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Original Article

Characteristics of brain metastases from esophageal carcinoma

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Abstract

Background: Esophageal carcinoma (EC) is a major malignancy with a poor prognosis. Although esophageal cancers rarely metastasize to the brain, the number of patients diagnosed with brain metastases (BM) from EC is steadily increasing. Therefore, the risk factors for BM from EC should be known. Here we reviewed our experiences and the previous literature regarding BM from EC.

Methods: Between 2000 and 2013, we retrospectively reviewed the clinical features and neurological findings of 19 patients diagnosed with and treated for BM from EC to determine the clinical risk factors and features.

Results: In all patients, the lesions were partially or completed located in the thoracic esophagus, and the average size of the EC lesion at diagnosis was 5.8 ± 2.9 cm, which was smaller than the previously reported size of EC lesions accompanied by BM. Patients without lung metastases were more common than those with lung metastases. The lesions in the 13 patients included squamous cell carcinoma (SqCC) in 9 (69.2%) and small cell carcinoma (SmCC) in 3 (23.0%). Six patients were not examined. Although there was no trend toward a higher incidence of BM in patients with adenocarcinoma and SqCC, this trend was observed in patients with SmCC. Excluding a single patient with SmCC, all patients had beyond stage III disease at EC diagnosis.

Conclusions: Our study suggests that BM can occur in patients with EC lesions smaller than those previously reported; moreover, SmCC may be a risk factor for BM from EC.

Key Words: Adenocarcinoma, brain metastases, esophageal carcinoma, small cell carcinoma, squamous cell carcinoma

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INTRODUCTION

Esophageal carcinoma (EC) is a major malignancy with a poor prognosis and a 5-year survival rate of 23%.[22] According to the comprehensive registry of EC in Japan, EC often develops in the 7th decade in males, with a male-to-female ratio of approximately 7:1.[11] EC frequently metastasizes to the lymph nodes, liver, lung, and bone, but

rarely to the brain; the incidence of brain metastases (BM) from EC is approximately 0.6-1.5%.[11,16,22,23] Therefore, it is a rare occurrence, with as few as 150 cases reported worldwide [Table 1].[1-7,9,12-14,16-22] However, the number of patients diagnosed with BM from EC is increasing, probably because of advances in diagnostic imaging and treatment of the primary EC lesion.[18,21] Therefore, there has been a steady increase in the number of clinical reports of BM from EC, with well-described treatments and outcomes in particular.[11-13,16,18,22,23] Till date, however, there has been insufficient discussion of the clinical risk factors and features of BM from EC. Therefore, we reviewed our clinical experiences together with the existing literature to evaluate recent trends in the occurrence of BM in patients with EC.

MATERIALS AND METHODS

Between 2000 and 2013, 19 patients with BM from EC were diagnosed and treated at Kumamoto University Hospital and Saiseikai Kumamoto Hospital in Kumamoto City in southern Japan. All patients with BM were diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). To determine the clinical risk factors and features of BM in patients with EC, we retrospectively reviewed their clinical features and neurological findings. Specifically, the following information was collected: Patient age and sex, time from EC diagnosis to BM occurrence, EC size, EC stage at diagnosis, treatment, EC location, BM location and imaging characteristics, neurological symptoms, histology, concurrent metastatic sites, and survival data. Time from EC diagnosis to BM occurrence was actuarially calculated using the Kaplan-Meier method. A probability level of 0.05 was set for statistical significance. Statistical analysis was performed using StatMate III, Version 3.19 (ATMS, Tokyo, Japan).

Table 1: Published reports of brain metastases (BM) from esophageal carcinoma (EC)[1, 3-19]

Syudy	Year	Patients with BM
Appelqvist	1975	1
Bosch *et al.*	1979	1
Mandard *et al.*	1981	5
Anderson and Lad	1982	1
Sons and Borchard	1984	3
Chan *et al.*	1986	2
Kaneko *et al.*	1991	4
Gabrielsen *et al.*	1995	12
Quint *et al.*	1995	3
Takeshima *et al.*	2001	8
Ogawa *et al.*	2001	36
Weinberg *et al.*	2003	27
Almasi *et al.*	2004	1
Yoshida *et al.*	2007	17
Agrawal *et al.*	2009	1
Kanemoto *et al.*	2011	12
Smith and Miller	2011	7
Song *et al.*	2014	26
Present study	2014	19

BM from EC is a rare occurrence, with approximately 150 cases reported worldwide
EC: Esophageal carcinoma, BM; Brain metastases

RESULTS

Table 2 provides the clinical summary of all 19 patients. Table 3 summarizes the EC-related clinical data and characteristics. The average age at EC diagnosis was 65.5 ± 6.9 years (range 52-78 years), and the male-to-female ratio was 18:1.

