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REVIEW

Incidence and treatment of brain metastasis in patients with esophageal carcinoma

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Abstract

Brain metastasis from esophageal carcinoma (BMEC) is very rare, but its incidence has increased in the United States, Japan, China and other counties. Reports on BMEC have largely been focused on examining whether adjuvant therapy for esophageal cancer influences the survival duration of BMEC patients and on the imaging characteristics of BMEC determined using new medical equipment. The difference between different pathological types of esophageal cancer, especially adenocarcinoma and squamous cell carcinoma, is one important factor used to assess the influence of BMEC. Adjuvant therapy, including radiotherapy and chemotherapy, for esophageal cancer with different characteristics in different countries may affect BMEC treatment outcomes. The degree of popularization of advanced medical equipment is a major concern related to the prevalence of BMEC. Furthermore, targeted BMEC treatment is under development in developed countries. In this article, we reviewed the debate surrounding BMEC and analyzed BMEC studies from different perspectives.

Key words: Brain metastasis; Esophageal carcinoma; Magnetic resonance imagin; Computed tomography

Core tip: The incidence of brain metastasis from esophageal carcinoma (BMEC) is extremely low but has increased in recent years. The relevant reports on this unique disease have primarily focused on issues such as whether the auxiliary treatment of esophageal cancer promotes BMEC, the correlation of survival duration with different treatment methods, and imaging characteristics determined using various

imaging approaches. We reviewed the different perspectives of BMEC and compared BMEC studies performed in different countries.

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INTRODUCTION

Metastatic brain tumors are the most common type of brain tumor in adults. Brain metastasis (BMs) occur in approximately 25%-35% of malignancies[1]. Lung cancer (48%) and breast cancer (15%) are the primary metastatic brain tumors[2,3]. However, BM from esophageal carcinoma (BMEC) is extremely rare. According to Bartelt and colleagues, the incidence of BM from gastrointestinal tumors, including esophageal, gastric, and colorectal carcinomas, is less than 4%[4]. As the incidence of esophageal cancer has been reported to have gradually increased in the United States[5], the number of reports on BMEC has also increased in recent years[6]. Advances in neuroimaging such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) have contributed to the early detection of BMEC. Esophageal tumor pathology can be classified as adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, all of which are likely to metastasize to the brain. We searched the literature in PubMed and found 346 articles from 13 countries on BMEC, 321 of which were original articles (United States 144, Japan 103, China 31, China and Japan 6, Germany and Austria 21, and Germany 16) and 25 of which were case reports (Japan 5, United States 8, Turkey 1, Italy 4, Ireland 1, Australia 1, Iran 1, India 1, United Kingdom 1, Canada 1, China 1). The literature discusses the incidence, clinical characteristics, survival and some unusual phenotypes of BMEC.

It is generally thought that BM only occurs with esophageal cancer recurrence or in the advanced disease stage. However, BM also occurs in the early stage of the primary esophageal lesion[7]. Regarding the treatment of BM from lung cancer, BMEC is treated *via* surgery, radiotherapy (RT), and chemotherapy. Generally, the therapeutic approaches for BM are determined based on the type of metastasis, *i.e.*, single, limited or multiple BMs. If a patient has a limited number of metastatic brain tumors (generally 1-3 tumors or a small number of tumors that are close to each other) and if the primary cancer is under control, surgery is performed to confirm the diagnosis and to remove the tumor, followed by RT. RT may involve whole-brain RT (WBRT), stereotactic radiosurgery, or both. However, if the primary cancer is not well controlled, treatment includes WBRT and possibly chemotherapy. In general, the primary treatment for multiple metastatic brain tumors (or multiple tumors that are not close to each other) is WBRT. If no primary cancer site is found, surgery may be performed to obtain a tissue sample, which is likely followed by WBRT. There is growing interest in the efficacy of chemotherapy for metastatic brain tumors. However, many unresolved issues regarding BMEC diagnosis and treatment merit further exploration. This review summarizes the issues concerning the diagnosis and treatment of BMEC and discusses possible solutions for these issues.

