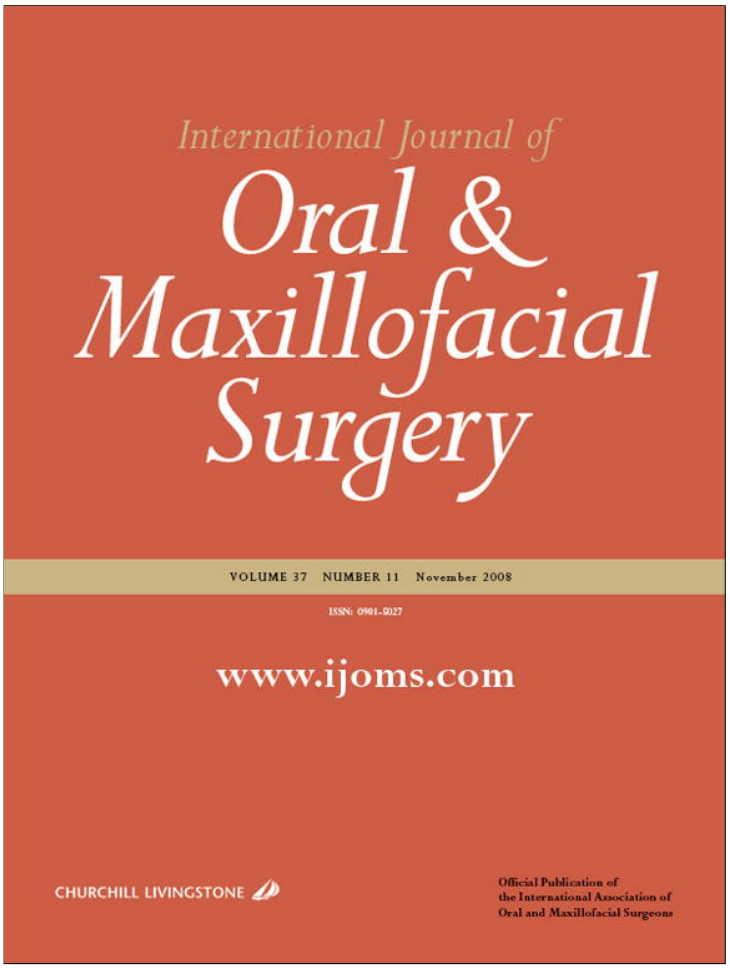

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Clinical Paper
Head and Neck Oncology

A clinicopathologic study on basaloid squamous cell carcinoma in the oral and maxillofacial region

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Abstract. Basaloid squamous cell carcinoma (BSCC) is a rare distinct variant of squamous cell carcinoma (SCC). To investigate its clinical behavior and prognosis, 15 patients with BSCC in the oral and maxillofacial region were clinically analyzed and compared with 15 patients with conventional SCC matched for site, stage, gender and age. To understand its immunohistochemical features, sections for cytokeratin AE1/AE3, CK 13. CK 7, CK 8, proliferating cell nuclear antigen (PCNA) and p53 were reviewed from 12 patients with BSCC. The rate of cervical lymph node metastasis of BSCC was as high as 67% and that of distant metastasis 13%. The tumor recurrence rate was 33% and the 3-year and 5-year survival rates were 53% and 32%, respectively. For conventional SCC, the cervical lymph node metastasis rate was 27%, that of distant metastasis 7%, tumor recurrence rate was 33%, and 3-year and 5-year survival rates were 80% and 70%, respectively. In most BSCC patients (10/12) the PCNA index was over 50%. Twelve BSCC patients were diagnosed with grade II or III conventional SCC when the original records of the primary diagnosis for the 15 patients with BSCC were reviewed. The biological behavior and prognosis of BSCC are similar to those of poorly differentiated SCC.

Keywords: basaloid squamous cell carcinoma; squamous cell carcinoma; oral mucosa; head and neck; diagnosis; prognosis; pathology; immunohistochemistry.

