Basaloid squamous cell carcinoma of the larynx: 16 years of experience at the otorhinolaryngology department of IPO-LFG

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ABSTRACT
Objectives: To identify prognostic factors of basaloid squamous cell carcinoma of the larynx (BSCCL) and to assess survival according to tumor stage, subsite, and treatment.
Study design: Retrospective.
Material and methods: We identified 43 patients (mean age, 59.7 y; male, 97.7%) with BSCCL diagnosed at the Instituto Português de Oncologia de Lisboa Francisco Gentil (IPO-LFG) between 2003 and 2019. Sociodemographic, stage, and treatment data were analyzed. Overall (OS) and disease-free (DFS) survival was determined. Data were analyzed using chi-squared tests (categorical variables), t-tests (continuous variables), and Kaplan-Meier curves (survival comparison).
Results and Conclusions: Stage: Local, T1 (7%), T2 (18.6%), T3 (27.9%), and T4a (46.5%); regional, N+ (60.5%); distant: M0 (95.3%). Location: supraglottis (58.1%), glottis (25.6%), and transglottic (16.3%). Among 95.3% of patients who were treated with curative intent, 95.2% were treated by total laryngectomy (70.7%), supraglottic partial laryngectomy (17.1%), cordectomy (7.3%), and 2.4% each were treated with RT and CRT. Among surgically treated patients, 87.2% and 92.3% underwent bilateral neck dissection and adjuvant CRT/RT, respectively. The DFS at 2 years was similar between patients with T1/T2 (63.6%) and T3/T4a (63.3%), higher in patients with N0, than N+ upon presentation (87.5% vs. 48%); p = 0.017), and lower in patients with supraglottic, than glottic tumors (52.0% vs. 90.9%, p = 0.031).
Basaloid SCCL is usually diagnosed at an advanced stage, and supraglottic sites and N+ neck lesions were the main factors associated with a poor prognosis.
Keywords: Basaloid squamous cell carcinoma; Larynx; Oncology

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INTRODUCTION

Basaloid squamous cell carcinoma (BSCC) is a rare histological variant of squamous cell carcinoma (SCC) that was initially described in 1986. It is a high-grade tumor with cells resembling those of the basal layer of stratified squamous epithelium[1;2]. Low differentiation, infiltrative profile, peripheral nuclear palisading, and high mitotic activity can cause difficulties with differentiating BSCC from adenoid cystic carcinoma. Alcohol consumption and smoking are the main risk factors for BSCC of the head and neck[3]. In terms of anatomical location, BSCC occurs most frequently in the oropharynx, with the larynx being the second most common site[2]. Within the larynx, the supraglottis is the most typical subsite of this carcinoma[3;4].

Because BSCCL is rare, the number of published studies is insufficient to determine prognostic factors and the survival of patients[5]. The largest studies on BSCCL published to date comprise a systematic review of 100 patients[3] and a multicenter study of 145 patients[6].

Although BSCCL is apparently more aggressive than SCC of the larynx, there is no clear consensus in the literature[5]. In this regard, BSCCL is associated with lower overall survival than SCC (adjusted for laryngeal subsite, stage, and treatment)[6]. However, others have found similar overall survival (OS) between SCC and its basaloid variant[7;8].

In the present study, we aimed to identify prognostic factors for this histological variant and determine survival in patients with BSCCL according to tumor stage, subsite, and treatment.

MATERIAL AND METHODS

We analyzed data from patients with BSCCL diagnosed at the Otorhinolaryngology (ORL) department at the cancer referral center, Instituto Português de Oncologia, Francisco Gentil (IPO-LFG) between June 2003 and June

2019. The clinical records of all patients diagnosed with BSCCL were retrospectively reviewed during the first trimester of 2021. These patients were identified by matching the databases of the ORL and Anatomical Pathology departments.

The sociodemographic data of the patients, TNM tumor stage (NCCN–V1.2021), and primary and adjuvant treatments were analyzed. Tumor recurrence and respective secondary treatments were characterized. Overall and disease-free (DFS) survival was determined. Categorical and continuous variables were assessed using chi-squared and t-tests, respectively, and between-group survival was compared using Kaplan-Meier curves. All data were statistically analyzed using SPSS® 25.0 (IBM Corp., Armonk, NY, USA). Values with $p < 0.05$ were considered statistically significant.

RESULTS

Characterization of patients

The mean follow-up of the 43 patients diagnosed with BSCCL was 85.2 (range, 1–192) months after diagnosis. The clinical and sociodemographic data have been summarized in Table 1.