INCIDENCE OF BMEC

In the 20th century, the most accurate method for confirming BMEC was autopsy; physicians were surprised by the initial discovery of BMEC based on autopsy. Since then, different groups have reported varying BMEC incidence rates: some have reported incidence rates of 1%-5%[8-11], whereas other studies based on autopsies of over 200 BMEC cases reported rates of 0%-0.9%[12-14]. However, it is difficult to determine the reliability of such reports because from the current perspective, it appears that finding tiny or single BMEC lesions during an autopsy is impossible. Therefore, the reliability of the incidence rates obtained during autopsy is debatable.

Historically, Dunlap was the first to report BMEC in one patient with esophageal cancer in 1932[15]. Since then, few new cases have been reported. In 1978, Irie and colleagues[16] stated that only four BMEC cases had been reported in the previous 50 years. This situation subsequently changed, and additional BMEC cases have been reported since CT imaging technology was applied in clinical practice in the 1970s. However, the BMEC cases initially detected on CT were considered as accidental events and not worthy of further exploration; thus, no relevant reports were published. In the 1980s, MRI provided a popular, powerful tool for diagnosing BM. It was difficult to detect small lesions in the brainstem and cerebellum using CT, but such lesions could be detected *via* MRI. Until recently, most BM cases were detected *via* MRI or CT. Of the BMs detected, only those treated surgically were pathologically confirmed.

Similar to the debate concerning the incidence of BMEC detected during autopsy, the incidence of BMEC based on CT or MRI remains controversial due to historical and technical issues. Regardless of the method used to determine the BMEC incidence, we cannot deny that there is an increasing number of BMEC patients in the clinic.

CHARACTERISTICS OF PATIENTS WITH BMEC IN DIFFERENT COUNTRIES

In previous years, most BMEC reports came from the

Table 1 Comparison of the clinical characteristics of brain metastasis from esophageal carcinoma patients in different countries *n* (%)

Clinical characteristic	Japan[19] *n* = 36 2003-2010	United States[20] *n* = 27 1993-2001	China[18] *n* = 31 2000-2012
Pathology			
Squamous cell carcinoma	23 (64)	2 (7)	26 (83.8)
Adenocarcinoma	5 (14)	22 (82)	3 (9.7)
Small cell carcinoma	5 (14)	0	2 (6.5)
Other	3 (8)	3 (11)	0
RPA class			
Ⅰ	3 (8)	2 (7)	9 (29)
Ⅱ	11 (31)	21 (78)	19 (61.3)
Ⅲ	22 (61)	4 (15)	3 (9.7)
Number of BMEC lesions			
Single	19 (53)	13 (48)	18 (58.1)
Multiple	17 (47)	14 (52)	13 (41.9)
Location of BMEC			
Cerebral hemisphere	25 (69)	5 (18)	47 (75.8)
Cerebellum	8 (22)		15 (24.2)
Other	3 (8)	22 (82)	
Other metastatic sites			
Yes	25 (69)	19 (70)	16 (51.6)
No	11 (31)	8 (30)	15 (48.4)
Treatment for BMEC			
Chemotherapy alone	3 (8)	0	3 (9.6)
RT alone	9 (25)	15 (56)	9 (29)
Surgery alone	12 (33)	6 (22)	
Surgery + RT	5 (14)	6 (22)	2 (6.5)
Surgery + chemotherapy	1 (3)		
Chemotherapy + RT	1 (3)		11 (35.5)
Surgery + RT + chemotherapy	0		4 (12.9)
Palliative care	5 (14)		2 (6.5)

BMEC: Brain metastasis from esophageal carcinoma.

