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A comparative analysis of clinicopathological factors between esophageal small cell and basaloid squamous cell carcinoma

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Abstract

Esophageal small cell carcinoma (E-SmCC) and basaloid squamous cell carcinomas (BSCCs) are both highly aggressive malignancies, but their detailed differences in clinical behaviors have remained virtually unknown. In addition, treatment strategies of the patients with E-SmCC have not been established. 29 cases of E-SmCC and 39 with BSCC were examined in this study to clarify the clinical features and outcome of the patients with E-SmCC and to compare the findings with those of BSCC. E-SmCCs presented a more advanced status than BSCC (TNM Stage: $P = .002$). Esophagectomy was performed in 15 small cell carcinoma patients and 14 were treated with non-surgical/systemic therapy. The clinical outcome of the small cell carcinoma cases was significantly worse than those with BSCC ($P = .001$), but results of a stage-stratified analysis revealed that the Stage I small cell carcinoma patients presented favorable prognosis (3-year survival rate 100%, n = 4). In contrast, among those with Stage II–IV, clinical outcome tended to be better in the systemic therapy group (3-year survival rate 49%, n = 13) than the surgically treated group (3-year survival rate 0%, n = 12). E-SmCC was a more aggressive neoplasm than BSCC. However, early detection could possibly improve the clinical outcome of patients with E-SmCC. Systemic therapy could also benefit the patients with advanced disease (Stage II–IV).

Abbreviations: BSCC = basaloid squamous cell carcinoma, CR = complete response, CT = computed tomography, DSS = disease specific survival, E-SmCC = esophageal small cell carcinoma, MST = median survival time, SCLC = small cell lung carcinoma, SqCC = squamous cell carcinoma.

Keywords: basaloid squamous cell carcinoma, esophageal small cell carcinoma, prognosis, treatment

1. Introduction

Small cell carcinoma is a highly aggressive neoplasm that predominantly occurs in the lung. Esophageal small cell carcinoma (E-SmCC) is rare, accounting for 0.05% to 3.1% of all esophageal malignancies[1,2] and approximately 2% of extrapulmonary small cell carcinomas.[3] In addition, the patients with E-SmCC manifest earlier dissemination and poorer prognosis than those with squamous cell carcinoma (SqCC).[4–6] E-SmCC is a high-grade neuroendocrine carcinoma, accounting for almost all neuroendocrine neoplasms arising in the esophagus.[7] Although the standard treatment strategy of the E-SmCC patients has not yet been established, advanced E-SmCC patients have been mostly treated with the chemotherapy along the regimens for small cell lung carcinoma (SCLC) patients.[8] In addition, some investigators have reported that surgery would also improve the prognosis of some E-SmCC patients.[9–11] Consequently, stage-specific treatment options for the E-SmCC patients have yet to be implemented in clinical practice.

Basaloid squamous cell carcinoma (BSCC) is a rare histological subtype of SqCC with a reported incidence of 0.07% to 11.8% of all esophageal carcinomas in Western countries,[12,13] and 1.2% of surgically operated patients in Japan.[14] BSCC is also developed in other organs, such as in lung, head and neck

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organs and reported to be one of the aggressive tumor types, especially in comparison with non-basaloid SqCC.[15,16] The clinical outcome of esophageal BSCC patients is significantly worse than SqCC patients[12] and a clinical trial specifically targeted BSCC patients is ongoing.[17]

To the best of our knowledge, comparative analyses in terms of their prognoses and clinical characteristics between the 2 aggressive esophageal malignancies have not been reported so far. In this study, we first compared the clinicopathological features and clinical outcome of the E-SmCC and esophageal BSCC. Second, we further discussed the potentially optimal treatment strategies for the patients based on the data in this study and in previous studies.

