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Clinicopathologic Characteristics and Clinical Outcomes of Esophageal Basaloid Squamous Carcinoma: Experience at a Single Institution

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This retrospective study investigated the clinicopathologic characteristics and clinical outcomes of esophageal basaloid squamous carcinoma (BSC). Among 190 patients with esophageal carcinoma treated surgically between 1998 and 2011, we identified 9 (4.7%) with BSC. All of the patients were male, with a median age of 65 years. The frequencies of venous invasion, lymphatic invasion, and lymph node metastasis were 56%, 89%, and 67%, respectively. A total of 2 patients were pathologic stage 1, 5 were stage 2, and 2 were stage 3. Tumor recurrence was observed in 56% of the patients. The 5-year survival rate for patients with esophageal BSC was 40%, which was compatible with the figure of 53.8% for control patients (n = 18) with typical squamous cell carcinoma matched for sex, age, tumor location, and pathologic stage ($P = 0.45$). Although esophageal BSC shows aggressive lymph-vascular invasion and has a high likelihood of recurrence, its prognosis seems identical to that of typical squamous cell carcinoma.

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Basaloid squamous carcinoma (BSC) is a rare but distinct variant of squamous cell carcinoma (SCC) that arises in a variety of anatomic sites, including the upper aerodigestive tract, thymus, uterine cervix, and anus.[1,2] The term "BSC" was first proposed by Wain *et al*[1] in 1986, but the first case of esophageal "basal cell carcinoma," a synonym of BSC, had already been reported by Yamamoto *et al*[3] in 1978. Although more than 3 decades have passed since the first description by Yamamoto *et al*,[3] the clinicopathologic features and clinical outcome of esophageal BSC have not been fully investigated because of the rarity of the disease. Here we analyzed the clinicopathologic features and prognosis of patients with esophageal BSC treated surgically at a single institution.

Materials and Methods

This study was approved by the local ethics committee of Saitama Medical Center, Saitama Medical University (Saitama, Japan).

Between April 1998 and December 2011, a total of 190 patients underwent surgical resection of esophageal carcinoma at the Department of Surgery, Saitama Medical Center, Saitama Medical University. Histologically, 9 of these patients (4.7%) had been diagnosed as having BSC. We retrospectively reviewed the 9 patients' age and sex; tumor location and macroscopic appearance; clinical outcomes; and histopathologic features of the primary and metastatic lesions. One experienced pathologist (K.N.) who was blinded to the clinical information conducted pathologic examinations on the basis of hematoxylin and eosin staining. Staging of esophageal cancer was done according to the seventh edition of the Tumor-Node-Metastasis (TNM) staging system of the International Union for Cancer.[4] Histologically, BSC was defined in accordance with the original description by Wain *et al*[1] as an invasive carcinoma that was composed of closely packed cells with hyperchromatic nuclei and scant cytoplasm, and had a solid growth pattern, small cystic spaces, and foci of necrosis. BSC is known to be intimately associated with dysplastic squamous epithelium, *in situ* SCC, invasive SCC, or islands of SCC among the basaloid cells. The proportion of BSC components (*i.e.*, >50%)[5,6] was not considered in relation to the histologic diagnosis because no such definition has yet been established. The depth of tumor invasion and macroscopic appearance were assessed in accordance with the 10th edition of the Japanese Classification of Esophageal Cancer.[7]

We also investigated the outcome of these 9 patients in comparison with 18 patients who had been treated surgically for typical SCC during the same period. The control patients were selected randomly by matching them to the BSC patients for sex, age (±10 years), tumor location, and pathologic stage.

Data are expressed as median and range. Survival curves were calculated by the Kaplan-Meier method, and the difference between them was evaluated using the log-rank test. Differences were considered to be significant at $P < 0.05$.

Results

Table 1 shows the clinicopathologic characteristics of the 9 patients with esophageal BSC, all of whom successfully underwent esophagectomy via a right thoracotomy without neoadjuvant treatment. All of the patients were men, with a median age of 64 years (range, 49–74 years). Two patients (22%) had a history of gastric cancer. The tumor was located in the lower thoracic esophagus in 4 patients, the middle thoracic esophagus in 3 patients, and both the middle and lower thoracic esophagus in 1 patient. Macroscopically, 7 of the tumors were the superficial type (type 0) and 2 were the ulcerative and localized type (type 2). Preoperative biopsy revealed SCC in 7 patients, SCC combined with BSC in 1 patient, and BSC in 1 patient. Histologic examination of the resected specimens showed that all of the tumors included a BSC component and an SCC component, the former being predominant in 7 patients (77%). Venous invasion and lymphatic invasion were detected in 8 patients (89%) and 5 patients (56%), respectively. Among the 5 patients with lymphatic invasion, the BSC component was detected exclusively in 4. Among the 8 patients with venous invasion, the BSC component and the SCC component were detected exclusively in 5 and 2 patients, respectively, and coexistence of BSC and SCC components was detected in the remaining 1 patient. Lymph node metastasis was found in 6 patients (67%). Among these 6 patients, the BSC and SCC components were detected exclusively in 3

