

## RESEARCH ARTICLE

# Clinical Outcomes of Basaloid Squamous Cell Carcinoma of the Esophagus: A Retrospective Analysis of 142 Cases

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### Abstract

**Background:** Basaloid squamous cell carcinoma of the esophagus (BSCCE) is a rare and distinctive tumor with no standard treatment. This study aimed to explore treatment in relation to prognosis of the disease. **Methods:** A total of 142 patients with BSCCE that underwent treatment in our hospital from March 1999 to July 2010 were retrospectively analyzed. All patients received surgery, 42 postoperative radiotherapy and 28 patients chemotherapy. **Results:** There were 26 patients included in stage I, 60 in stage II, 53 in stage III and 3 in stage IV. The clinical symptoms and macroscopic performances of BSCCE did not differ from those of typical esophageal squamous cell carcinoma. Among 118 patients receiving endoscopic biopsy, only 12 were diagnosed with BSCCE. The median survival time (MST) of the entire group was 32 months, with 1-, 3- and 5-year overall survival (OS) of 81.4%, 46.8% and 31.0%, respectively. The 5-year OS of stage I and II patients was significantly longer than that of stages III/IV, at 60.3%, 36.1% and 10.9%, respectively ( $p < 0.001$ ,  $p = 0.001$ ). The MST and 5-year OS were 59.0 months and 47.4% in patients with tumors located in the lower thoracic esophagus, and 27.0 months and 18.1% in those with lesions in the upper/middle esophagus ( $p = 0.002$ ). However, the survival was not significantly improved in patients undergoing adjunctive therapy. Multivariate analysis showed TNM stage and tumor location to be independent prognostic factors. Furthermore, distant metastasis was the most frequent failure pattern, with a median recurrence time of 10 months. **Conclusion:** BSCCE is an aggressive disease with rapid progression and a propensity for distant metastasis. It is difficult to make a definitive diagnosis via preoperative biopsy. Multidisciplinary therapy including radical esophagectomy with extended lymphadenectomy should be recommended, while the effectiveness of radiochemotherapy requires further validation for BSCCE.

**Keywords:** Esophageal neoplasm - basaloid squamous cell carcinoma - surgery - multidisciplinary therapy - prognosis

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### Introduction

Basaloid squamous cell carcinoma of the esophagus (BSCCE) is a rare and recently recognized variant of squamous cell carcinoma (SCC) (Sarbia et al., 1997; Morice et al., 1998; Gabbert et al., 2000; Li et al., 2004), which is distinctly characterized by a solid growth pattern with a nesting, lobular, or trabecular arrangement of basaloid cells, small cystic spaces and foci of comedo-type necrosis in central areas of the tumor. The incidence of BSCCE varies from 0.77-5.0% (Sarbia et al., 1997; Morice et al., 1998; Cho et al., 2000; Li et al., 2004; Chen et al., 2012). Actually, with the wide acceptance of the histological concept, the number of cases has been gradually increasing in recent years.

However, previous reports (Morice et al., 1998; Cho et al., 2000; Owonikoko et al., 2001; Li et al., 2004; Chen et al., 2012) have focused mainly on the histopathological features based on small sample studies and anecdotal

experiences. The current treatment options for BSCCE are based mainly on the experience gained from the treatment of typical esophageal SCC. However, some researches (Sarbia et al., 1997; Li et al., 2004) have found that BSCCE exhibits relatively undifferentiated characteristics and undeveloped cell organelles. It has also been observed that the proliferative activity and apoptotic indices of BSCCE are higher and its biological behavior is more aggressive than typical SCC (Sarbia et al., 1997; Lam et al., 2001; Imamhasan et al., 2012). Therefore, BSCCE should be differentiated from typical esophageal SCC. The clinical characteristics and optimal therapy for this subtype of esophageal cancer, especially the role of surgical resection should be further studied. This study retrospectively analyzed the clinical data of 142 cases of BSCCE. However, to our knowledge, this is the largest study from a single institution to explore the clinical features, treatment modalities and prognosis of the disease.

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## Materials and Methods

From March 1999 to July 2010, all patients diagnosed with BSCCE and received treatment at the Cancer Hospital of the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College were identified. Medical records of these patients were systematically reviewed. The study has been approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences.