2. Materials and methods

2.1. Cases

We assembled 29 E-SmCCs and 39 BSCCs and corresponding clinical information of the patients. Formalin-fixed and paraffin embedded tissue specimens of the corresponding tumors were retrieved from the surgical pathology files. The clinical information about E-SmCCs patients was obtained by reviewing the charts in 6 institutions in Japan (Tohoku University Hospital, Saitama Cancer Center, Nihonkai General Hospital, Iwate Prefectural Central Hospital, Iwate Prefectural Isawa Hospital, and Kesennuma City Hospital). Macroscopic classification was defined according to the 11th Japanese Classification of Esophageal Cancer.[18] Clinical data of the BSCC patients were also retrieved from the chart review of Tohoku University Hospital, Miyagi, Japan. Histopathological diagnosis was independently reviewed by 3 pathologists (AK, FF, and HS) according to the histological criteria of the WHO 2010 classification.[19] The absence or presence of the co-existing SqCC component and lymphovascular invasion were also carefully determined in this review. In tumors with mixed histology, E-SmCC was defined by its features detected in >70% of the total area.[4,19] The tumors without any other concomitant histological type were also defined as pure type, while those with other histological type in <30% of all tumor areas as mixed type. The TNM staging was determined according to the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system for esophageal carcinoma.[20] The pathological TNM staging was used when relevant surgical pathology materials were available for the assessment. In other cases, the TNM staging was clinically determined. Fifteen of the E-SmCCs of this study were also included in our previous study.[4] The study protocol was approved by the ethics committee of each participating institution and informed consents were obtained from all patients.

2.2. Patients monitoring

The patients were monitored every 4 months for 2 years and every 6 months thereafter with computed tomography (CT) and gastroscopy. ^{18}F-2-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was also performed when the progression of the disease was clinically suspected. Disease-specific survival (DSS) was defined as the time from initial pathological diagnosis of disease-related death or last observation. Follow-up duration of the E-SmCC and the BSCC patients were 3 to 96 months (median 14) and 3 to 150 months (median 39), respectively.

2.3. Statistical analyses

JMP Pro version 13.0.0 software (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. Continuous data were analyzed using Student t test or the Mann–Whitney U test. Relationships and correlations between 2 variables were identified using the Pearson chi-square test, Fisher exact test, or Mann–Whitney U test as appropriate. DSS curves were constructed according to the Kaplan–Meier method and compared using the log-rank test. A P value of $<.05$ was considered statistically significant.

3. Results

3.1. Clinicopathological features of the E-SmCCs compared with the BSCCs

The clinicopathological characteristics of the patients with E-SmCC and BSCC were summarized in Table 1. The majority of E-SmCC macroscopically demonstrated ulcerative or diffuse type (70% vs 20%, $P=.002$). The TNM stage of the E-SmCCs was also more advanced than the BSCCs (T: $P<.001$, N: $P=.049$, Stage: $P=.002$). The mixed SqCC component was detected in 27% of the E-SmCCs and 36% of the BSCCs examined in this study.

3.2. Treatment of the E-SmCC patients with comparison to that of BSCC

Of the 29 E-SmCCs, esophagectomy was performed in 15 (52%), of which post-operative chemotherapy or chemoradiotherapy was administered in 5 cases. The other 14 cases (48%) did not undergo surgery and were treated with non-surgical/systemic therapy (Table 1) - 10 with chemoradiotherapy, 2 with chemotherapy, and 2 with radiotherapy. The chemotherapy regimens were as follows; carboplatin /etoposide 39%, cisplatin /etoposide 28%, cisplatin/5-fluorouracil 16% cisplatin/irinotecan 11%, irinotecan 6%. Irradiation dose ranged from 30 to 60 Gy.

All BSCC patients were surgically operated. Three received preoperative chemotherapy (cisplatin/5-fluorouracil, 2 courses). One was operated due to the recurrent disease after radiation therapy. Postoperative chemotherapy or chemoradiotherapy was performed in 9 cases and none died perioperatively or within a month after the surgery.

3.3. Clinical outcome of the E-SmCCs compared with the BSCCs

The 1- and 3-year DSS of the E-SmCC patients were 68 and 26%, respectively, with a median survival time (MST) 16 months. The 1- and 3-year DSS of the BSCC patients were 90 and 77%, respectively (MST, not reached). DSS of the E-SmCCs was significantly worse than that of the BSCCs ($P=.001$, Fig. 1a and Table 2). When stage adjusted analysis was performed, 3-year DSS of the Stage I E-SmCCs was 100%, and none of the Stage I E-SmCC patients died of the original cancer, which was equivalent to that of Stage I BSCCs (100 and 92%, respectively) (Fig. 1b). In contrast to the early disease stage, the clinical outcome of the E-SmCCs in Stage II–IV was significantly more adverse than that of BSCCs ($P=.003$, Fig. 1c). In particular, the survival rates after 3 years were notably different between these 2 histological subtypes of esophageal malignancy (14% in E-SmCC, 69% in BSCC). Among the E-SmCC patients, 19 (66%) died of the disease and

Table 1

Clinicopathological features of the 29 esophageal small cell carcinoma patients and 39 basaloid squamous cell carcinoma patients.