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Basaloid squamous cell carcinoma (BSCC), first described in the head and neck by WAIN et al[25] in 1986, is a rare distinct variant of squamous cell carcinoma (SCC). The most common sites of the tumor in the head and neck are the hypopharynx, base of the tongue and supraglotic larynx[10–12,20,23,25]. It has also been described in the nasal cavity, oesophagus, tonsil and oral cavity.[7,8,15,18] The histopathologic appearance and immunohistochemistry of BSCC are different from those of conventional SCC[5] and opinions vary as to its clinical behavior and prognosis compared with conventional SCC.[29]

The aim of this paper is to report on 15 patients with BSCC in the oral and maxillofacial region and compare the clinical behavior and prognosis of BSCC and conventional SCC.

Materials and methods

Between January 1987 and October 2003, 1936 patients with SCC in the oral and maxillofacial region were diagnosed and/or treated. The registered pathology slides

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in the Department of Oral Pathology were reviewed by two authors (GAO and CHEN). Among them, 20 cases met the diagnostic criteria for BSCC. All patients (except for one who received non-surgical therapy) were treated surgically in the Department of Oral and Maxillofacial Surgery. Two patients were lost to follow-up. Two patients had received surgery in other hospitals and were excluded from the analysis. The remaining 15 patients, with a follow-up of more than 3 years after operation, were included in this study.

Laboratory technique

Hematoxylin-eosin (H&E) and immunohistochemical sections for cytokeratin AE1/AE3, CK13, CK7, CK8, proliferating cell nuclear antigen (PCNA) and p53 from 12 patients with BSCC and 15 patients with conventional SCC were reviewed.

For immunohistochemical staining, formalin-fixed and paraffin-embedded specimens were cut into 5-μm sections, deparaffinized in xylene and rehydrated through a graded ethanol series. Sections were incubated with fresh 3% H_2O_2 in methanol for 20 min at room temperature to quench endogenous peroxidase and incubated in blocking serum for 20 min at room temperature to prevent non-specific protein binding. After washing three times in triethanolamine buffered saline (TBS), the sections were incubated with primary antibodies (monoclonal anti-p53, 1:200, Santa Cruse, USA; mouse monoclonal anti-PCNA, 1:100, DAKO, monoclonal antibodies for AE1/AE3, CK13, CK7 and CK8 with the dilution 1:100, Zymed Laboratories Inc., San Francisco, USA) and then incubated with secondary antibody and streptavidin for 30 min at room temperature. They were washed three times in TBS and sites of bound antibody were visualized by diaminobenzidine (DAB). The sections were lightly counterstained with Mayer's hematoxylin. Negative controls were prepared by substituting TBS for each primary antibody, and no detectable staining was evident. Brown nuclear staining was considered positive for p53 and PCNA; cytoplasm staining was positive for cytokeratins.

Clinical evaluation

The 15 BSCC patients had been followed-up for 3–15 years with a mean follow-up period of 8.1 years. A group of 15 patients with conventional SCC matched for site, stage, gender and age were similarly evaluated (Table 1). The difference in age between the 2 groups was less than 5 years. Their ages ranged from 45 to 72 years with a median age of 60 years. The follow-up period was 2–26 years with a mean of 7.9 years.

The rate of cervical lymph node metastasis, tumor recurrence rate and survival rate were compared in the two groups. Survival rate was calculated using the Kaplan–Meier method. The differences in the rates of cervical lymph node metastasis, distant metastasis and survival between the two groups were assessed using Fisher's exact test and a nonparametric test. A probability of less than 0.05 was assumed to be statistically significant.

Results

All 15 patients with BSCC were male. Their ages ranged from 43 to 70 years, most were older than 50 years and the median age was 58 years. The tumor sites are listed in Table 1; the most common sites were maxillary sinus and tongue, followed by gingiva, floor of the mouth, and buccal mucosa.

The case history varied from 10 days to 2 years, but in 10 patients it was within 3 months. According to the standard tumor-node-metastasis (TNM) staging provided by AJCC in 2002[1], 4 patients presented in stage II, 2 in stage III, and 9 in stage IV.

When the records of the original histopathologic diagnosis were reviewed, 2 patients were diagnosed as grade 1 conventional SCC, 8 as grade 2, and 2 as grade 3. One patient was diagnosed with less differentiated mucoepidermoid carcinoma. Only 2 patients were recognized as having BSCC at the time of initial diagnosis.