The average EC size at diagnosis was 5.8 ± 2.9 cm in the 15 patients whose size data were collected. EC location ranged from cervical esophagus (Ce) to abdominal esophagus (Ae). The data on EC location were collected in 17 patients. EC that was partly or completely located in the middle thoracic esophagus (Mt) was the most common (12/17 patients), and the lesions were partly or completely located in the thoracic esophagus (Te) in all patients. In the 15 patients whose staging data were collected, EC at diagnosis was stage IV in 10 patients, stage III in 4 patients, and stage II in 1 patient; therefore, excluding 1 patient with small cell carcinoma (SmCC), all patients had beyond stage III disease.

The clinical data and characteristics of BM in the 19 patients are summarized in Table 4. The median time from EC diagnosis to BM occurrence was 7.0 months (range - 4 to 36 months. Time from EC diagnosis to BM occurrence was statistically significant, regardless of whether or not surgery was performed for EC [HR, 0.31 (0.038, 0.60); $P = 0.007$]. At diagnosis, 8 patients were asymptomatic and 11 had various neurological symptoms, including hemiplegia, seizure, visual disturbance, memory disturbance, and aphasia. Multiple BM lesions were found in eight patients. Among these, one patient had multiple metastases throughout the brain and the remaining seven had a total of 28 lesions: 9 each in the frontal and parietal lobes, 4 in the occipital lobe, 3 in the cranium, 2 each in the cerebellum and temporal lobe, and 1 in the corpus callosum. With regard to the features of BM on CT and/or MRI, 6 of 19 (31.5%) patients exhibited a cystic mass with an enhanced rim, 11 of 19 (57.8%) patients exhibited a solid mass with necrosis, and 2 of 19 (10.5%) patients exhibited a mass with bone destruction. Surgical resection of BM and/or EC was performed in 13 patients. Histological examination for these 13 patients revealed squamous cell carcinoma (SqCC) in 9 (69.2%), SmCC in 3 (23.0%), and basal cell carcinoma in 1 (7.6%). Six patients were without surgical resection and histological examination. Of note, the proportion of patients without lung metastasis was higher (57.8%) than that of patients

Table 2: Summary of the 19 patients with brain metastases from esophageal carcinoma (EC)

Age/ sex	Histology	Location of EC	Size of EC (cm)	Time from EC	Neurological symptoms	Lung metastases	Outcome (months)
67/M	SqCC	Te (Ut, Lt)	4	1Y, 11M	No symptoms	Yes	Died (8)
68/M	SmCC	Te (Mt)	2	2Y	No symptoms	Yes	-
67/M	SqCC	Te (Ut-Mt)	6	2Y	Convulsion	Yes	Died (18)
67/M	SqCC	Te (Lt)	6	3Y	Hemiplegia	No	Died (12)
68/F	SqCC	Te (Mt-Lt)	3	4M before	Memory disturbance	No	Died (12)
73/M	SqCC	Ce-Te (Mt)	7	6M	Hemiplegia	No	Died (2)
72/M	SqCC	Te (Mt-Lt)	6	1Y, 10M	No symptoms	No	Died (2)
59/M	-	Te (Mt)-Ae	5	1M	No symptoms	Yes	-
58/M	SqCC	Ce-Te (Ut)	5	3M	No symptoms	No	Died (2)
60/M	-	Te (Mt)-Ae	13	Same time	Hemiplegia, aphasia	No	Died (3)
60/M	-	Te (Mt), Lt	5	Same time	Hemianopsia	Yes	Died (4)
52/M	BasalCC	Te (Mt)	-	1Y	Disturbance of consciousness, hemianopsia	Yes	Died (34)
66/M	SmCC	-	-	4Y	Headache	Yes	Died (11)
69/M	SqCC	Te (Ut-Mt)	-	2M	Headache	No	-
52/M	-	-	-	3Y	No symptoms	No	-
70/M	-	Te (Mt)	3	Same time	No symptoms	No	Died (1)
71/M	SqCC	Te (Mt-Lt)	10	2Y	Headache, hemiplegia	No	Died (17)
69/M	-	Te (Lt)-Ae	9	7M	No symptoms	Yes	Alive (3)
78/M	SmCC	Te (Lt)	4	6M	Convulsion	No	Alive (1)