TABLE 1
Clinical and sociodemographic data

Parameter	43 (100%)
Median age at diagnosis (y) Mean age at diagnosis (y)	60 59,7 (±9,4)
Sex Male Female	 42 (97,7%) 1 (2,3%)
Tumor location Supraglottic Glottic Transglottic	 25 (58,1%) 11 (25,6%) 7 (16,3%)
T Stage T1 T2 T3 T4a	 3 (7%) 8 (18,6%) 12 (27,9%) 20 (46,5%)
N Stage N0 N+	 17 (39,5%) 26 (60,5%)
Recurrence during follow-up	13 (30,2%)*

*Data are shown as n (%) except for age. Median and mean intervals between diagnosis and recurrence: 24 and 30.9 (12–72) months, respectively.

All patients underwent a complete objective ORL examination, including flexible nasopharyngolaryngoscopy as well as neck and chest computed tomography (CT). No synchronous tumors were detected.

Initial staging

The initial disease stages were as follows.

Local (T): T1 (7%), T2 (18.6%), T3 (27.9%), T4a (46.5%).

Regional (N): N0 (39.5%); N1 (7%); N2a (20.9%); N2b (14%); N2c (11.6%); N3 (7%).

Distant (M): M0 (95.3%); M1 (4.7%; lung metastases).

Most (58.1%) primary tumors were located in the supraglottis, 25.6% were in the glottis, and 16.3% were transglottic with simultaneous involvement of the supraglottis, glottis, and subglottis. No tumors were confined to the subglottis.

Primary and adjuvant treatment

Primary treatment with curative intent was applied to 95.3% of the patients, and the others with distant disease metastasis received palliative care.

Among the 95.2% patients who were treated with curative intent, surgery comprised total laryngectomy (TL; 70.7%), supraglottic horizontal partial laryngectomy (SPL; 17.1%), laser cordectomy (7.3%), and 2.4% each received radiotherapy (RT) and chemoradiotherapy (CRT) as the sole primary treatment (Table 2).

Among the surgically treated patients, 92.3% received adjuvant CRT (48.7%) or RT (43.6%).

TABLE 2
Primary treatment

Treatment	41 (100%)
RT	1 (2,4%)
CRT	1 (2,4%)
Total laryngectomy	29 (70,7%)
Supraglottic partial laryngectomy (open surgery)	4 (9,8%)
Supraglottic partial laryngectomy (LASER)	3 (7,3%)
Cordectomy (LASER)	3 (7,3%)

Data are shown as n (%). Patients with distant metastases were excluded. Among the surgically treated patients, 87.2% underwent bilateral neck dissection (100% considering only patients treated by open surgery).

Disease recurrence and secondary treatment

Disease recurred in 13 (31.7%) patients. The mean interval between initial treatment to recurrence was 30 (12–72) months. Tumor relapse occurred at distant, local, and regional sites in 84.6%, 7.7%, and 7.7% of the patients, respectively.

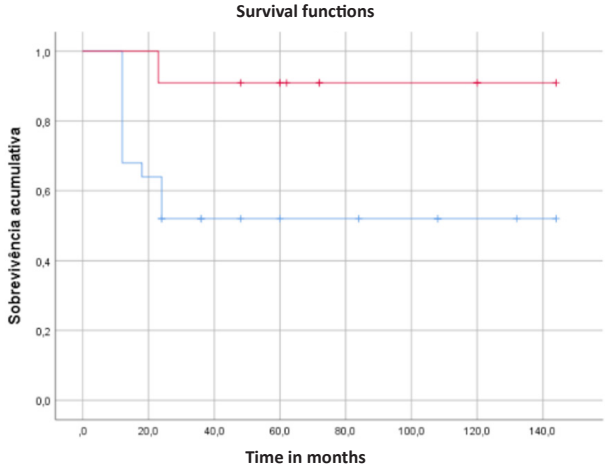
All 13 patients with recurrent disease received secondary treatment comprising chemotherapy (n = 10), CRT (n = 1), and monoclonal antibodies (pembrolizumab+cisplatin+fluorouracil and cetuximab+cisplatin+fluorouracil; n = 1 each).

