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ORIGINAL ARTICLE

Brain metastases in patients with upper gastrointestinal cancer is associated with proximally located adenocarcinoma and lymph node metastases

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Abstract

Background As cancer patients are surviving longer, more patients manifest brain metastases (BRMs). However, the rate of BRMs from upper gastrointestinal cancer is unclear. We therefore evaluated the frequency and prognostic effect of BRMs in this setting.

Methods We analyzed records of 2348 patients who were treated between January 2002 and December 2016 for upper gastrointestinal cancer, including esophageal and gastroesophageal junction adenocarcinoma (EAC; proximal EAC, Siewert types I and II), esophageal squamous cell carcinoma (ESCC), and gastric adenocarcinoma (GAC; Siewert type III and stomach cancer) in our Gastrointestinal Medical Oncology Database. Frequency, risk factors, and survival after BRMs were evaluated.

Results Of 2348 patients, 68 (2.9%) had BRMs upon follow-up. The BRM rates were as follows: proximal EAC, 4.8%; Siewert type I, 5.9%; Siewert type II, 2.2%; Siewert type III, 0.7%; ESCC: 1.2%; and stomach cancer, 0%. Among EAC patients, Siewert type I and lymph node metastases were independent the risk factors for BRMs in the multivariable analysis. The median overall survival (OS) in the 68 patients with BRMs was only 1.16 years (95% CI 0.78–1.61). However, OS for patients who had a solitary BRM, who had BRM but no other distant metastasis, or who underwent surgery or stereotactic radiosurgery favorable.

Conclusion Patients with proximally located adenocarcinoma, or with lymph node metastases are at a higher risk for BRMs and patients fare better after treatment of isolated BRM.

Keywords Esophageal adenocarcinoma · Esophageal squamous-cell carcinoma · Gastroesophageal junction adenocarcinoma · Gastric adenocarcinoma · Brain metastases

Introduction

Upper gastrointestinal cancers (UGC) including esophageal and gastroesophageal junction adenocarcinoma (EAC; proximal EAC, Siewert types I and II), esophageal squamous cell carcinoma (ESCC), and gastric adenocarcinoma (GAC; Siewert type III and stomach cancer) are very common worldwide [1], and have a poor prognosis [2].

Approximately 70,000 new cases of brain metastases (BRMs), were diagnosed in 2007 in the United States, which was 6% of patients with newly diagnosed invasive cancers [3]. Almost 90% of BRMs result from lung, breast, melanoma, colon, or renal cancers [3]. Because BRM is often diagnosed later in the clinical course, its incidence has increased as overall survival (OS) has lengthened in many solid tumors patients [3]. Therefore, understanding BRM incidence and prognostic implications are important. However, frequency of BRM from UGC remains unclear.

A few reports have evaluated BRM incidence in UGC. Cagney et al. used data from the Surveillance, Epidemiology,

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and End Results (SEER) program to show that 1.7% of patients with esophageal cancer and 0.6% patients with gastric cancer had BRM at diagnosis, [4] but lacked details, as SEER is a national database. Several cohort and case reports of BRMs from UGC are available [5–7], but their sample size is small to correlate with clinical features (such as location or histology). Here, we analyzed 2,348 patients with UGC to evaluate frequency, risk factors, and survival influence of BRMs.

Patients and methods

Patients

We searched our prospectively maintained databases in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center (Texas, USA) and identified 2348 patients who were treated for EAC, ESCC, or GAC between January 2002 and December 2016, and included them in this analysis. No other selection criteria were applied.

Patients had extensive baseline staging, including CT and PET studies, esophagogastroduodenoscopy with endoscopic ultrasonography, and blood tests. Routine pretreatment brain imaging was not performed unless patients describe symptoms related to central nervous system disease. Tumor staging was based on the American Joint Commission on Cancer Staging Manual (8th edition) [8]. The institutional review board approved this analysis.

Treatment and follow-up strategy

Patients were treated according to the NCCN guidelines [2, 9]. Multidisciplinary teams of medical oncologists, thoracic surgeons, surgical oncologists, radiation oncologists, gastroenterologists, thoracic radiologists, pathologists, and supporting team personnel evaluated all patients before starting any treatment. Patients were followed at 3- to 12-month intervals for at least 5 years after treatment. When patients (many of whom lived some distance away) were followed up locally, we collected their information by letter or patient referral documents. HER2 status had been tested only in patients with adenocarcinoma who have distant metastases. Head CTs or MRIs were performed only when BRM was suspected. We designated a case as having BRM(s) when solid mass(s) were noted on imaging studies. Occasionally, biopsy was performed, but it was not necessary to diagnose BRM. Meningeal dissemination was excluded from BRMs in the absence of a solid mass. Treatment for BRM(s) was decided by the multidisciplinary teams.