Histopathologically, BSCC of the oral and maxillofacial region consisted of tumor islands of varied size. The tumor cells were mainly basaloid, with high nuclear/cytoplasmic ratios, hyperchromatic nuclei and moderate cellular pleomorphism. The cytoplasm was lightly eosinophilic, with distinct cell borders. There were areas of typical squamous differentiation among the basaloid cells or as separate foci of tumor, but keratinization was not common. One of the remarkable characteristics was comedo-like necrosis within the tumor islands (Fig. 1). Nuclear mitoses were often noted. The epithelia adjacent to the tumor frequently showed different degrees of dysplasia (Fig. 2). Tumor tissues often infiltrated neighboring muscle, acinus and occasionally bone. The stroma was composed of fibrous tissue with hyaline degeneration, mucoid substance was not noted. The histological features of conventional SCC were different from those

Table 1. The clinical features of the patients with BSCC and SCC

BSCC						SCC					
Case	Age/gender	Location	Stage	Final outcome	Follow-up period (yr)	Case	Age/ gender	Location	Stage	Final outcome	Follow-up period (yr)
1	62/M	Tongue	II	Dead	5	1	60/M	Tongue	II	Alive	11
2	58/M	Tongue	IV	Alive	3	2	62/M	Tongue	IV	Alive	7
3	63/M	Tongue	II	Alive	3	3	58/M	Tongue	II	Alive	6
4	50/M	Tongue	IV	Dead	1	4	55/M	Tongue	IV	Dead	0.5
5	70/M	Floor of mouth	II	Dead	4	5	67/M	Floor of mouth	II	Alive	4
6	57/M	Floor of mouth	IV	Alive	5	6	61/M	Floor of mouth	IV	Alive	2.5
7	61/M	Gingiva	II	Alive	10	7	60/M	Gingiva	II	Alive	5
8	56/M	Gingiva	IV	Alive	15	8	60/M	Gingiva	IV	Dead	0.5
9	65/M	Gingiva	III	Dead	2.5	9	61/M	Gingiva	III	Alive	12
10	59/M	Maxillary sinus	IV	Dead	1	10	64/M	Maxillary sinus	IV	Alive	3
11	47/M	Maxillary sinus	IV	Dead	1	11	48/M	Maxillary sinus	IV	Alive	5
12	69/M	Maxillary sinus	IV	Dead	2.5	12	72/M	Maxillary sinus	IV	Alive	2
13	48/M	Maxillary sinus	IV	Alive	3.5	13	53/M	Maxillary sinus	IV	Dead	4
14	50/M	Center of mandible	IV	Dead	1	14	45/M	Center of mandible	IV	Dead	2
15	43/M	Oropharynx	III	Dead	1	15	48/M	Oropharynx	III	Alive	2

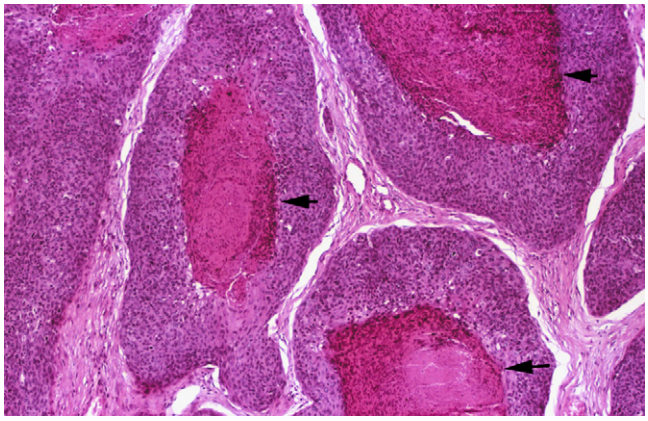

Fig. 1. BSCC tumor nests consisting of basaloid cells showing central comedo-like necrosis (arrows). H&E staining, ×150.

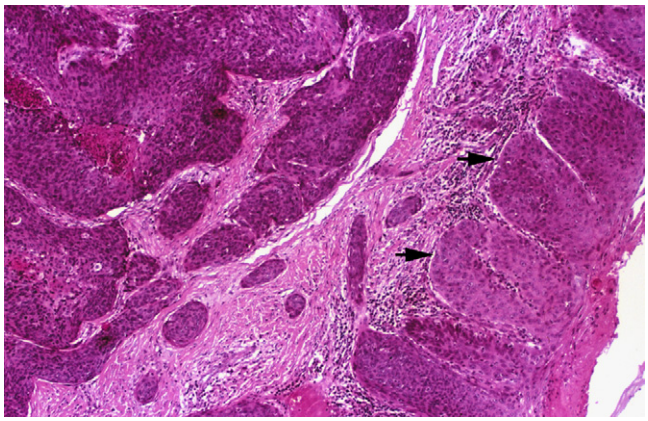

Fig. 2. Epithelium adjacent to BSCC foci displays epithelial dysplasia. H&E staining, ×150.

of BSCC and included the formation of obvious keratinized peals and limited basaloid cells in the outer layer of tumor nests.