Overall and disease-free survival

The mean overall survival (OS) of the patients diagnosed with BSCCL was 59.88 (range, 1–144; median, 48) months. Excluding the two patients who did not receive curative treatment (M1), the mean OS was 62.63 (12–144) months, and the median was 48 months. The

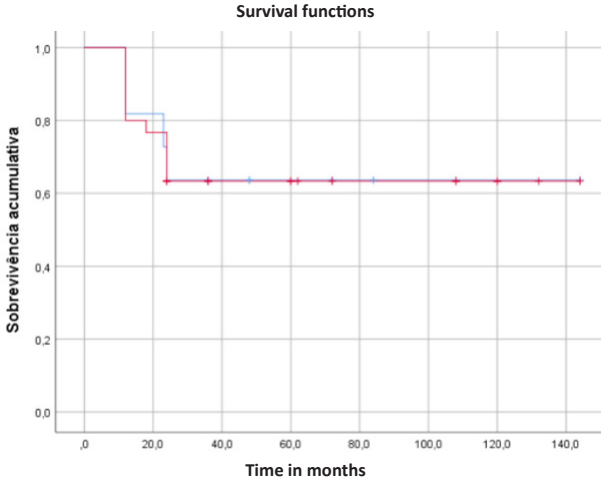
mean DFS was 52.51 (1–144) months and the median was 36 months. Excluding the two patients with distant disease on presentation, the mean DFS was 54.90 (12–144) months and the median was 36 months.
The DFS at 2 years was significantly lower for patients with supraglottic than for those with glottic BSCC (52.0% vs. 90.9%, p = 0.031; Graph 1), but did not significantly differ between patients with stage T1/T2 and T3/T4a (63.6% vs. 63.3%, p = 0.99; Graph 2). In contrast, DFS at 2 years was significantly higher in patients with stage N0 than those with stage N+ (87.5% vs. 48.0%; p = 0.017; Graph 3).

GRAPH 1
Disease-free survival according to tumor subsite. Red and blue indicate glottic and supraglottic tumors, respectively*



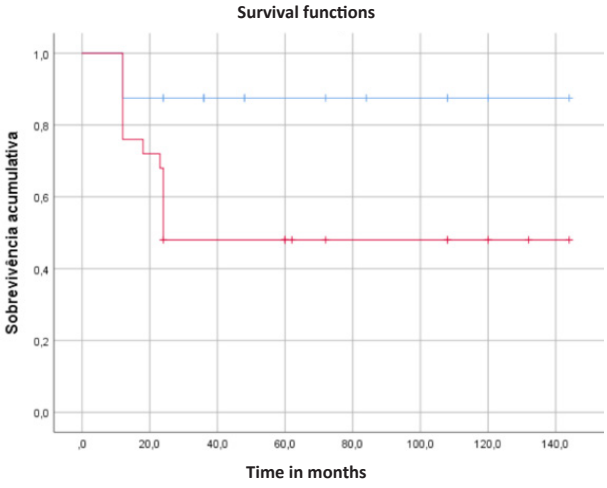
*Transglottic tumors were excluded

GRAPH 2
Disease-free survival according to T stage. Blue and red indicate T1/T2 and T3/T4a, respectively

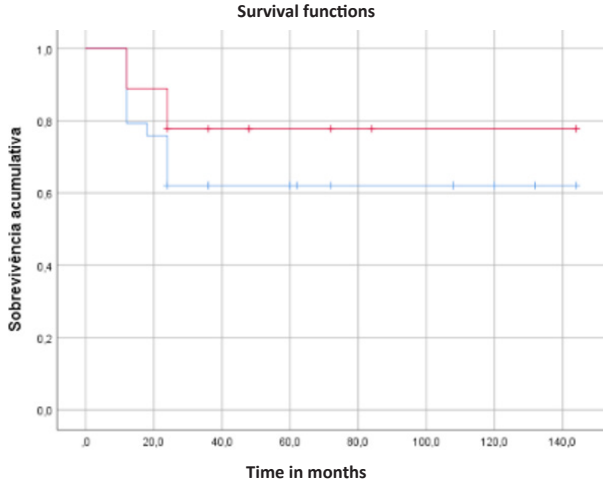


The 2-year DFS did not significantly differ between patients treated with TL and less extensive surgery (62.1% vs. 77.8%, p = 0.39; Graph 4).
The OS at 3 years showed that 68% and 100% of patients treated with TL and other techniques, respectively, remained alive, but the difference between the two

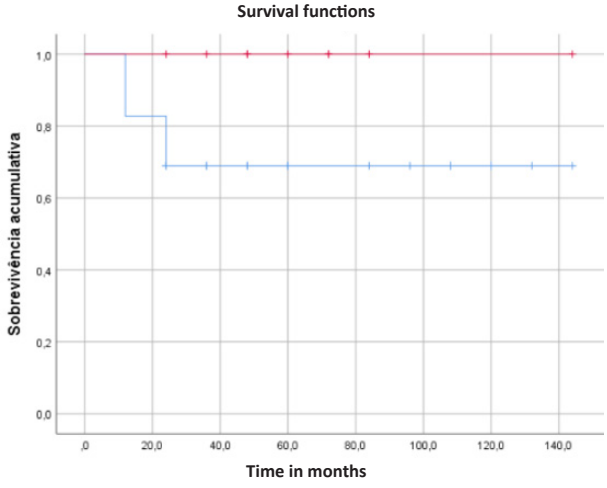
GRAPH 3
Disease-free survival according to N stage. Blue and red indicate N0 and N+, respectively