M: Male, F: Female, SqCC: Squamous cell carcinoma, SmCC: Small cell carcinoma, Ce: Cervical esophagus, Te: Thoracic esophagus, Ut: Upper thoracic esophagus, Mt: Middle thoracic esophagus, Lt: Lower thoracic esophagus, Ae: Abdominal esophagus, EC: Esophageal carcinoma

with lung metastasis. The survival period from diagnosis in the 13 patients whose survival data were collected ranged from 1 to 34 (average 9.7 ± 9.4) months.

DISCUSSION

According to the comprehensive registry of EC in Japan, EC progresses in 2% males and 0.4% females.[11] There are significant racial variations in the histological types of EC. According to the study of Chalasani *et al*., SqCC was predominant (92%) while adenocarcinoma was rare among black patients. On the other hand, adenocarcinoma was more common (66%) than SqCC (32%) among white patients.[8] With regard to the histological type of primary EC in the Japanese population, SqCC is more common (86.9%) than adenocarcinoma (4.3%).[11] In a study by Weinberg *et al*., histology did not appear to be a risk factor for BM, and among the patients with BM in that study, 82% had adenocarcinoma and 7% had SqCC.[22] Although Gabrielsen *et al*. reported that adenocarcinomas were more prone to metastasize to the brain compared with SqCC, their data were not significant ($P = 0.16$).[9] In contrast, there were no cases of adenocarcinoma in the present study; SqCC accounted for 9 of the 13 patients (69.2% BM cases), while SmCC and basal cell carcinoma accounted for 3 (23% BM cases) and 1 (7.6% BM cases) of the 13 patients, respectively. According to the comprehensive registry of EC in Japan, where SqCC occurs in 87.5% patients and adenocarcinoma in 4.3%, there is no trend toward a higher incidence of BM with adenocarcinoma or SqCC.[11] The proportion of patients with SmCC in our study was higher than that of EC in Japan, suggesting that SmCC is a specific risk factor for BM from EC. Further research is required to confirm this assertion. The features of BM on CT and/or MRI were not significantly correlated with histology (OR, 2.0; $P = 0.85$). However, compared with BM from lung cancer (cystic, 15%; solid, 85%), BM from EC show a greater tendency to become cystic masses with necrosis.[15]

Although it is well known that EC rarely metastasizes to the brain, the number of patients diagnosed with BM from EC is increasing. Metastases are thought to occur via local invasion and hematogenous spread,[22] with the latter being the most likely mechanism for BM. Typically, lung metastasis is rarely found in patients with BM from EC. Indeed, of the 27 patients in the study by Weinberg *et al*., 7 (26%) had lung metastases.[22] In our study, 8 of the 19 patients (42.1%) had lung metastases, probably because hematogenous spread to the brain occurred via the Batson venous plexus. The Batson venous plexus is a network of valveless veins that connect the systemic veins to the internal vertebral venous plexuses.[5] Because of their location and lack of valves, they are thought to be a route for the lesion to metastasize to the brain without metastasizing to the lungs.[16,22] In particular, because the esophagus contains the esophageal venous plexus, EC lesions are likely to metastasize to the brain through the Batson venous plexus. This is supported by

Table 3: Clinical data and characteristics of esophageal carcinoma (EC) in the 19 patients

Clinical data and characteristics (total number of patients)	Number of patients	(%)
Age at EC diagnosis		
Range	52-78 (years)	-
Average±SD	65.5±6.9 (years)	-
Sex		
Male	18	(94.7)
Female	1	(5.2)
Size of EC (*n*=15: No data in 4 patients)		
Range	2-13 (cm)	-
Average±SD	5.8±2.9 (cm)	-
Location of EC (*n*=17: No data in 2 patients)		
Ce	2	(11.7)
Te		
Ut	5	(29.4)
Mt	12	(70.5)
Lt	9	(52.9)
Ae	3	(17.6)
Stage of EC at the diagnosis (*n*=15: no data in 4 patients)		
Tumor staging		
0 -I	0	(0)
II	1	(6.6)
III	4	(26.6)
IV	10	(66.6)
TNM classification		
Tx	2	(13.3)
Tis-T1	0	(0)
T2	2	(13.3)
T3-T4	11	(73.3)
Nx	1	(6.6)
N0	1	(6.6)
N1	13	(86.6)
Mx	0	(0)
M0	5	(33.3)
M1	10	(66.6)
Treatment for EC		
S+R+C	6	(31.5)
R+C	6	(31.5)
S+C	1	(5.2)
S+R	1	(5.2)
R	1	(5.2)
C	1	(5.2)
BSC	3	(15.7)