United States and Japan, whereas fewer reports have come from China, where more cases of this disease have been found[17] but where the investigation has been focused on the diagnosis and treatment of BMEC[18]. The United States was the first to attach great importance to BMEC; this emphasis was followed by substantial research worldwide on the diagnosis and treatment of BMEC. However, one issue arose from those studies: the repeated submission of case reports by diligent Japanese doctors resulted in a large number of repeated cases being reported. Ogawa and colleagues[19] believed that excluding the 36 cases that they had reported, there were only 61 cases of BMEC in Japan prior to 2002, of which 35 cases were published in 13 English journals and the remaining 26 cases were published in 14 Japanese journals. If this is the case, retrospective studies on the diagnosis and treatment of BMEC based on previous literature would be very difficult. Thus, in this review, only the 36 cases reported in the Japanese literature after 2002 were included for comparison. As improved chemotherapy and novel chemotherapeutic agents have been used in the clinic in China, the overall survival of esophageal cancer patients has been prolonged to a certain extent, and more BMEC patients have sought clinical assistance. BMEC cases confirmed by autopsy in China remain rare because of local customs; Chinese patients are typically unwilling to permit autopsy after their death. A comparison of the clinical characteristics of BMEC cases in China[18], the United States[20], and Japan[19] is shown in Table 1; 31 Chinese patients were diagnosed and treated at our hospital. We have also included published reports from the MD Anderson Cancer Center in the United States in this review.

As shown in Table 1, it is evident that the pathological characterization of BMEC varies between the three countries. Adenocarcinoma was primarily detected in the United States, which is a Western country; squamous cell carcinoma was more common in Japan and China, which are Asian countries. Small cell esophageal cancer was identified in patients from both Japan and China, whereas more patients from the United States had multiple lesions, of which adenocarcinoma was the most frequent. In terms of therapy, standard treatment was commonly used in the United States, whereas additional therapeutic approaches were provided in Japan and China. For squamous cell carcinoma cases, Chinese patients were generally in good condition, whereas 61.1% of Japanese patients were in recursive partitioning analysis class Ⅲ.

The Japanese study records of 36 patients (1.4%) with BMEC who were treated between 1986 and 2000 were reviewed. A total of 2554 patients with esophageal carcinoma were treated at three different hospitals. An American study conducted at The University of Texas M. D. Anderson Cancer Center identified 1588 patients with primary esophageal carcinoma between June 1, 1993 and July 31, 2001. Of these patients, 27 (1.7%) were diagnosed with BMEC. A Chinese study was based on more than 10 000 patients with esophageal carcinoma from 1953 to 2003 at Zhejiang Cancer Hospital. Only 31 patients (approximately 0.3%) with BMEC were found. As mentioned above, autopsy performance and historical and technical factors are the key factors that explain the different incidences between the three countries.

AUXILIARY TREATMENT OF ESOPHAGEAL CANCER PROMOTES BMEC

Thomas *et al*[21] first proposed the hypothesis that the auxiliary treatment of esophageal cancer promotes BMEC in 2006. In their study, they included 403 patients with esophageal cancer who received only

esophageal radical resection and 369 patients who received adjuvant therapy in addition to radical resection from 1985 to 2002; the latter group included 118 patients who received preoperative adjuvant therapy, 124 patients who received postoperative adjuvant therapy, and 127 patients who received both forms of adjuvant therapy. The risk of BM occurrence between the two groups was compared. Years later, they found that 29 patients (6 from the control group and 23 from the intervention group) developed BM, 20 of whom developed BM within one year. The risk of BM occurrence was 2.5%, 4%, 7.0%, and 18.4% in the control, preoperative intervention, postoperative intervention, and preoperative and postoperative intervention groups, respectively. Thus, preoperative and postoperative adjuvant therapy and distant metastasis were identified as risk factors affecting the survival of BMEC patients. In that study, the overall median survival of BMEC patients was only 3.5 mo. Moreover, some authors proposed that not only the disease itself but also the adjuvant chemo-radiation therapy affects the development of BMEC. In 2007, Kawabata *et al*[22] reported a retrospective study of 254 esophageal cancer patients who received either surgery alone or surgery and adjuvant chemotherapy from 1984 to 2004. They showed that of the 73% of patients who received chemotherapy, 11 patients developed BM. The clinical stage and the performance of chemotherapy treatment during surgery were closely related to BMEC development. Furthermore, it is unclear whether patients receiving trimodal therapy should be screened for BM. In 2013[23], 518 esophageal adenocarcinoma patients receiving trimodal therapy were retrospectively analyzed. In that study, distant metastasis was found in 188 cases (36.3%), including 20 cases of BM (3.9%). Most patients (90%) with BM were diagnosed within 24 mo of surgery. Although 17 of these 20 patients received therapy for BM, their median overall survival was only 10.5 mo (95%CI: 6.6-14.0). It is difficult to detect BM by screening EC patients who receive adjuvant RT or chemotherapy because the incidence of BM after adjuvant therapy is relatively low. This conclusion should be considered with caution because patients who receive chemotherapy and adjuvant treatment are often in the very late stages of esophageal cancer (Ⅲ-Ⅳ), in which immune function may be impaired by the progression of the disease, resulting in tumor metastasis.