### Patient selection

Patients were included in the study according to the following criteria: 1) the presence of a detailed medical history record and physical examination prior to the treatment; 2) availability of barium meal, computed tomography (CT) scans of the chest, Doppler ultrasound or CT examination of the abdomen to complete the clinical staging evaluation; 3) receiving esophagectomy with two-field lymphadenectomy.

The final study population consisted of 148 patients, which accounted for 2% of all patients with primary malignant esophageal neoplasms treated in our hospital in the past 11 years. 142 patients met the inclusion criteria. Because of invasion into adjacent organs, distant metastases, or other complications, five patients failed to receive surgery and were excluded. And one patient was excluded because of incomplete medical records. The included patients' stage of disease was reclassified based on the seventh edition of the AJCC (American Joint Committee on Cancer) cancer staging manual.

### Surgery

All 142 patients received curative transthoracic esophagectomy with two-field lymphadenectomy (mid and inferior mediastinal, upper abdominal lymph nodes) using the stomach or colon as the esophageal substitute. The choices of surgical approach depended on the tumor location and lymph node metastases. Left thoracotomy was performed in 124 cases with middle and lower thoracic BSCCE, and Ivor-Lewis thoracotomy in 7 cases with upper thoracic BSCCE or upper mediastinal lymph node enlargement. Another 11 patients were treated via the cervicothoracoabdominal approach to achieve radical resection of the tumors in the upper thoracic esophagus. Upper mediastinal lymphadenectomy were also performed in patients treated via Ivor-Lewis or cervicothoracoabdominal approach. A total of 2834 lymph nodes were removed (range of 3-57 nodes with median of 19 nodes) with 203 metastases. Radical resection was achieved in 128 cases and palliative resection in 14 cases. Postoperative complications occurred in 14 patients (10.2%). These complications included incisional infection (5), anastomotic leakage (2), chylothorax (2), respiratory failure (2), pyothorax (1), hemorrhage (1), and diaphragmatic hernia (1). Two patients died of sepsis because of anastomotic leak and respiratory failure and the mortality in the perioperative period was 1.4% (2/142).

### Adjunctive therapy

After operation, 11 patients received additional

chemotherapy, 25 received radiotherapy, and 17 received radiochemotherapy, respectively. Postoperative radiotherapy was begun 3-4 weeks after surgery using 6-MV photons. A median radiation dose of 60.0 Gy (range from 30-70 Gy) was delivered with a conventional fraction (1.8-2.0 Gy per fraction). Overall, 28 cases received combination chemotherapy, mainly based on platinum regimens (cisplatin or carboplatin plus Taxol, cisplatin plus 5-Fluorouracil plus Etoposide, Nedaplatin plus Taxol). A median course of four cycles (range, 1-7 cycles) of chemotherapy was provided and some patients received alternating regimens.

### Statistical Analysis

The patients' data were analyzed using the SPSS software ver. 15.0 (Chicago, IL, USA). The  $\chi^2$  test was used to assess the differences between groups for dichotomous variables. Survival time was calculated from the date of the initial treatment to the date of death or the last follow-up. The patients lost to follow-up or alive at the end of the study were considered censored. The overall survival rates (OS) and median survival time (MST) were estimated by the Kaplan-Meier method and the differences between groups were compared using the Log-rank test. Significance was determined with a two-sided p-value of less than 0.05. Cox proportional hazard regression models were used to determine the prognostic significance of variables that were significant on univariate analysis.

## Results

### Patient Characteristics

The patient characteristics are summarized in Table 1. The study group was composed predominantly of males with a median age of 61 years (range from 32 - 79 years). The main manifestations in the initial diagnosis included progressive dysphagia, weight loss, retrosternal/back

**Table 1. Patient Clinical Characteristics**

Characteristics	No.of patients(%)
Sex	Men 122(85.9%)
	Women 20 (14.1%)
Age(y)	Median 61
	Range 32-79
Symptoms	Dysphagia 127(89.4%)
	Weight loss 37(26.1%)
	Retrosternal/back pain 19(13.4%)
	Odynophagia 12(8.5%)
Tumor location	Upper esophagus 14(9.9%)
	Middle esophagus 70(49.3%)
	Lower esophagus 58(40.8%)
Tumor length (cm)	Median 5
	Range 1.0-15.0
Macroscopic type	Medullary 69(48.6%)
	Fungoid 28(19.7%)
	Ulcerative 14(9.9%)
	Intraluminal 9(6.3%)
TNM stage	Plaque/erosive 22(15.5%)
	Stage I 26(18.3%)
	Stage II 60(42.3%)
	Stage III 53(37.3%)
	Stage IV 3(2.1%)