Stage: using TNM classification, SD: Standard deviation, S: Surgery, R: Radiotherapy, C: Chemotherapy, BSC: Best supportive care, EC: Esophageal carcinoma

the fact that the thoracic esophagus, which lies in the region of the esophageal venous plexus, was the most common location for EC in our study. This phenomenon may account for the low rate of lung metastases in patients with BM from EC.

Table 4: Clinical data and characteristics of brain metastases (BM) in the 19 patients

Clinical data and characteristics (Total number of patients)	Number of patients	(%)
Time from EC diagnosis and BM occurrence		
Range	−4-36 (months)	-
Average±SD	14.2±15.0 (months)	-
Median	7	-
Neurological symptoms		
No symptoms	8	(42.1)
Hemiplegia	4	(21.0)
Headache	3	(15.7)
Visual disturbance	2	(10.5)
Seizure	2	(10.5)
Memory disturbance	1	(5.2)
Aphasia	1	(5.2)
Location of BM		
Brain		
Frontal	9	(50)
Parietal	9	(50)
Occipital	4	(22.2)
Temporal	2	(11.1)
Cerebellar	2	(11.1)
Corpus callosum	1	(5.6)
Cranium	3	(16.7)
Feature of BM on images		
Cystic mass with enhanced rim	6	(31.5)
Solid with central necrosis	11	(57.8)
Bone destruction	2	(10.5)
Treatment for BM		
S+R	5	(26.3)
R	8	(42.1)
S	3	(15.7)
BSC	3	(15.7)
Histological type of BM and/or EC (*n*=13: No data in 6 patients)		
Squamous cell carcinoma	9	(69.2)
Small cell carcinoma	3	(23.0)
Basal cell carcinoma	1	(7.6)
Other metastatic sites		
Without lung metastasis	11	(57.8)
With lung metastasis	8	(42.1)
With LN metastasis	12	(63.1)
Survival period from BM diagnosis (*n*=13: No data in 6 patients)		
Range	1-34 (month)	-
Average±SD	9.7±9.39 (month)	-
Median	8 (month)	-

BM: Brain metastasis, EC: Esophageal carcinoma, BSC: Best supportive care, LN: Lymph node, SD: Standard deviation

In the study by Ogawa *et al.*, the primary lesions were stage III or stage IV in 81% patients with BM.[16] Our

study supported this finding, with 93.2% patients having stage III or stage IV disease. If we further restrict the sample to only patients with SqCC, all had stage III or stage IV disease. One patient with SmCC had stage II disease. In the study of Gabrielsen *et al*., the mean size of EC in patients with and without BM was 8.6 ± 2.8 cm and 5.1 ± 2.5 cm, respectively, suggesting a highly significant correlation between increased EC size and BM risk ($P < 0.001$).[9] On the basis of this study, Go *et al*. concluded, "preoperative neuroimaging is not indicated for routine staging of patients with EC except large tumors (>8 cm)."[10,11] However, in our study, the mean EC size in patients with BM was 5.8 ± 2.9 cm, suggesting that BM can occur in association with EC lesions that are smaller than those generally estimated.

This study was limited by the fact that the risk factors for metastases were not statistically evaluated because no data was available for EC patients without BM. However, our retrospective review of patients with BM from EC revealed valuable findings.

CONCLUSION

Our study suggests that BM can occur in association with EC lesions that are smaller than those previously reported and that SmCC may be a risk factor for BM from EC. The findings from this study and previous studies suggest that BM should be considered in patients with beyond stage III EC lesions, those with EC lesions located partly or completely in the thoracic esophagus, which cannot be removed by surgery, and those with local invasion or lymph node metastasis,[10,11] regardless of the presence or absence of neurological symptoms or lung metastasis. Further research and case reports are necessary to clarify the clinical risk factors for BM in patients with EC.

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