MISDIAGNOSIS OF BMEC THAT OCCURS EARLIER THAN THE DIAGNOSIS OF ESOPHAGEAL CANCER

BM typically occurs after treatment[4,6,7,18,20-23], although concurrent BM and EC have been rarely reported (less than 10 cases in the literature). In some individual case reports[7,24-26], especially in misdiagnosed cases[7,25,26], BM was found before the primary lesion of the esophagus was detected. In those cases, BM was often misdiagnosed as meningitis, a pituitary tumor, or glioma. BM predominantly occurs after treatment[4,6,7,18,20-23] based on the results of BM occurrence at 5[27], 6.7[17], 8.4[28], or 10 mo[29] after treatment, ranging from 4 to 57 mo. Clinical staging and adjuvant therapy are considered to be associated with BMEC, but the factors influencing the interval from treatment to BMEC occurrence have not been clarified.

UNCERTAIN VALUE OF THE UNIQUE IMAGING CHARACTERISTICS OF BM

Although there has been an increase in the number of reports on BMEC due to the clinical application of CT, few studies have analyzed the CT data from BMEC patients. In 1995, Gabrielsen *et al*[30] reported 334 esophageal cancer cases, which included 230 cases of adenocarcinoma (male:female ratio = 202:28) and 104 cases of squamous cell carcinoma (male: female ratio = 61:43). BM ultimately developed in only 10 cases of adenocarcinoma and two cases of squamous cell carcinoma. Therefore, it was believed that the incidence rate of BMEC in that study was low (only 3.6%). At that time, CT was not recommended as a routine examination tool due to its cost. Since their report was published nearly 20 years ago, many changes have been made in clinical diagnosis because of the fast-growing economy. In recent decades, additional CT findings of BM have been reported. Among those reports, that by Takeshima and colleagues[28] of CT data from eight BMEC cases is considered as a classic report even today. Their study reported that CT displayed enhanced thin-walled cystic lesions in four of six squamous cell carcinoma cases and in both cases of small cell carcinoma. They stated that the enhancement of thin-walled cystic lesions in the CT images was the primary characteristic of BMEC. Although many have cited this report in the past decade, the number of cases in these reports is smaller than the number of cases in the original report. Moreover, the MRI characteristics of BM from adenocarcinoma remain unknown. Thus, further investigations exploring the imaging characteristics of BM are needed. Additional imaging characteristics of BM aside from the thin-walled cystic contents and the enhanced thin-wall cystic lesions reported by Takeshima and colleagues are anticipated because BM is often mistaken for other diseases, as some BM cases do not exhibit any symptoms to support the diagnosis of BM.

VARIED SURVIVAL DURATION AFTER THE TREATMENT OF BMEC

The efficacy of BM treatment is an interesting topic. Until recently, there were no prospective randomized controlled clinical trials or comprehensive analyses

Table 2 Outcomes of different treatment methods

Study	Number of patients	Treatment	Median survival (mo)	Factors influencing prognosis
Ogawa *et al*[19]	12	SR + WBRT	9.6	Treatment plan
	24	WBRT	1.8	KPS score
Total	36 (MOS)		3.9	
Weinberg *et al*[20]	4	SR + WBRT	9.6	Liver metastasis
	6	SR	3.8	RPA class
	15	WBRT	3.9	
	2	SRT	2.5	
Total	27 (MOS)		3.8	
Wadhwa *et al*[23]	20 (MOS)		10.5	None
Kanemoto *et al*[27]	6	WBRT	1.6	None
	2	SR + WBRT	4.1	
	2	SRT	4.0	
	1	SRS	18.2	
	1	None	0.4	
Total	12 (MOS)		2.1	
Yoshida[36]	3	SR + WBRT	65.5	None
	7	SR	17.7	
	4	SRT	9.5	
	3	WBRT	27.1	
	(No MOS)			