	Esophageal small cell carcinoma, N = 29 (%)	Basaloid squamous cell carcinoma, N = 39 (%)	*P* value
Age			
<60	7 (24)	8 (21)	.721
≥60	22 (76)	31 (79)	
Gender			
male	22 (76)	36 (92)	.058
female	7 (24)	3 (8)	
Macroscopic classification			
Superficial type	6 (20)	21 (54)	.002
Protruding type	3 (10)	10 (26)	
Ulcerative and localized type	10 (35)	5 (12)	
Ulcerative and infiltrative type	8 (28)	3 (8)	
Diffusely infiltrative type	2 (7)	0 (0)	
Location			
upper	4 (14)	3 (8)	.704
middle	14 (48)	21 (54)	
lower	11 (38)	15 (38)	
* Size			
<50mm	7 (46)	21 (54)	.636
≥50mm	8 (54)	18 (46)	
* Concomitant with SqCC			
absent (pure type)	11 (73)	25 (64)	.519
present (mixed type)	4 (27)	14 (36)	
* Lymphvascular invasion			
absent	1 (7)	9 (23)	.164
present	14 (93)	30 (77)	
p/cT			
T1/2	7 (24)	26 (67)	<.001
T3/4	22 (76)	13 (33)	
p/cN			
N0	8 (28)	20 (51)	.049
N1/2/3	21 (72)	19 (49)	
TNM Stage			
I	4 (14)	14 (36)	.002
II	5 (17)	13 (33)	
III	13 (45)	12 (31)	
IV	7 (24)	0 (0)	
Treatment			
Surgery only	10 (34.5)	26 (67)	—
Surgery + CT	3 (10)	8 (21)	
Surgery + CRT	2 (7)	1 (2)	
CT + Surgery	0 (0)	3 (8)	
RT + Surgery	0 (0)	1 (2)	
CT	2 (7)	0 (0)	
RT	2 (7)	0 (0)	
CRT	10 (34.5)	0 (0)	

CT = chemotherapy, CRT = chemoradiotherapy, RT = radiotherapy, SqCC = squamos cell carcinoma.
* Surgical resected specimens only.

1 (3%) of an unrelated cause. Two (7%) locally relapsed, and 20 (69%) developed distant metastatic disease (16 in liver, 7 in para-aortic nodes, 3 in lung, 2 in brain, 1 in bone). Among the BSCC patients, 14 (36%) died of the disease, 5 (13%) of unrelated causes. One (3%) locally relapsed, 13 (33%) developed distant metastasis (3 multiple sites, 7 in lung, 5 in liver, 3 in bone, 1 in brain).

3.4. Prognostic analysis of the patients with E-SmCC

The results of prognostic analysis of the E-SmCC patients were summarized in Table 2. The ulcerative or diffusely infiltrative microscopic features ($P = .017$), local tumor extension (T3–4, $P = .034$), nodal metastasis (N1–3, $P = .022$) were all identified as poor prognosticators. The tumors located in the mid esophagus emerged as a favorable prognostic factor ($P = .035$).

No apparent differences were detected in clinicopathological features between the surgically operated (surgery group, n = 15) and non-surgical/systemic treated groups (non-surgery group, n = 14) (Table supplement 1, http://links.lww.com/MD/C795). The 1- and 3-year DSS of the non-surgery group were 77 and 55%, respectively (MST, not reached), while those of surgery group were 60 and 9%, respectively (MST, 15 months). The clinical outcome of the E-SmCCs of the non-surgery group tended to be better than that of the surgery group ($P = .143$, Fig. 2a). A stage adjusted analysis, including those with Stage II–IV revealed that none survived in the surgery group, but a favorable prognosis was detected in the non-surgery group with 1- and 3-