Statistical analysis

Patient characteristics were summarized using descriptive statistics, by frequency (%) for categorical variables, and by median and range for continuous variables. Comparisons between groups were conducted using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. OS was defined as the time interval between date of diagnosis and date of death from any cause. Patients were censored at the last follow-up if they were alive at that time. The OS probabilities were estimated using the Kaplan–Meier method; log-rank tests were used to compare OS across groups. Univariate and multivariable logistic regression models were fit to assess the association between patient characteristics and the binary outcome, BRM, where variables with significance levels less than 0.05 in univariate analysis were included in the multivariable regression model except for the baseline clinical stage. All statistical analyses were performed using R 3.5.1.

Results

Characteristics of patients with BRM

Of 2348 patients, 68 (2.9%) were found to have BRMs. The median time interval between BRMs diagnosis and initial treatment was 1.27 years (95% CI 1.10–1.56) in clinical Stage I-IVa patients. Of 19 clinical Stage IVb patients with BRMs, 5 were had BRMs at diagnosis. The median time interval between the BRMs diagnosis and initial treatment in 14 clinical Stage IVb patients was 1.16 years (95% CI 0.63–2.00). Table 1 shows clinical features of these patients. Incidence of BRMs was significantly higher in patients whose primary tumor was located at proximal sites (proximal EAC, 4.8%; Siewert type I, 5.9%; Siewert type II, 2.2%; Siewert type III, 0.7%; ESCC, 1.2%; Fig. 1). No BRM developed in the stomach cancer cohort. The incidence of BRMs for EAC (4.3% for proximal esophagus, Siewert type I and type II) was significantly higher than for ESCC (1.2%; $P = 0.009$). Incidence of BRMs was associated with younger age, higher T stage, higher N stage, and higher clinical stage.

In clinical Stages I-II, only 2 patients developed BRMs; one in ESCC and one in Siewert type I. In clinical Stages III-IVa, 47 patients had BRMs. The incidence of BRMs was significantly higher in patients whose primary tumor was located at proximal sites (proximal EAC, 6.7%; Siewert type I, 7.3%; Siewert type II, 2.0%; Siewert type III, 1.8%; ESCC, 0.8%; Fig. 1). In clinical Stage IVb patients, 19 had BRMs. The incidence of BRMs was higher in patients with proximal EAC, Siewert type I, Siewert type II (Fig. 1).

Table 1 Clinical characteristics of patients with and without brain metastasis ($n = 2347$)

Clinical feature	Brain metastasis		
	Positive 68 (2.9%)	Negative 2280 (97.1%)	*P*
Mean age ± SD	59.8 ± 10.59	62.7 ± 11.49	0.03
Sex			0.09
Male	60 (3.2)	1809 (96.8)	
Female	8 (1.7)	471 (98.3)	
Cancer type			< 0.001
Proximal EAC	6 (4.8)	119 (95.2)	
Siewert type I	44 (5.9)	707 (94.1)	
Siewert type II	14 (2.2)	612 (97.8)	
Siewert type III	1 (0.7)	152 (99.3)	
ESCC	3 (1.2)	240 (98.8)	
Stomach	0 (0)	450 (100)	
Histological Type			0.20
Adenocarcinoma	64 (3.1)	1996 (96.9)	
Squamous cell	3 (1.2)	241 (98.8)	
Endocrine	1 (2.9)	33 (97.1)	
Undetermined	0 (0)	10 (100)	
Tumor differentiation			0.23
Well differentiated	0 (0)	26 (100)	
Moderately differentiated	34 (3.7)	883 (96.3)	
Poorly differentiated	34 (2.5)	1319 (97.5)	
Undetermined	0 (0)	52 (100)	
Baseline T category			< 0.001
T1	0 (0)	298 (100)	
T2	4 (2.2)	179 (97.8)	
T3	61 (3.6)	1616 (96.4)	
T4	2 (1.2)	171 (98.8)	
TX	1 (5.9)	16 (94.1)	
Baseline *N* category			< 0.001
N0	8 (0.9)	930 (99.1)	
N1	35 (4.4)	763 (95.6)	
N2	13 (3.9)	321 (96.1)	
N3	12 (4.6)	252 (95.4)	
NX	0 (0)	14 (100)	
Baseline clinical stage			< 0.001
I	0 (0)	333 (100)	
II	2 (0.7)	271 (99.3)	
III	30 (3.1)	924 (96.9)	
IVa	17 (8.7)	178 (91.3)	
IVb	19 (3.2)	567 (96.8)	
X	0 (0)	7 (100)	

Of 551 patients who underwent HER2 testing, 85 (15.4%) tumors were HER2 positive. Six patients (7.1%) in the HER2 positive cohort and 27 patients (5.8%) in the HER2 negative cohort had BRMs. Therefore, HER2 status was not associated with BRMs ($P = 0.66$).