In BSCC, cytokeratin AE1/AE3 staining was noted in all cases. Cytokeratin 13 immunostaining showed a limited positive result in areas of squamous differentiation (Fig. 3), but was negative in basaloid cells. CK8 was locally weakly positive in 4 patients and CK7 in 1 patient. The PCNA index in most patients (10) was over 50% (Fig. 4). P53 was positive in 7 patients (Fig. 5). Cytokeratin 13 reactivity was more extensive in conventional SCC than in BSCC; in most patients (13), the PCNA index was less than 50%.

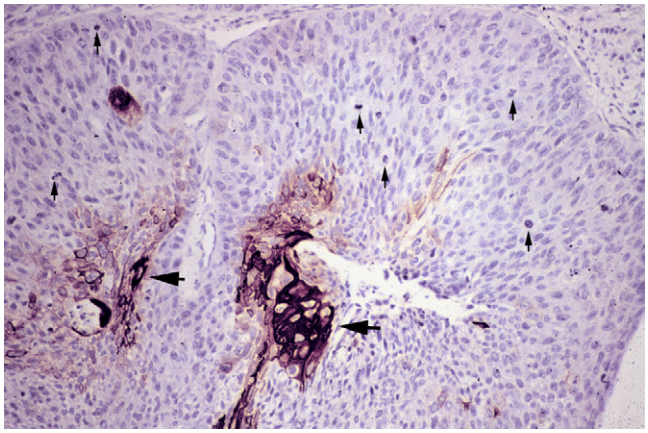

Fig. 3. Cytokeratin 13 positive staining demonstrates small area of squamous differentiation in BSCC (larger arrows). Most areas of basaloid cells are negative. Nuclear mitosis is noted (smaller arrows). Immunohistochemical staining, ×300.

All 15 patients with BSCC received radical surgery. Ten underwent neck dissection. Histopathologic examination showed cervical lymph node metastasis in the surgical specimens of the first operation in 6 patients.

One patient received preoperative radiotherapy (dosage 40 Gy). Of 8 patients received postoperative radiotherapy, 1 had been given preoperative and postoperative radiotherapy (dosage 70 Gy). The remaining 7 patients received postoperative radiotherapy (dosage 46–50 Gy).

Metachronous multiple primary carcinoma occurred in 2 patients. One patient had had a malignant transformation of branchial cyst in the right neck one year ago and a BSCC in the right lower gingiva. Another patient, who was not included in this study, had had a conventional SCC in the left lower lingual gingival 5 years ago and a BSCC in the left buccal mucosa.

During follow-up, relapse of the primary tumor occurred in 5 patients (33%). Cervical lymph node metastasis occurred in 4 patients (27%). The total rate of metastasis, including the metastasis found on admission and follow-up, was 67% (10/15). Recurrence of cervical metastatic tumor occurred in 4 patients (27%). Distant metastasis occurred in 2 patients (13%), one located in the lung, and another in bone. Eight patients died of their tumors. One patient died of brain hemorrhage without recurrence or metastasis of the tumor 5 years after operation. The overall 3-year survival rate was 53%, and the 5- year survival rate was 32%.

Among 15 patients with conventional SCC, cervical lymph node metastasis in the surgical specimens of the first operation was found in 3 cases (20%). Cervical metastasis occurred during follow-up in 1 patient (7%). The total rate of cervical lymph node metastasis was 27% (4/15). Bone metastasis occurred in 1 patient (7%). Recurrence of the primary tumor after treatment occurred in 5 patients (33%). Four patients died of the tumor. The overall 3-year survival rate was 80%, and the 5-year survival was 70%.