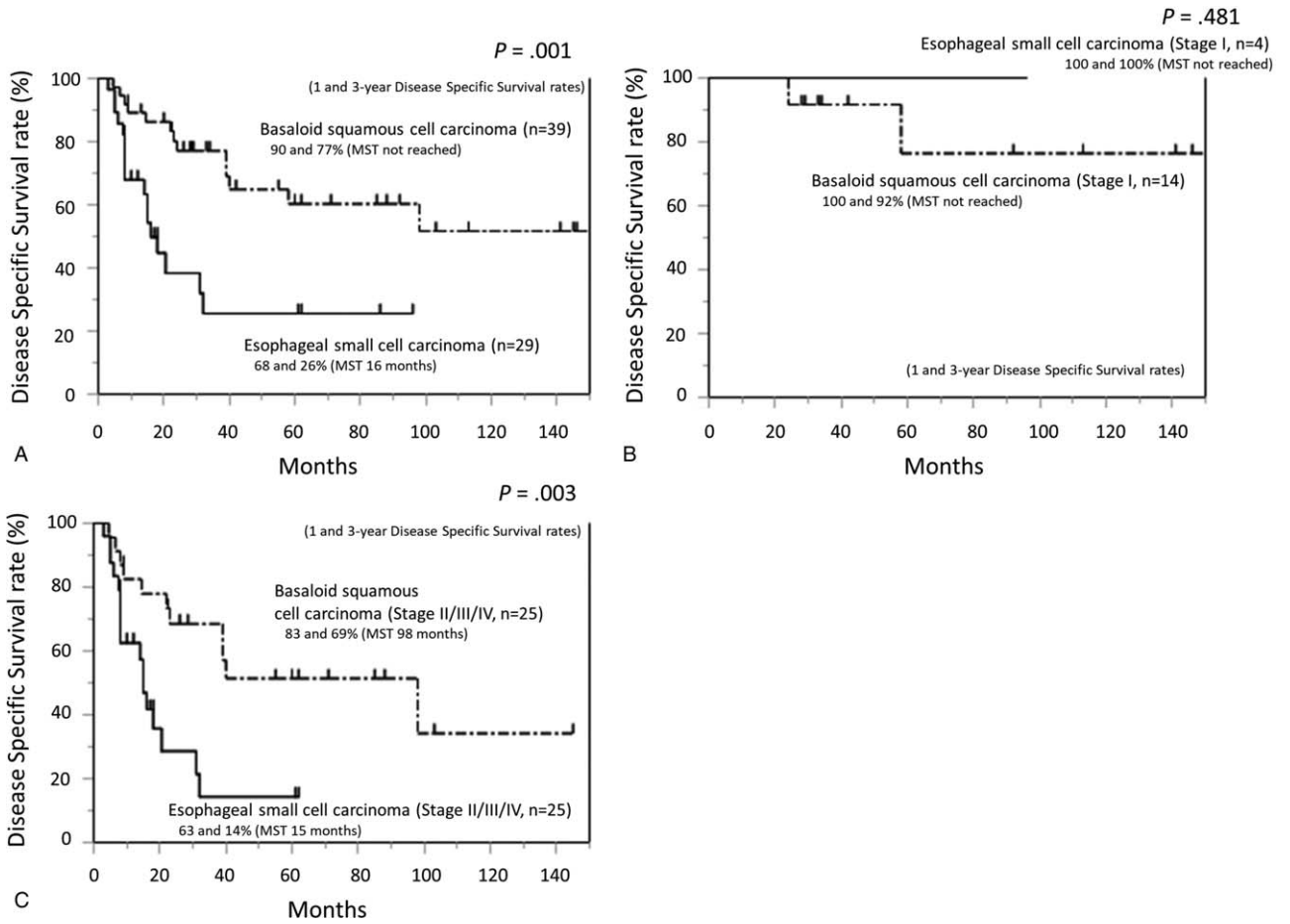

Figure 1. Kaplan–Meier curves according to DSS rate of E-SmCC patients compared with BSCC patients. (A) DSS rate of the E-SmCC patients was significantly worse than those of BSCC ($P = .001$). (B) DSS rate of the Stage I E-SmCC patients was almost equivalent to those of Stage I BSCC ($P = .481$). (C) In contrast DSS rate of the E-SmCC patients with Stage II–IV was significantly lower than that of BSCC ($P = .003$). BSCC = basaloid squamous cell carcinoma, DSS = disease specific survival, E-SmCC = esophageal small cell carcinoma.

year DSS as 73 and 49%, respectively ($P = .097$, Fig. 2b). MST of the non-surgery group was 16 months, 3 lived more than 5 years, and another 3 achieved complete response (CR) status until their last observation. Three out of the 4 Stage I cases underwent surgery; the other was treated by chemoradiotherapy. None of the Stage I E-SmCC patients presented metastasis nor recurrence.