Risk factors for BRMs among patients with EAC

Among the total 2347 patients, 1502 (64%) were EAC patients. Clinical characteristics were summarized for these EAC patients, grouped by brain metastasis status (Table 2).

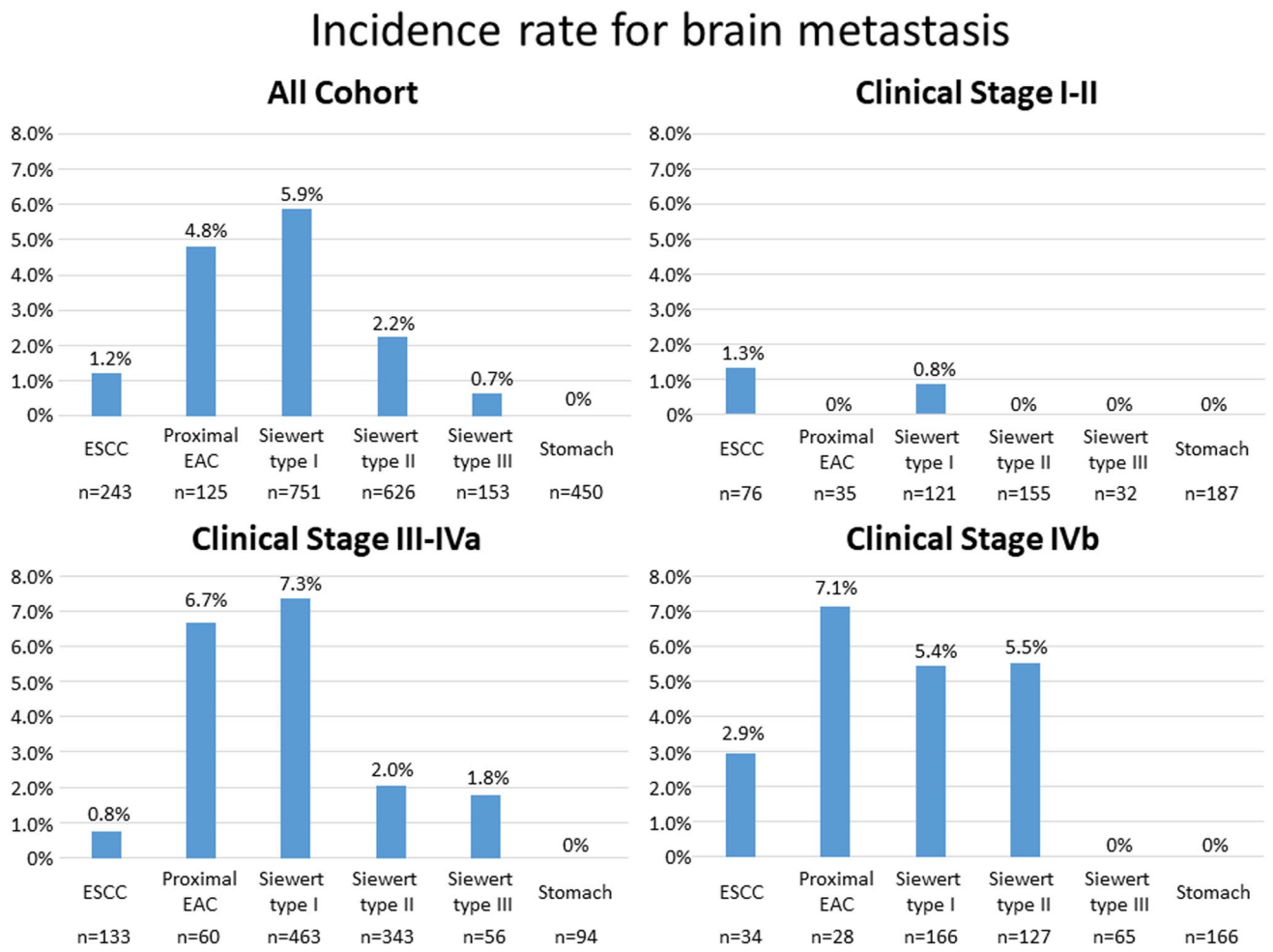

Fig. 1 Incidence rates for BRMs in all cohort and patients with clinical Stage I–II, clinical Stage III–IVa, and clinical Stage IVb

We performed univariate and multivariable logistic regression analyses to identify factors that predicts BRM in patients with EAC (Tables 3). Univariate analyses showed that younger age, location of tumor, tumor depth, lymph node metastases, and clinical stage were significantly associated with the BRMs incidence. Compared with Siewert type II, Siewert type I was a significant risk factor for BRMs (overall risk [OR]: 2.72, 95% confidence interval [CI] 1.48–5.01), whereas proximal EAC tended to be a risk factor for BRMs, but not significantly so (OR: 2.20, 95% CI 0.83–5.85). In multivariable analysis, tumor location and lymph node metastasis were significantly associated with BRMs (Table 3). In multivariable analysis, Siewert type I was a significant risk factor for BRM (OR: 2.44, 95% CI 1.31–4.54), compared with Siewert type II, whereas proximal EAC was only marginally associated with BRMs (OR: 2.30, 95% CI 0.86–6.19).