GRAPH 4
Disease-free survival according to type of surgery. Blue and red indicate TL and other techniques, respectively



GRAPH 5
Overall survival according to type of surgery. Blue and red indicate TL and other techniques, respectively



therapeutic arms did not reach significance (p = 0.007; error, 0.07). Therefore, the type of surgical approach did not have a significant effect on OS at 3 years.

DISCUSSION

The main aim of the present study was to identify factors associated with a poor prognosis and data relative to the survival of 43 patients diagnosed with BSCCL over a period of 16 years in a cancer referral center. The mean OS of the patients was slightly longer than that described in the most extensive study on BSCCL (59.88 vs. 55.00 months)[5].

Similar to previous findings, the region most frequently affected by BSCCL in our patients was the supraglottis (58.1%)[3;4]. This differed from that of SCC of the larynx, in which SCC is three-fold more prevalent in glottic than in supraglottic sites[9].

With regard to DFS according to anatomical sites, fewer patients with supraglottic than glottic BSCCL remained disease-free (52% vs. 90.9%; p = 0.031). Higher rates of lymph node involvement are associated with supraglottic than any other sites of laryngeal tumors[9]. Another feature of supraglottic lesions is that symptoms usually appear later and are more likely to be diagnosed at more advanced stages[10]. The present findings indicated that the supraglottic location of BSCCL is a factor in a poor prognosis. In contrast, some studies have indicated that the intrinsic histological characteristics of BSCCL per se predict a poor prognosis, and that the laryngeal subsite does not influence DFS[6].

Neck lymph node involvement on presentation was another factor that was significantly associated in the present study with lower 2-year DFS (N0 vs. N+: 87.5% vs. 48.0%; p = 0.017). The relevance of the N stage in terms of DFS has been rejected in at least one study, which found that stage did not independently affect survival in BSCCL[6].

The present study found that the 2-year DFS did not significantly differ between T1/T2 and T3/T4a. This similarity between less (T1/T2) and more (T3/T4a) advanced tumors can be explained by considering the selection of treatment according to tumor stage; all patients who were treated by TL + bilateral neck resection + adjuvant RT/CRT were T3/T4, whereas patients with less advanced T1/T2 tumors were treated with more conservative types of surgery.

The type of surgery was also not associated with significant differences in 2-year DFS or 3-year OS. Among the 39 patients who were treated surgically, 29 underwent TL and only 10 were treated with other surgical techniques. This difference in the numbers of patients between the two therapeutic arms might be a factor involved in why survival was not significantly associated with the surgical technique.

This study has some limitations. One is the retrospective nature of the study. Another is that the small sample size did not allow analyses of some variables. For example, only two patients received RT/CRT as the primary treatment, which prevented understanding regarding its effects compared with surgical approaches. Only 7.7% of the surgically treated patients did not receive adjuvant therapy, due to which we could not draw conclusions about the effectiveness of the adjuvant treatment. However, considering that BSCCL is such a rare entity, the sample size was quite significant, especially as it originated from a single clinical center. The study also did not include a comparative group of patients with usual SCC of the larynx.

CONCLUSION

Supraglottic location and N+ stage on presentation were the main factors associated with a poor prognosis of BSCCL in this population. Although previous studies have indicated that the prognosis is worse for BSCC of the head and neck than for SCC, more recent findings have not confirmed this trend. The most current data on BSCC of the larynx indicate that survival rates are similar to those of SCC of the head and neck[7].

Published data combined with the present findings indicate that the prognosis of BSCCL is mainly affected by its preference for the supraglottis and a tendency towards neck metastases rather than by characteristics intrinsic to basaloid histology.

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Conflict of Interest

The authors declare no conflict of interest regarding this article.

Data confidentiality

The authors implemented all protocols at their workplaces and all data remained in house.

Human and animal protection

This study proceeded according to regulations established by the Ethics and Clinical Research Committee and the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and ethics approval

The authors received written informed consent from the patients to include images of them in this article. All data were rendered innominate to protect the privacy of the patients. The Ethics and Clinical Research Committees at IPO and all participating centers approved this study.

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Availability of scientific data

No datasets related to this study are available to the public.

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