4. Discussion

This is the first study to analyze clinicopathological features of E-SmCC in comparison with those of BSCC. So far datasets for E-SmCC that addressed on clinical characteristics, including follow up have been almost exclusively restricted in Chinese population (9–11, 21, 22) and evidence from other ethnic groups are scarce and not fully investigated.

The results of our present study first revealed that the E-SmCC and the BSCC were male-predominant and occurred in the mid to distant part of the esophagus. E-SmCCs were diagnosed as large tumors with locally advanced status and high incidence of nodal involvement at the time of clinical detection. In addition, recurrent disease of the E-SmCC was more frequent than the BSCCs and the clinical outcome of the E-SmCC patients was significantly more adverse than those with BSCC. When compared with the clinical outcome of the poorly differentiated SqCC patients that we previously studied, the prognosis of the BSCC patients in this study was slightly worse than those with the poorly differentiated SqCC (1- and 3-year survival rate: 95 and 76%, respectively).[4]

Despite the number of the cases examined in this study being relatively small, there was an interesting difference in clinical outcome between Stage I and Stage II–IV E-SmCCs. The Stage I E-SmCC patients presented a relatively high 3-year DSS rate (100%), almost equivalent to that of Stage I BSCC patients (92%). This suggested that E-SmCC was not inherently aggressive when confined to its early stage. However, 76% of the Stage II–IV E-SmCCs (19 out of 25) died of the disease with far worse clinical outcome (3-year DSS of 14%) than the Stage II–IV BSCCs (40% died of the disease and 3-year DSS 69%). Favorable prognosis of the Stage I E-SmCCs was also previously reported.[9] These findings indicate that the tumor progression could be accelerated during the early development of E-SmCC possibly extending into the muscular layer of the esophagus. Xie et al and Situ et al both reported the absence of lymph node metastasis as a favorable prognostic factor of the E-SmCCs.[10,11] However, lymph node status was not the most optimal indicator in our present study because 2 out of 4 cases with T3N0 died of the disease. Therefore, appropriate determination of Stage I, rather than nodal status alone, is considered optimal in accurately predicting the eventual prognosis of E-SmCCs.

Table 2

Univariate prognostic analysis of 29 esophageal small cell carcinoma patients.

Clinicopathological factors	Esophageal small cell carcinoma (N = 29)				*P* value
	Number of cases (%)	MST (months)	1-year DSS (%)	3-year DSS (%)	
Age					
<60	7 (24)	15	71	18	.835
≥60	22 (76)	18	67	29	
Gender					
male	22 (76)	21	73	31	.067
female	7 (24)	11	50	0	
Macroscopic classification					
Superficial or Protruding type	9 (31)	not reached	89	57	**.017**
Ulcerative or Diffusely infiltrative type	20 (69)	15	58	10	
Location					
upper	4 (14)	31	100	0	**.035**
middle	14 (48)	not reached	69	59	
lower	11 (38)	14	55	0	
* Size					
<50mm	7 (46)	18	71	36	.358
≥50mm	8 (54)	12	50	0	
* Concomitant with SqCC					
absent (pure type)	11 (73)	18	64	11	.559
present (mixed type)	4 (27)	12	50	25	
* Lymphvascular invasion					
absent	1 (7)	11	0	0	.685
present	14 (93)	15	57	9	
p/cT					
T1/2	7 (24)	62	86	64	**.034**
T3/4	22 (76)	15	62	10	
p/cN					
N0	8 (28)	not reached	86	86	**.022**
N1/2/3	21 (72)	15	62	14	
TNM Stage					
I	4 (14)	not reached	100	100	**<.001**
II	5 (17)	31	75	0	
III	13 (45)	18	85	25	
IV	7 (24)	6	14	0	

DSS = disease specific survival, MST = median survival time, SqCC = squamos cell carcinoma.
* Surgical resected specimens only.