**Table 2. Univariate Analysis of the Prognosis of 142 Patients with BSCCE**

Variables	No.of patients	5 yr OS (%)	MST(m)	P value
Gender				0.204
Male	122	32.9	36	
Female	20	14.7	25	
Age(yr)				0.795
≤60	70	32.3	36	
>60	72	29.4	31	
Family history				0.198
No	116	33.4	32	
Yes	26	21.9	27	
Tumor location				0.002
Upper & middle	84	18.1	27	
Lower	58	47.4	59	
Tumor length				0.077
≤5cm	73	35.5	38	
>5cm	69	26.3	26	
Pathological T				<0.001
T1	30	56.1	NR	
T2	28	28.8	36	
T3	59	30	35	
T4	25	5.6	13	
Pathological N				0.001
N0	83	42	42	
N1	41	20.1	21	
N2/3	18	0	23	
No.of nodes resected				0.505
≤18	68	29.2	36	
>18	74	33.1	31	
TNM stage				<0.001
I	26	60.3	NR	
II	60	36.1	38	
III/IV	56	10.9	19	
Radiotherapy				0.168
No	100	33.1	38	
Yes	42	26.2	24	
Chemotherapy				0.015
No	114	35.9	38	
Yes	28	12.8	23	

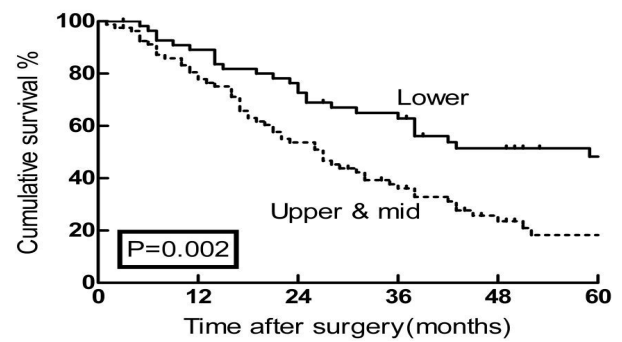
OS, overall survival; MST, median survival time; NR, not reached

pain, odynophagia, which are identical to those of typical esophageal SCC. The primary lesions were most often located in the middle and lower thoracic esophagus. Of 131 cases that underwent preoperative esophagoscopy, 118 received biopsy and only 12 cases were diagnosed with BSCCE. However, typical SCC was the most frequently misdiagnosed tumor type (77/118, 65.3%).

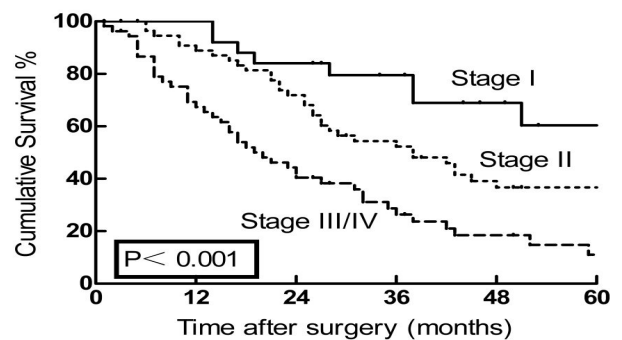
The pathological diagnosis of BSCCE was made according to the World Health Organization classification criteria in all patients. Immunohistochemical examinations were performed in 59 patients. Immunoreactivity for CK34BE, AE1/AE3, Bcl-2, and CK18 was seen in 100%, 96.8%, 84.6%, 76.2% of these patients, respectively.

#### Prognostic factors analysis

To August 2012, the median follow-up of the whole group was 27 months, ranging from 1 to 144 months. Follow-up information until death or a maximum of 60 months was complete for 78.9% of patients (112/142) at the time of this study. At the end of follow-up, 87 patients died. Of those, 82 died of tumor recurrence, 2 died of



**Figure 1. Survival Curves for BSCCE Comparing Patients with Tumors Located in the Lower Thoracic Esophagus (n=58) Versus vs. Patients with Tumors Located in the Upper/Middle Thoracic Esophagus (n=84)**



**Figure 2. Survival Curves for BSCCE Comparing Patients with Pathological Stage I (n=26) vs. Patients with Stage II (n=60) and Patients with Stage III/IV (n=56)**

postoperative complications, 1 died of heart disease and 2 died of unknown reasons, respectively. Eight patients were alive with tumor recurrence, 36 patients were alive free of disease and the remaining 11 cases were lost to follow-up. The overall median survival time (MST) of the entire group was 32 months (95% confidence interval, 24.8-39.2 months). The 1-, 3- and 5-year overall survival rates (OS) were 81.4%, 46.8% and 31.0%, respectively. A total of 33 patients survived more than 48 months after radical esophagectomy.