Table 1 Clinicopathologic features of 9 patients with esophageal basaloid carcinoma

No.	Age, y/ sex	Location	Macroscopic appearance/ biopsy histology	Pathologic diagnosis	Depth of invasion	pN (tumor type)	ly (tumor type)	v (tumor type)	Stage
1	49/M	Lt	0-I+IIb/SCC	BSC>SCC	T1b	–	–	–	1
2	72/M	Mt	0-IIa/SCC	SCC>BSC	T1b	–	–	+(SCC)	1
3	64/M	Lt	0-IIc/SCC+BSC	BSC>SCC	T2	–	–	+(BSC)	2a
4	57/M	Mt	0-I+IIb/SCC	BSC>SCC	T1b	+(SCC)	+(BSC)	+(BSC)	2b
5	66/M	Lt	0-Is/SCC	BSC>SCC	T1b	+(BSC)	+(BSC)	+(BSC + SCC)	2b
6	65/M	Mt/Lt	0-I+IIb/SCC	SCC>BSC	T1b	+(BSC)	+(BSC)	+(BSC)	2b
7	60/M	Mt	2/SCC	BSC>SCC	T2	+(BSC)	+(BSC)	+(BSC)	2b
8	74/M	Lt	0-IIa/BSC	BSC>SCC	T1b	+(SCC)	–	+(SCC)	3a
9	62/M	Mt	2/SCC	BSC>SCC	T3	+(BSC>SCC)	+(SCC)	+(BSC)	3b

Lt, Lower thoracic esophagus; ly, lymphatic invasion; Mt, Middle thoracic esophagus; pN, pathological N stage; v, venous invasion.

patients and 2 patients, respectively, and coexistence of both components with BSC component predominance was detected in 1 patient.

Postoperatively, 2 patients received adjuvant chemotherapy consisting of cisplatin and 5-fluorouracil, and another 2 patients received 60 Gy of irradiation to the upper mediastinum because of their clinical situation assessed during surgery, or following our standard treatment protocol (2 courses of postoperative chemotherapy consisting of cisplatin and 5-fluorouracil (5FU) for patients with pathologically confirmed lymph node metastasis). A total of 5 of the 9 patients (56%) experienced tumor recurrence (stage 1, 0/2; stage 2, 4/5; and stage 3, 1/2) with a median follow-up period of 16 months (range, 2–75 months). The type of recurrence was both hematogenous and lymphatic in 3 patients and lymphatic in 2 patients. The median period between surgery and recurrence in the 5 patients who developed recurrence was 8 months (range, 6.1–44.8 months). All of the patients with recurrence received chemotherapy (5-fluorouracil chemotherapy in 4 patients, docetaxel in 1 patient), and 1 patient with recurrence in the cervical lymph nodes also received 60 Gy of irradiation, resulting in a complete response and relapse-free survival for 56 months. The 5-year survival rate was 40.0% for the patients with BSC and 53.8% for the patients with SCC. There was no significant difference in survival between the 2 patient groups ($P = 0.45$) (Fig. 1).

Discussion

We have shown that esophageal BSC is associated with a high frequency of lymph-vascular invasion and a high likelihood of recurrence after curative esophagectomy. In addition, despite its aggressive nature, the prognosis of esophageal BSC seems very similar to that of SCC. Although these results are considered important, they should be confirmed in a large series.

In view of the rarity and uncertain definition of esophageal BSC, it has been difficult to fully grasp its clinicopathologic characteristics and clinical outcome. Some important reports published between 1996 and 2009 indicated that the frequency of esophageal BSC among all esophageal carcinomas ranged from 0.4% to 11.3%.[8–14] This wide range may have been partly attributable to subject selection bias (*i.e.*, esophagectomy specimens or endoscopically resected specimens). In addition, the definition of BSC may strongly influence the frequency of its diagnosis. Because esophageal BSC often coexists with SCC, it remains undetermined how to consider the proportion of the BSC component when making a histologic diagnosis. In most previous studies, the definition of BSC was made according to the original description by Wain *et al*, whereas in others[1] it was assigned if the component of BSC cells exceeded 50% of all malignant cells. Takubo *et al*[15]