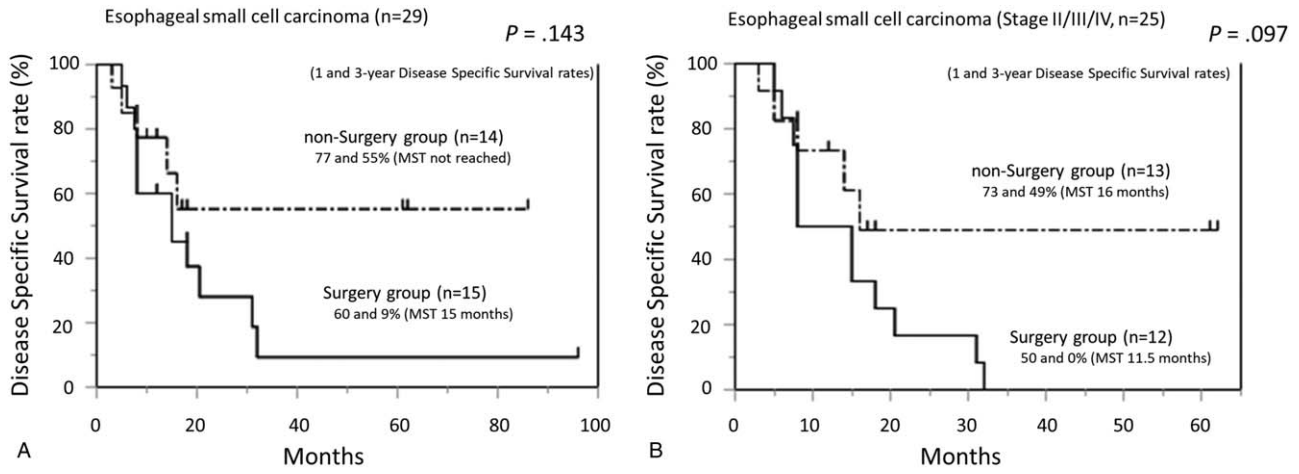

Figure 2. Kaplan–Meier curves according to DSS rate of E-SmCC patients treated by surgery (surgery group) and non-surgical/systemic treatment (non-surgery group). (A) The prognosis of the non-surgery group E-SmCC patients (14 patients, 48%) tended to be better than those of the surgery group (15 patients, 52%) (*P* = .143). (B) Among the Stage II–IV patients, no patient survived by the last observation in the surgery group, in contrast, the favorable DSS rate was observed in the non-surgery group (*P* = .097). MST of the non-surgery group was 16 months, 3 patients lived more than 5 years, and the other 3 patients have achieved a CR status until their last observation. CR = complete response, DSS = disease specific survival, E-SmCC = esophageal small cell carcinoma, MST = median survival time.

In the E-SmCC patients with Stage II or higher in the 8th TNM classification (pT3–4 and/or pN1–3), we did not detect any survival benefit of the surgery. Although the number of the cases examined in this study was limited, all the surgery-treated patients died of the disease with MST of 11.5 months. In contrast, we demonstrated the favorable prognosis of the non-surgery group patients with MST 16 months. Ninety-three % (13 out of 14) patients treated with systemic treatment were with Stage II or higher disease status. Among these patients, CR was achieved in 9 (69%), of which 3 (33%) with more than 5-year survival and other 3 (33%) kept CR status until their last observation, while disease-related events were clinically detected only in the other 3 patients (33%, a patient died of multiple liver metastasis, the others of para-aortic node recurrence). Although it is true that our present study was a retrospective study with a limited number of the patients, distinct prognostic differences detected between the non-surgery and the surgery groups indicated importance of systemic treatment for E-SmCC patients with Stage II or higher. These results also indicated that the E-SmCC with advanced disease, especially with Stage II or higher, should be carefully clinically followed, and once the recurrence or the progression of the disease are suspected, the additional therapy should be considered. However, the additional therapy effect, including radiotherapy, has still remained in dispute. A previous study of a meta-analysis including 313 E-SmCC patients favored chemotherapy combined with local treatment, eventually additional radiotherapy, as standard treatment.[23]

In contrast, surgery was considered to be a clinically reasonable option for E-SmCC patients, if an advanced disease status (Stage II or higher) could be clinically excluded. The clinical benefit of the surgery for E-SmCC patients has been previously discussed but the patient selection criteria have been indistinctly proposed, merely stated as limited-diseases or locally advanced diseases.[9–11,22] However, our present study did demonstrate that the distinction of Stage I from Stage II (or higher) was considered the border for clinical outcome prediction and disease stage should be also considered in the algorithm of E-SmCC treatment. Additional therapy for the Stage I patients may not be required, but further studies are needed for clarification. The systemic treatment incorporating surgery for Stage I E-SmCC patients did not contribute to the improvement of the patients' outcome relative to surgical treatment alone.[21]