The relationship between the clinicopathologic features and prognosis of BSCCE are compared in Table 2. The MST and 5-year OS were 59.0 months and 47.4 %, respectively, in patients with tumors located in the lower thoracic esophagus, and 27.0 months and 18.1 %, respectively, in patients with tumors in the upper/middle esophagus (Figure 1,  $p=0.002$ ). The 5-year OS of the patients with stage I and II were also significantly longer than that of the stages III/IV, which were 60.3 %, 36.1 % and 10.9 %, respectively (Figure 2,  $p<0.001$  and  $p=0.001$ ). Other factors including Pathological T ( $p<0.001$ ), Pathological N ( $p=0.001$ ), and Chemotherapy (Yes versus No) ( $p=0.015$ ) were also found to have a statistically significant relationship with prognosis. But the survival of patients who received chemotherapy was worse than those who did not receive chemotherapy. Patients' gender, age, family history, tumor length (≤5cm versus >5cm), number of lymph nodes resected (≤18 versus >18) and radiotherapy were not associated with the prognosis.

Among patients with pathological stage II, the MST

of 36.0 months for the group receiving radiotherapy (n = 12) was insignificantly different from that of 38.0 months for the group not receiving radiotherapy (n = 48, *p* = 0.628). Furthermore, the MST for the group receiving chemotherapy (n = 5) was 26.0 months, which was insignificantly different from the MST of 38.0 months for the group not receiving chemotherapy (n = 55, *p* = 0.415). Among patients with pathological stages III/IV, the MSTs for the group receiving radiotherapy (n = 29) and the group not receiving radiotherapy (n = 27) were 19.0 and 20.0 months, respectively (*p* = 0.678). No significant difference was observed in the MSTs between the group receiving chemotherapy (n = 22) and the group not receiving chemotherapy (n = 34) (MST of 18 vs. 19 months, *p* = 0.649). Therefore, postoperative radiotherapy and chemotherapy did not significantly improve the overall survival of BSCCE even in patients with relatively advanced diseases.

In multivariate analysis, which included tumor location (upper/mid versus lower), Pathological T, Pathological N, TNM stage and Chemotherapy (Yes versus No) as entry factors, the TNM stage (Hazard ratio of 2.162 with the 95% CI of 1.228-2.999, *p*<0.001), and tumor location (Hazard ratio of 0.497 with the 95% CI of 0.315- 0.782, *p*=0.003) were found to be independent prognostic factors. Failure patterns in 71 cases

The first failure sites found during the follow-up in 71 cases included distant metastases in 39 cases (54.9%), distant metastases with locoregional recurrences in 24 cases (33.8%) and locoregional recurrences in eight cases (11.3%), respectively. Distant metastases were usually

occurred in the lung (28 cases), liver (18 cases), bone (8 cases), pleura (4 cases), brain (3 cases), adrenal (1 case) and distant lymph nodes (19 cases). Some patients experienced simultaneous metastases to more than one location. The median time from treatment to failure was 10.0 months (95% CI, 5.9-14.1).

The patterns of recurrence after different treatment are shown in Table 3. The frequency of locoregional recurrence in patients without radiotherapy (including S and S+C groups in Table 3) was significantly higher than that of the patients who received radiotherapy (including S+R and S+R+C groups in Table 3) (*p*=0.024). However, there was no difference in the frequency of distant recurrences between groups who received chemotherapy (S+C and S+C+R groups in Table 3) or did not receive chemotherapy (S+R and S groups in Table 3) (*p*=0.786).

### Discussion

In this study, we provided a comprehensive evaluation of the clinical characteristics and treatment outcomes for BSCCE based on the largest series from a single institution. Based on our results, BSCCE was an aggressive disease with poor prognosis. Its MST and 5-year OS were only 32.0 months and 31.3%, respectively, which are consistent with previous studies (Chen et al., 2012; Imamhasan et al., 2012). However, several recent large cohort studies (Mariette et al., 2008; Yang et al., 2012) have shown that the MST of typical esophageal SCC varied from 48.3 - 54.8 months, and the 5-year OS varied from 47%- 48.2%, longer than those for BSCCE. In addition, we demonstrated that the TNM stage and tumor location were independent factors in the prediction of prognosis. Patients with early-stage tumor and lower tumor location had a favorable survival rate.