MOS: Overall median survival; KPS: Karnofsky performance status; SR: Surgical resection; SRS: Stereotactic radiosurgery; SRT: Stereotactic radiotherapy; RPA: Recursive partitioning analysis; WBRT: Whole-brain radiation therapy.

involving a large cohort of BMEC cases demonstrating the effectiveness of different treatments. Moreover, many publications have reported varying results for different BM treatment approaches. In general, the BM treatment approaches include simple surgery, chemotherapy, RT, or a combination of two or all of these approaches. There are three types of surgery for BM: punch partial excisional biopsy[26], subtotal tumor removal[31], and single lesion resection[21-23]. Combined 5-fluorouracil (5-FU) and platinum is the most commonly used chemotherapy for BM. Other drugs such as doxorubicin, irinotecan, and cetuximab are also used[23]. RT includes WBRT, partial brain irradiation combined or not combined with WBRT, conformal RT, intensity-modulated RT, and stereotactic body RT[23]. The use of local heavy ion and proton irradiation has been reported in Japan. Chemotherapy can be administered before surgery, after surgery, or both. The primary tumor and metastatic lesions can be treated simultaneously in some patients in whom BM and esophageal cancer are detected simultaneously[26].

Some BM patients may abandon treatment for various reasons, leading to a short survival duration that ranges from 10 d to 2 mo[27]. Survival duration as a treatment outcome in several reports is summarized in Table 2. However, because of the limited number of cases, we were unable to compare the effectiveness of different treatments. There are a few reports of patients with esophageal cancer with longer survival durations, *e.g.*, exceeding 6 years and 11 years[32-36]. We treated a patient with squamous cell carcinoma who had survived for almost 14 years and who had undergone brain surgery and chemotherapy for BMEC that was discovered 15 mo after postoperative chemotherapy for esophageal cancer. At present, this is likely the longest survival duration among BMEC patients[18]. Prolonged survival confirms the hypothesis that surgery combined with RT and chemotherapy leads to better treatment effects for patients with a single brain lesion. The difference in the survival duration of patients with adenocarcinoma-associated BMEC and those with squamous cell carcinoma-associated BMEC has recently been debated[6]. This issue should not be overlooked. Regarding the mechanism underlying tumor metastasis, the primary tumor may develop simultaneously metastatic tumors in the brain and in other organs. Therefore, targeted therapy may also be effective for BMEC. Data from the Shizuoka Cancer Center in Japan[27] showed that BMEC patients with squamous cell carcinoma had a median survival duration of only 2.1 mo; the majority of these patients had multiple lesions, double primary cancers, and low Karnofsky performance status scores. That study also reported that the examined patients died soon after treatment, indicating the association of survival with the time at which MRI was performed. In that study, MRI was performed after the BM patients had developed symptoms from the lesion, *i.e.*, in the very late stage of BM.

Small cell carcinoma is the most common type of esophageal cancer in regions such as China and Japan. Currently, there is a great deal of information regarding this disease in China[37]. Small cell esophageal carcinoma is more aggressive than esophageal adenocarcinoma or squamous cell carcinoma[38]. Among the 31 patients with BMEC at our hospital[18], two patients with small cell esophageal cancer had multiple lesions in the brain and metastatic tumors in other organs. One patient in particular had multiple metastatic tumors in the cerebrum, the cerebellum, the brainstem, and the spinal cord. These patients exhibited neurological symptoms during treatment of their esophageal lesion. RT displayed a higher treatment efficacy in the patients with small cell esophageal cancer. After treatment, the cerebral spinal lesions disappeared from CT or MRI scans. This finding indicates the primary difference between small cell esophageal cancer and esophageal adenocarcinoma or squamous cell carcinoma. Given its many cystic lesions, esophageal adenocarcinoma and squamous cell carcinoma do not respond to RT.