So far, there has been no universal agreement on treatment for the E-SmCCs. In clinical practice, it is widely accepted to adopt the chemotherapy regimen established in SCLC patients. Due to the extreme rarity of E-SmCC, multi-institutional prospective clinical study is indispensable for the establishment of the treatment strategies for patients with E-SmCC. Currently, a randomized Phase III comparative study of cisplatin/etoposide and cisplatin/ irinotecan therapy for nonresectable/ recurrent neuroendocrine carcinoma of gastrointestinal and hepatobiliary pancreas is ongoing by the Japan Clinical Oncology Group (JCOG 1213).

Interestingly, in lung cancer treatment, surgical resection of SCLC is much more frequently performed in Japan than in the Western countries. In Japan, post-operative 5-year survival of the SCLC patients (53%) was almost equivalent to that of bronchopulmonary SqCC patients (59%).[8] In addition, recent widespread use of CT in Japan enables early detection of lung cancer, including SCLC, with a significant increased ratio of small tumor (<2 cm) from 23% in 1994 and to 38% in 2004. Surgery has been therefore recommended for the patients with Stage I SCLC, especially cT1N0M0 in the Japanese guideline for treatment of carcinoma of the lung,[24] and a relatively high incidence of the operable SCLCs patients was also reported by other Japanese groups.[25,26] Therefore, surgical treatment could be an option for carefully selected patients with small cell carcinoma arising in the other organs. However, survival of the patients with small cell carcinoma seems to be different among different primary sites, thus the treatment strategies should be considered separately in each organ.[3] Recently, we have reported remarkably similar clinical and biological features of E-SmCC and SCLC, which supports the hypothesis that the 2 malignancies may arise from the common embryonic origin.[4] Therefore, it is rational to expect that the chemotherapy regimen for SCLC patients could also benefit E-SmCC patient. In addition, a surgical resection of the Stage I E-SmCC patients should still be kept open for further discussion.

It is also important to note the following limitations in this study. First, the number of the E-SmCCs was limited, especially of the patients diagnosed at the early stage, which could limit the reliability of the results obtained from our assessment. The limited patient number of this study is largely due to the very low incidence, particularly in early-stage cases of this disease. Second, the retrospectively assembled data in this study may have been affected by multiple biases. Again, due to the rarity of the disease, prospective analysis is practically difficult for most individual medical faculty. A nationwide prospective survey is required to investigate a more detailed and objective characterization and to establish the standard treatment of the disease. Third, the potential interinstitutional variability in treatment and in monitoring could not be completely excluded. Platinum-based chemotherapy had been performed in 16 patients, but their regimen considerably varied (carboplatin/etoposide 39%, cisplatin/etoposide 28%, cisplatin/5-fluorouracil 16% cisplatin/irinotecan 11%, irinotecan 6%). Fourth, some clinical data were not available in our multi-institutional studies such as smoking index, or WHO performance status. These limitations are very hard to avoid in studying such a rare tumor type. Nevertheless, we believe despite all above mentioned limitations, much can be learned from our data.

In summary, among the two aggressive esophageal malignancies namely E-SmCC and BSCC, we first demonstrated that the former is associated with a more progressive clinical presentation than the latter. However, the Stage I E-SmCC can demonstrate remarkably favorable prognosis, therefore it is important to accurately differentiate Stage I from Stage II or higher in the diagnostic process. Non-surgical/systemic treatment was considered to be optimal for the E-SmCC patients with Stage II or higher. Moreover, the Stage I patients might benefit from the radical esophagectomy. Prospective and multi-institutional investigation is urgent to establish treatment strategy for E-SmCC patients.