As reported previously (Sarbia et al., 1997; Lam et al., 2001; Owonikoko et al., 2001; Imamhasan et al., 2012), the clinical symptoms and macroscopic performances did not differ from those of typical esophageal SCC. Therefore, it was difficult to make a definitive diagnosis without histopathological examination. However, endoscopic biopsy could only cover the superficial and small parts of the tumor. Considering the histological

**Table 3. Recurrence in the Different Treatment Groups**

Treatment Group	No.of Patients	Locoregional (No.)	Distant (No.)	Locoregional+ distant (No.)	MPT (m)
S	38	6	17	15	11
S+R	17	1	11	5	14
S+C	5	1	2	2	15
S+C+R	11	0	9	2	7

S, surgery; R, radiotherapy; C, chemotherapy; MPT, median progression time; Distant metastases included hematogenous and distant lymph node metastases

**Table 4. Review of the Literature for Characteristics and Prognosis of BSCCE**

Reference	No.of cases	Treatment (No. of cases)	MST/OS	Prognosis
Huang et al., 1995	5	Surgery (5), Radiotherapy (2)	Mean survival time, 12.5 m	Poor prognosis.
Abe et al., 1996	7	Surgery (7), Radiochemotherapy (6)	----	2 died of recurrence 20 and 13 m later, 2 of other causes, 3 alive after 10 m.
Sarbia et al., 1997	17	Surgery (17)	5-year OS 19.2 %	No significant difference between BSCCE and typical SCC.
Zhang et al., 1998	16	Surgery (16), Chemotherapy (11)	2-year OS 20 %	Poor outcome.
Cho et al., 2000	18	Surgery (18), Chemotherapy (7) Radiotherapy (2)	3-year OS 51%	3-year OS of BSCCE was higher than 34% of typical SCC.
Lam et al., 2001	30	Surgery (30)	MST 26 m, 5-year OS 12%	No significant difference between BSCCE and typical SCC.
Chen et al., 2012	26	Surgery (26), radiotherapy (2)	MST 29m, 5-year OS 36.6%	Worse than WDSCC cases, similar to PMSCC.
Imamhasan et al., 2012	22	Surgery (22)	5-year OS, 42%	Worse than WDSCC cases, similar to PMSCC.

LNM, lymph node metastasis; OS, overall survival; MST, median survival time; WDSCC, well differentiated typical squamous cell carcinoma; PMSCC, poorly and moderately differentiated typical squamous cell carcinoma.



diversity of BSCCE, Morice et al. (1998) and Chen et al. (2012) reported that it was difficult to differentiate BSCCE from typical SCC, adenoid cystic carcinoma (ACC) and small cell carcinoma via biopsy alone. In this study, only 12 cases were diagnosed as BSCCE by endoscopic biopsy and typical SCC was the most commonly differentiated tumor type. Thus, the true incidence of BSCCE is likely higher than previously reported because of the possibility of misdiagnosis in patients without surgical treatment. We recommend taking deep tissue samples from multiple sites in the tumor during biopsy.

The diagnosis of BSCCE depends mainly on the microscopical appearance using routine hematoxylin and eosin stain. However, several recent reports (Li et al., 2004; Kobayashi et al., 2009) have demonstrated that BSCCE was accompanied by various histopathological components including ductal differentiation, myoepithelial cells, and adenoid cystic carcinoma-like features in some cases. Furthermore, some BSCCE had concomitant *in situ* or invasive SCC components and even the presence of small cell carcinoma (Cho et al., 2000), and therefore requires careful differentiation. Some reporters (Sarbia et al., 1997; Morice et al., 1998; Cho et al., 2000) have stated that the immunoreactivities for cytokeratin subtypes, Bcl-2, beta-catenin, S-100, and neuroendocrine markers, are different among these tumors and might assist in the distinction. However, none of these markers are specific for BSCCE.