Statistical analysis showed that the rate of cervical lymph node metastasis in BSCC was significantly higher than that in conventional SCC ($P = 0.028 < 0.05$). No significant differences in tumor recurrence rate ($P = 1$) and rate of distant metastasis ($P = 0.550$) between the two groups was noted. Although the 3-year and 5-year survival rates in the patients with BSCC (53% and 32%, respectively) were lower than those of patients with

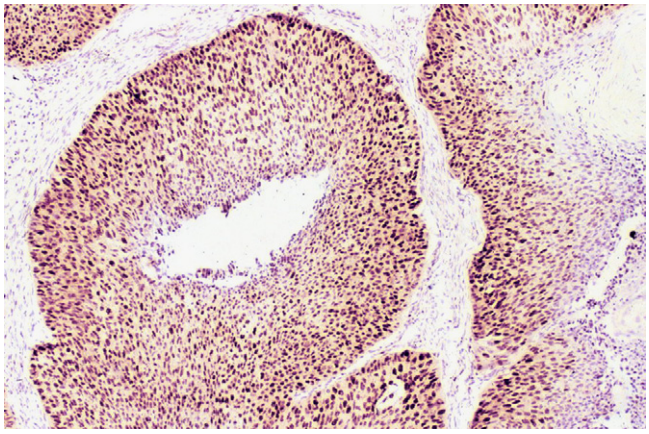

Fig. 4. PCNA positive immunoreactivity in BSCC. Immunohistochemical staining, ×150.

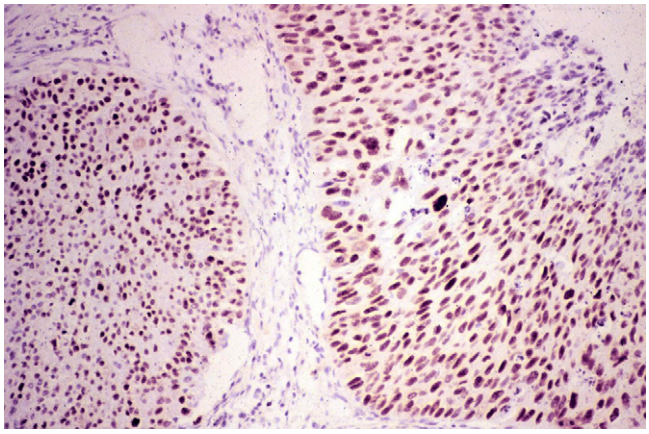

Fig. 5. p53 immunohistochemical positive staining in BSCC. Immunohistochemical staining, ×250.

conventional SCC (80% and 70%, respectively), this difference was not statistically significant ($P = 0.1127$).

Discussion

BSCC is a rare malignant tumor. It is commonly located in the head and neck, but may also present in the esophagus[18], trachea, lung[13], cervix[14], vagina[17] penis[6], and urinary bladder[24]. It occurs most often in older males;[25,29] in this series, all 15 patients were male and 6 of them were older than 60 years. The phenomenon of older age is more obvious in BSCC than in conventional SCC. The history of the disease is short because the carcinoma grows rapidly and is associated with pain. Among the 15 patients in this series, the disease history was less than 3 months in 10 patients.

BSCC occurs in various locations in the head and neck, especially the maxillary sinus, tongue and gingiva. Tumor presentation in the maxillary sinus is a characteristic of BSCC. According to the standard TNM staging provided by AJCC, BSCC patients at stage III and IV account for 65% of all known cases. Ide et al[15] reviewed 46 patients with oral BSCC in the literature and reported 62% of the patients to be in the advanced stage.

The rate of cervical lymph node metastasis reported in the literature varies between 40% and 70%[15,16,22] while that of distant metastasis was up to 75%[2,25,27,28]. In some reports, the distant metastasis rate was less than 10%[11,21]. In this series, the rate of initial cervical lymph node metastasis was 40% (6/15) and that of cervical lymph node metastasis during follow-up was 26.7% (4/15). The overall cervical lymph node metastasis rate was as high as 66.7% (10/15) and the metastasis usually involved the whole neck. Distant metastasis occurred in 2 patients, in the lung in one and in the bone in the other. These results indicate that the biological behavior of BSCC is that of a high grade malignant tumor.

No clinical features of BSCC distinguish it from conventional SCC. The diagnosis depends mainly on the histopathologic and immunohistochemical manifestations.[4] When the bulk of the tumor consists of solid nests of basaloid cells, with typical comedo-like necrosis, moderate nuclear mitotic activity and cellular pleomorphism, and epithelial dysplasia of adjacent superficial epithelium, a pathological diagnosis of BSCC can be made.