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References

[1] Wang SY, Mao WM, Du XH, et al. The 2002 AJCC TNM classification is a better predictor of primary small cell esophageal carcinoma outcome than the VALSG staging system. Chin J Cancer 2013;32:342–52.
[2] Feng JF, Huang Y, Zhao Q, et al. Clinical significance of preoperative neutrophil lymphocyte ratio versus platelet lymphocyte ratio in patients with small cell carcinoma of the esophagus. SciWorld J 2013;2013:1–7.
[3] Haider K, Shahid RK, Finch D, et al. Extrapulmonary small cell cancer: a Canadian province's experience. Cancer 2006;107:2262–9.
[4] Ishida H, Kasajima A, Kamei T, et al. SOX2 and Rb1 in esophageal small-cell carcinoma: their possible involvement in pathogenesis. Mod Pathol 2017;30:660–71.
[5] Pantvaidya GH, Pramesh CS, Deshpande MS, et al. Small cell carcinoma of the esophagus: the Tata Memorial Hospital experience. Ann Thorac Surg 2002;74:1924–7.
[6] Zhu Y, Qiu B, Liu H, et al. Primary small cell carcinoma of the esophagus: review of 64 cases from a single institution. Dis Esophagus 2014;27:152–8.
[7] Estrozi B, Bacchi CE. Neuroendocrine tumors involving the gastro-enteropancreatic tract: a clinicopathological evaluation of 773 cases. Clinics (Sao Paulo) 2011;66:1671–5.
[8] Sawabata N, Miyaoka E, Asamura H, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol 2011;6:1229–35.
[9] Xu L, Li Y, Liu X, et al. Treatment strategies and prognostic factors of limited-stage primary small cell carcinoma of the esophagus. J Thorac Oncol 2017;12:1834–44.
[10] Xie MR, Xu SB, Sun XH, et al. Role of surgery in the management and prognosis of limited-stage small cell carcinoma of the esophagus. Dis Esophagus 2014;28:476–82.
[11] Situ D, Lin Y, Long H, et al. Surgical treatment for limited-stage primary small cell cancer of the esophagus. Ann Thorac Surg 2013;95:1057–62.
[12] Chen SB, Weng HR, Wang G, et al. Basaloid squamous cell carcinoma of the esophagus. J Cancer Res Clin Oncol 2012;138:1165–71.
[13] Bellizzi AM, Woodford RL, Moskaluk CA, et al. Basaloid squamous cell carcinoma of the esophagus: assessment for high-risk human papillomavirus and related molecular markers. Am J Surg Pathol 2009;33:1608–14.
[14] Tachimori Y, Ozawa S, Numasaki H, et al. Comprehensive registry of esophageal cancer in Japan, 2008. Esophagus 2015;12:130–57.
[15] Moro-Sibilot D, Lantuejoul S, Diab S, et al. Lung carcinomas with a basaloid pattern: a study of 90 cases focusing on their poor prognosis. Eur Respir J 2008;31:854–9.
[16] Fritsch VA, Lentsch EJ. Basaloid squamous cell carcinoma of the larynx: analysis of 145 cases with comparison to conventional squamous cell carcinoma. Head Neck 2014;36:164–70.
[17] Nakamura K, Kato K, Igaki H, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol 2013;43:752–5.
[18] The Japan Esophageal Society. The 11th Japanese Classification of Esophageal Cancer (Japanese) Tokyo: KANEHARA& CO., LTD; 2015.
[19] Bosman FT, Carneiro F, Hruban RH, et al. Tumours of the oesophagus WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: WORLD HEALTH ORGANIZATION; 2010.
[20] James DB, Mary KG, Christian W. Oesophagus and Oesophagogastric Junction TNM Classification of Malignant Tumours. 8th ed. New York: JOHN WILEY & SONS, LTD; 2017.
[21] Zou B, Li T, Zhou Q, et al. Adjuvant therapeutic modalities in primary small cell carcinoma of esophagus patients: a retrospective cohort study of multicenter clinical outcomes. Medicine 2016;95:e35071–10.
[22] Lu XJ, Luo JD, Ling Y, et al. Management of small cell carcinoma of esophagus in China. J Gastrointest Surg 2013;17:1181–7.
[23] Al Mansoor S, Ziske C, Schmidt-Wolf IG. Primary small cell carcinoma of the esophagus: patient data metaanalysis and review of the literature. Ger Med Sci 2013;11:1–9.
[24] The Japan Lung Cancer Society. Guideline for Diagnosis and Treatment of the Lung Cancer 2017 (Japanese). Tokyo: KANEHARA & CO., LTD; 2017.
[25] Kasajima A, Ishikawa Y, Iwata A, et al. Inflammation and PD-L1 expression in pulmonary neuroendocrine tumors. Endocr Relat Cancer 2018;25:339–50.
[26] Asamura H, Kameya T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 2006;24:70–6.