Table 4 summarizes the previously published studies with more than five cases of BSCCE, which described surgery as the principal treatment. The prognosis of BSCCE was poor and the 5-year OS varied from 12%-42%. The survival difference between BSCCE and typical esophageal SCC remains controversial. Sarbia et al (1997) reported that there was no significant difference in the prognosis between patients with BSCCE and that of typical SCC. But some other researchers (Chen et al., 2012; Imamhasan et al., 2012) demonstrated that the MST and 5-year OS of patients with BSCCE, which are close to our results, were significantly worse than those with well differentiated SCC, and similar to those of poorly and moderately differentiated SCC. Soriano et al. (2008) recommended that basaloid squamous cell carcinoma be considered as a poor histo-pathological entity and careful attention should be paid to its management. Actually, we currently devise our therapeutic plans based on the concept that BSCCE is, in itself, a criterion of an unfavorable prognosis. And adapted treatment strategies are recommended according to the therapy experience of typical esophageal SCC with one or two unfavorable prognostic factors.

Because of the rarity of BSCCE and the absence of clinical studies on the therapeutic strategy specific to BSCCE, no standard therapy for this disease has been established. In this study, surgical resection was the most important method. After radical resection, 33 patients survived more than 48 months. In multivariate analysis, the TNM stage was found to be one of the independent prognostic factors. The MSTs of stage I and II were significantly higher than for stages III/IV. Therefore, based on our experience, surgical therapy should be

recommended in patients with resectable diseases because it could help to make a definitive diagnosis and provide a chance for cure. Radical resection in early-stage patients could achieve acceptable results. Occasionally, surgical intervention in BSCCE patients with metachronous solitary lung metastasis could also achieve good results (Takemura et al., 2012; Yoshino et al., 2012).

In the present study, left thoracotomy was the principal operation type and extended lymphadenectomy was performed only in a small number of patients. Cho et al. (2000) and Lam et al. (2001) reported that up to 66.7%-76.7% of the BSCCE had regional lymph node metastases. This rate was found to be 41.5% in this study. Among the initial failure sites in 71 patients, locoregional lymph node recurrence occurred in 32 cases. Therefore, considering the high malignancy potential of BSCCE, special attention should be paid on the lymph node dissection. Matsubara et al. (1998) and Altorki et al. (1997) reported a 25%-35% incidence of cervical nodal metastasis in esophageal cancer regardless of tumor location or T stage. Stilidi and Lerut (Stilidi et al., 2003; Lerut et al., 2004) demonstrated that an extended two-field or three-field lymphadenectomy could provide a higher rate of radical resection and improve the survival of esophageal SCC. Furthermore, based on the Worldwide Esophageal Cancer Collaboration data (Rizk et al., 2010), it was found that more extensive lymphadenectomy was associated with an improved survival in patients with esophageal cancer. Therefore, radical esophagectomy with extended lymph node dissection should be recommended to improve the prognosis of BSCCE.

Our results show BSCCE is a fatal disease with a high rate of local recurrence and distant metastasis. And distant metastasis is the most frequent failure pattern, with a median recurrence time of 10 months. Chen et al. (2012) suggested that it should be regarded as equivalent to moderately or poorly differentiated SCC. Therefore, adjuvant radiotherapy and chemotherapy should be considered in these patients. Previous studies of typical esophageal SCC (Fok et al., 1993; Schreiber et al., 2010; Berger et al., 2011) have approved that adjuvant radiochemotherapy could decrease loco-regional recurrence and improve the long-term survival. Although such improvements were not observed in our study, the frequency of locoregional recurrence in patients without radiotherapy was significantly higher than for patients who received radiotherapy, showing that postoperative radiotherapy could reduce the locoregional recurrence rate. However, considering that adjunctive therapy was administered in selected and relatively advanced cases in our study, it is difficult to draw a firm conclusion. Furthermore, because of the pathological and molecular differences between BSCCE and typical esophageal SCC, the effectiveness of traditional radiochemotherapy recommended for typical esophageal SCC requires further validation for BSCCE.

In summary, our study focused exclusively on the clinical characteristics and treatment outcomes of BSCCE. The data from this large series demonstrated that BSCCE was an aggressive disease with rapid progression and propensity for distant metastases. It is difficult to

make a definitive diagnosis via preoperative biopsy. Multidisciplinary therapy including radical esophagectomy with extended lymphadenectomy should be recommended to achieve better results, while the effectiveness of radiochemotherapy requires further validation for BSCCE. The distinctive pathological characteristics and propensity for distant metastases in BSCCE illustrate the need for developing new multidisciplinary therapeutic strategies to improve the prognosis.

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