According to the results of immunohistochemical staining, reactivity for cytokeratin AE1/AE3 in BSCC confirmed its epithelial origin. The active cell proliferation, as demonstrated by higher PCNA index and histologically high mitosis rate, and comedo-like necrosis suggest the higher grade malignant nature of BSCC.

CK 13 positive staining was limited to the area of well differentiated squamous cells but most basaloid cells in the tumor showed no immunoreactivity, which was different from conventional SCC. This immunostaining pattern may be used to identify squamous differentiation in this tumor and differentiate it from conventional SCC. Occasionally CK7 and CK8 expression in BSCC might indicate an origin in glandular epithelium.

The pathological differential diagnosis of BSCC includes mainly solid type adenoid cystic carcinoma (ACC) of the salivary glands and small cell undifferentiated carcinoma. Squamous differentiation, mitosis, nuclear pleomorphism and necrosis are characteristic of BSCC but rare in ACC. Adjacent epithelial dysplasia seen in BSCC is rarely evident in ACC. ACC often shows immunocytochemical reactivity for S-100 and smooth muscle actin but BSCC is negative for these. Immunohistochemical staining for p-63 may be helpful in distinguishing between ACC and BSCC.[9]

Small cell undifferentiated carcinoma is rare in the oral cavity, sometimes with pseudoglandular space and focal necrosis, but squamous differentiation is exceptional. Its immunohistochemical activity for neuroendocrine markers or ultrastructural evidence of neurosecretory granules are not the features of BSCC.

Other tumors to be considered in the differential diagnosis of BSCC may include polymorphous low-grade adenocarcinoma, basal cell adenocarcinoma, salivary duct carcinoma and adenosquamous carcinoma. Tubular structures, bland and uniform nuclear features, diverse morphological patterns in polymorphous low-grade adenocarcinoma can be used to distinguish them from BSCC. Focal necrosis and squamous differentiation, usually seen in BSCC, are less frequent in basal cell adenocarcinoma.

Eosinophilic cytoplasm and irregular shaped cystic spaces lined by papillary projections revealed by salivary duct carcinoma are not encountered in BSCC. Adenosquamous carcinoma is usually easy to distinguish from BSCC by real duct structures.

There are different opinions on the prognosis of patients with BSCC.[29] Some authors think that the prognosis of patients with BSCC is poorer than that of patients with conventional SCC[15,29], others consider that prognosis does not differ for patients with BSCC of the oral cavity and those with conventional oral SCC[3,8]. Wedenberg et al[26] compared the clinical data of patients with BSCC of the head and neck with those of patients with poorly differentiated SCC and reported that the distant metastasis rate of BSCC was 52% compared with 13% in SCC.

The local recurrence rate of BSCC is similar to that of poorly differentiated SCC. Erdamdar et al[10] compared the local recurrence rate of 10 patients with BSCC with that of 44 patients with conventional SCC and found significant difference between the two groups. There was no difference for the cervical lymph node metastasis rate on admission, cervical recurrence, and distant metastasis rate between the two groups. The 3-year survival rate of patients with BSCC was 50%, compared with 72% for conventional SCC. Luna et al[19] matched the tumor location, treatment options, clinical stage, and compared the clinical data of 6 patients with BSCC in the sinus with those of 47 patients with conventional SCC. There was no difference in survival and cervical lymph node metastasis. Banks et al[3] reviewed the clinical data of 40 patients with head and neck BSCC. When the clinical staging was matched, the biological behavior and treatment of head and neck BSCC were similar to those of conventional SCC. In the present series, the biobehavior of the tumor and the prognosis of patients with BSCC and conventional SCC were compared by site, stage, gender and age matching. The overall cervical lymph node metastasis rate of BSCC (67%) was higher than that of conventional SCC (27%). The recurrence rate of BSCC (33%) was the same as that of conventional SCC (33%). The 3-year and 5-year survival rates for BSCC were 53% and 32%, respectively, which was lower than those for conventional SCC (80% and 70%, respectively). The differences in survival rates between the two groups were not statistically significant, mainly because of the small number of patients. This indicates that a study with a large number of patients from multiple institutions is necessary.

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