POTENT TARGETED THERAPY FOR BMEC TREATMENT

As the majority of BM of gastroesophageal junction cancer is adenocarcinoma, it is possible to use targeted therapy to treat BMEC in the same manner as it is used to treat lung cancer. For example, Geldart

and Astras[39] reported in 2011 that one case of adenocarcinoma BM in which lesions developed rapidly did not respond to chemotherapy. However, after using trastuzumab combined with chemotherapy, the lesion in the brain shrank and was controlled.

In 2012, Abu *et al*[40] performed a retrospective study of 142 cases of esophageal cancer in the past 10 years. In that report, the overexpression of human epidermal growth factor receptor type 2 (HER2) was detected *via* immunohistochemistry in five (56%) out of nine patients with BM. The authors suggested that HER2 overexpression correlated with postoperative BM. In 2013, Preusser *et al*[41] reported a similar study involving 21 cases of esophageal cancer and BM in which only one case was squamous cell carcinoma and all of the others were adenocarcinoma. Among these tumors, three (14%), seven (33%), nine (43%), 18 (86%), and 0 were positive for HER2, epidermal growth factor receptor (EGFR), phosphorylated signal transducer and activator of transcription 3 (pSTAT3), hypoxia-inducible factor-1α (HIF1-α), and BRAF V600E, respectively. Moreover, the median Ki-67 index was 59%, and the microvessel density was 20/21 (95%). That study also showed that HER2 and EGFR expression correlated with the primary tumor and brain lesions, suggesting that HER2 and EGFR might be angiogenic factors that can be used as targets for the treatment of BMEC. In 2014, Niu *et al*[42] reported a HER2-positive esophageal adenocarcinoma patient who was treated with trastuzumab and lapatinib; brain metastasis occurred after the liver metastases responded well to treatment. Negative HER2 expression was detected in the brain lesion. Another study reported a young patient (33-year-old) with Williams Syndrome, a multisystem neurodevelopmental disorder[43], and concomitant esophageal cancer who ultimately developed BM[24]. The patient was diagnosed based on hemizygosity for 7q11.23, as assessed by FISH. The report proposed the hypothesis that a genetic abnormality may cause BM.

CONCLUSIVE EVIDENCE FOR EC METASTASIS TO THE BRAIN

The development of BM occasionally results in unusual phenotypes that warrant investigation. In the report by Santeufemia *et al*[32], a 51-year-old female patient with stage Ⅱ esophageal cancer (PT2N0M0) developed metastatic tumors, including a 3 cm × 3 cm nodule in the left breast and a 1 cm × 1 cm nodule in the right frontal cortex six months after surgery. After one cycle of chemotherapy, the left breast nodule shrank, and excision of the intracranial and breast metastatic lesions was subsequently performed. The patient had subsequently survived for 11 years when the case was reported. An increasing incidence of cancer of unknown primary (CUP) has been observed. For most CUP patients with BM, the primary tumor is difficult to detect, but evidence can be found in some cases. In a case of BM with initial neural symptoms, the postoperative pathological examination of brain lesions showed that they were poorly differentiated adenocarcinoma and ganglioneuroma. Subsequently, the primary esophageal lesions were identified[44]. This case may have been the first example of BM coincident with ganglioneuroma. As another example, a 72-year-old male patient with both prostate and esophageal cancer[45] underwent brain lesion resection, and the pathological findings comprised a 2.5-cm cerebellar lesion containing both esophageal and prostate cancer components.

In conclusion, studies on BMEC are limited, and these studies have primarily been performed in Japan and the United States (a total of 260 cases). Moreover, studies in this field are not as thorough as those of lung cancer. Due to the issue of inconsistent data, it is difficult to compare the results provided by different hospitals in different countries. In recent years, additional attention has been focused on BMEC development and its diagnosis and treatment. In 2014, the median survival of thirty BMEC patients who underwent gamma knife radiosurgery was only 4.2 mo[46]. We expect that more joint projects, including basic and clinical studies, on BMEC will be conducted by researchers in different countries. We believe that further investigation of the diagnosis and treatment of BMEC will benefit many patients with esophageal cancer.

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