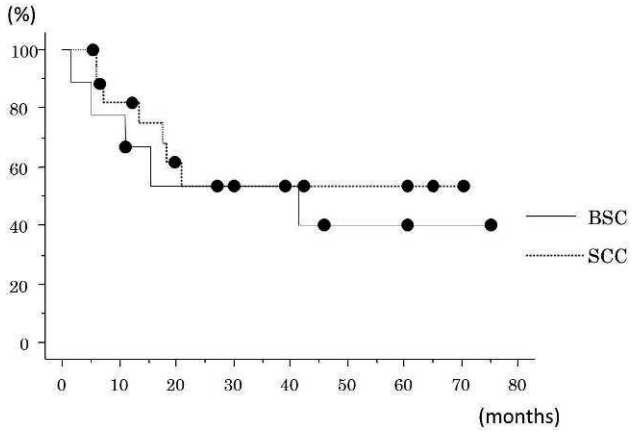

Fig. 1 Five-year survival rate of patients with BSC was 40.0%, whereas that of patients with SCC was 53.8%. There was no significant difference in survival between the groups ($P = 0.5$).

studied 178 consecutive esophageal carcinomas and found 17 (9.3%) with BSC components. Among these 17 cases, 4 (2.3%) were BSC predominant. The frequency (4.7%) in our series was within the range of previous reports, but some form of worldwide definition of esophageal BSC based on the proportion of the BSC component is warranted to minimize the degree of selection bias of this relatively rare malignant tumor.

Only a few reports[5,11] have described lymphvascular invasion of esophageal BSCs in detail. From an investigation of 14 esophageal BSCs, Saito *et al*[5] reported that the rates of lymphatic invasion, venous invasion, and lymph node metastasis were 71%, 64%, and 57%, respectively. In our series, the corresponding rates were 56%, 89%, and 67%, respectively, which are compatible with the data of Saito *et al*.[5] Notably, among patients with lymphovascular invasion, the BSC component was observed exclusively in 80% of patients who were positive for lymphatic invasion, and in 88% of those positive for venous invasion. To our knowledge, similar findings have not been reported previously, and this may warrant further investigation. The reason for the high frequency of lymphovascular invasion associated with esophageal BSC still remains unclear. In relation to the biologic aggressiveness of BSCs, Ki-67, p53, cyclin D1, E-cadherin, EGFR, and bcl-2—all of which are known to correlate with cell proliferation activity, apoptosis, the cell cycle, and cellular invasion—have been investigated previously.[5,9,11,12,16] Sarbia *et al*[9,16] reported that BSCs had higher proliferative activity (in terms of the MIB-1 labeling index) and stronger expression of the apoptosis regulatory protein bcl-2 than typical SCCs. These findings may partly explain the aggressive biologic behavior of esophageal BSC, and suggest that further investigations would be informative.

There are currently insufficient data on the prognosis of patients with esophageal BSC, despite the fact that many case reports[17,18] have indicated that it has a poor prognosis; this situation might be partly attributable to publication bias. In a review of the Japanese literature, Yoshioka *et al*[19] collected 60 cases of esophageal BSC and reported that the survival rates of patients with early-stage BSC (stage 2 or earlier) were similar to those of patients with typical SCCs, based on data in the Comprehensive Registry of Esophageal Cancer in Japan. They also reported that there were no 2-year survivors among patients with stage 3/4 BSC. Sarbia *et al*[9] analyzed data for 150 surgically treated patients with esophageal carcinoma and identified 17 patients with BCS. On the basis of multivariate Cox proportional regression analysis, they concluded that BSC was not an entity that independently affected prognosis, as compared with SCC. Here we performed a case-match study comparing patients with BSC and those with SCC using a 1:2 sample size ratio. This is the first reported study to have investigated the prognosis of esophageal BSC using this approach, which has often been used in many previous studies when the number of participants was limited.

Saito *et al*[5] reported that 3 patients with esophageal BSC who received chemotherapy or chemoradiotherapy preoperatively all responded to the treatment. In addition, there have been limited case reports of recurrent BSCs that were treated successfully by chemotherapy or chemoradiotherapy.[20,21] To our knowledge, no reported studies have investigated the utility of chemotherapy or chemoradiation chemotherapy for patients with esophageal BSC. To establish the optimal chemotherapy and/or radiotherapy regimen for this relatively rare tumor, further collection of cases will be necessary.

In conclusion, despite including a very limited number of participants, this retrospective study has revealed that BSC shows some distinct clinicopathologic characteristics and a clinical outcome that is not necessarily poor. We believe that our data will help to clarify the oncologic characteristics of esophageal BSC and provide a useful basis for establishment of an effective treatment strategy.

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