the effect of basaloid component proportion on disease prognosis. Some authors like Winzenburg and colleagues[6] observed that purely basaloid BSCC have a relatively favourable prognosis, whilst others, like Erisen and colleagues,[13] found no association between the proportion of basaloid component and rates of survival, which is in accordance with our results. Based on the findings of this study, we propose that BSCC be considered as a histo-pathological entity of poor prognosis, which requires careful management planning. Once the diagnosis is pre-operatively made, extensive work-up is required to rule out the occurrence of sub-clinical metastatic lesions: the lungs, being the most frequent site of BSCC metastasis, have to be primarily investigated. Previous studies have shown that chest X-ray has a low sensitivity, as compared to chest CT scan, in detecting metastasis to the thorax.[22,23] In addition, the results of the current study revealed that 50% of BSCC metastasis involved multiple organs, which justifies early screening for metastatic lesions all over the body. Consequently, we recommend that all patients diagnosed with BSCC of the UADT systematically undergo a chest CT-scan to rule out the lung metastasis and a 2-deoxy-2[^{18}F]-fluoro-D-glucose–positron emission tomography (FDG–PET) to detect the presence of extra-pulmonary asymptomatic metastatic lesions.[24] Laboratory biochemical blood tests must not be performed, as none so far was found to be of value in the screening of metastasis in patients with head and neck cancer.[22]

To this date, there are no clinical studies that allow the proposal of a therapeutic strategy specific to BSCC. The treatment recommendations that we are suggesting are extrapolated from the therapeutic strategies recommended for SCC in the presence of one or more criteria of poor histo-prognosis. In fact, we are basing our reasoning on the principle that the presence of a basaloid component is in itself a criterion of poor histo-prognosis.

In the case of resectable lesion with no evidence of metastasis, surgery should be the mainstay treatment as it offers a chance for cure. The basaloid component of the tumour should not be considered a contraindication to surgery. In fact, we found in this study that the rates of loco-regional control are identical in both groups of patients (75% for the SCC and 74% for the less BSCC). Tumour resection should be as wide as possible, with subsequent reconstruction, whenever necessary, with distant free flaps.[25] In addition, considering the high rate of lymph node metastasis, neck dissection should be performed in all cases even in the absence of clinically or radiologically detectable lymph node enlargement. Histo-pathologic analysis of the resected specimen would confirm the diagnosis of BSCC and detect lymphovascular invasion and embolization.

Once the diagnosis of BSCC is confirmed, patients have to receive post-operative adjuvant chemoradiotherapy, regardless of tumour stage and/or poor histo-pathologic factors: peri-neural invasion, positive resection margins and lymph node metastasis with capsular rupture. Indeed, this practice was found to decrease loco-regional recurrence of head and neck squamous cell carcinoma and improve patient survival rates.[26,27]

In the case of locally-advanced laryngeal BSCC (T3–T4), taking into consideration the high risk of metastasis, the potential surgical treatment may be too mutilating and a conservative approach should be considered. These tumours can be treated with initial chemotherapy and assessed for therapeutic response.[28,29] In case of favourable response, defined as more than 50% tumour shrinkage, radiotherapy is administered subsequently with optimised modalities allowing for dose escalation: three-dimensional conformal therapy and/or modulated intensity.[30] In case of contraindication to chemotherapy, such as in cases of poor renal function, radiotherapy can be associated with anti-epidermal growth factor (EGF) antibody therapy. This association was shown to be more efficient than radiotherapy alone in head and neck cancer, without additional morbidity.[31]

The recommendations on follow-up intervals and investigation tools for patients with head and neck squamous cell carcinomas are not clear cut. Some authors recommend a follow-up PET-scan 6 months after the beginning of treatment.[24] We agree that a baseline PET-scan is important to rule out early local recurrence and post-operative metastasis in patients with BSCC. However, in the absence of curative treatment for extra-pulmonary metastases, there is no benefit from routine screening PET-scan. Follow-up PET-scan should only be performed for confirmation of clinically suspicious distant lesion. On the other hand, routine chest CT-scan may reveal a resectable unique pulmonary lesion, and thus justifies bi-annual testing.

5. Conclusion

The knowledge of tumour behaviour and evolution helps in designing appropriate management protocols. The presence of a basaloid component does not change the fundamental therapeutic principles of UADT cancer. However, in the case of BSCC, given its demonstrated aggressive characteristics and poor prognosis, adapted management is required to improve the patient's quality of life. Specifically, an exhaustive metastatic work-up should be performed in the case of BSCC prior to any therapeutic attempt.

Conflict of interest statement

None declared.

Acknowledgement

We thank our colleague K. Chahine M.D. for reading the manuscript.

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