Next, we performed univariate and multivariable logistic regression analyses in clinical Stage III-IVa and clinical Stage IVb. Among 866 patients with clinical Stage III-IVa EAC, the multivariable analysis showed that the primary tumor location and lymph node metastases were significantly associated with BRMs (Supplemental Table 1). Compared with Siewert type II, Siewert type I was a significant risk factor for BRMs (OR: 3.26, 95% CI 1.61–8.44), whereas proximal EAC was only marginally associated with BRMs. (OR: 3.26, 95% CI 0.92–11.6). However, among 321 patients with clinical Stage IVb, neither the primary tumor location nor lymph node metastases was not associated with BRMs (Supplemental Table 2).

BRM characteristics

Of the 68 patients with BRM(s), 37 patients had solitary BRM, 8 patients had 2 metastatic sites, and 22 patients had 3 or more BRMs. Forty-one patients had BRM(s) but no extracranial metastases, of whom 7 patients developed other extracranial metastases; thus 34 patients had only BRMs during follow-up. Twenty-seven patients had BRMs and extracranial metastases. Of the 68 patients, 31 underwent

Table 2 Clinical characteristics of EAC patients with and without brain metastasis ($n = 1502$)

Clinical feature	Brain metastasis		
	Positive 64 (4.3%)	Negative 1438 (96.7%)	*P*
Mean age ± SD	59.5 ± 10.85	62.7 ± 11.09	0.03
Sex			≥ 0.99
Male	58 (4.3)	1287 (95.7)	
Female	6 (3.8)	151 (96.2)	
Location of tumor			0.002
Proximal esophagus	6 (4.8)	119 (95.2)	
Siewert type I	44 (5.9)	707 (94.1)	
Siewert type II	14 (2.2)	612 (97.8)	
Tumor differentiation			0.46
Well differentiated	0 (0)	16 (100)	
Moderately differentiated	33 (5.1)	618 (94.9)	
Poorly differentiated	31 (3.9)	765 (96.1)	
Undetermined	0 (0)	39 (100)	
Histology			≥ 0.99
Adenocarcinoma	63 (4.3)	1407 (95.3)	
Endocrine	1 (4.0)	24 (96.0)	
N/A	0 (0)	7 (100)	
Signet ring cell carcinoma			0.86
Yes	9 (3.9)	222 (96.1)	
No	55 (4.4)	1206 (95.6)	
N/A	0 (0)	10 (100)	
Baseline T category			< 0.001
T1	0 (0)	231 (100)	
T2	3 (2.6)	113 (97.4)	
T3	59 (5.4)	1033 (94.6)	
T4	1 (1.9)	51 (98.1)	
TX	1 (9.1)	10 (90.9)	
Baseline N category			< 0.001
N0	8 (1.3)	610 (98.7)	
N1	32 (6.2)	485 (93.8)	
N2	13 (6.8)	178 (93.2)	
N3	11 (6.6)	157 (93.4)	
NX	0 (0)	8 (100)	
Baseline clinical stage			< 0.001
I	0 (0)	230 (100)	
IIA	1 (1.2)	80 (98.8)	
III	29 (4.1)	680 (95.9)	
IVA	16 (10.2)	141 (89.8)	
IVB	18 (5.6)	303 (94.4)	
X	0 (0)	4 (0)	

resections, 8 underwent stereotactic radiosurgery, 23 underwent whole brain radiation only, and 6 patients were lost to follow-up or had no treatment.

Prognosis of patients with BRM

Median OS in the 68 patients with BRMs was only 1.16 years after BRM diagnosis (95% CI 0.78–1.61). Of the initial 2347 patients, 1136 developed distant metastases; 68 with BRMs and 1068 without BRM. Among the 1136 patients who had distant metastasis, OS after BRMs was significantly longer than survival after distant metastases to other organs (Median OS, 1.16 vs 0.91 years; Fig. 2a). Similarly, among the 734 EAC patients who had distant metastasis, OS after BRMs was significantly longer than

Table 3 Univariate and multivariable logistic regression models for brain metastasis in patients with EAC ($n = 1502$)

Clinical feature	Univariate		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age[a]	0.98 (0.96–1.00)	0.03	0.98 (0.96–1.00)	0.07
Sex				
Male	1 (reference)			
Female	0.88 (0.37–2.08)	0.77		
Location of tumor				
Proximal Esophagus	2.20 (0.83–5.85)	0.11	2.30 (0.86–6.19)	0.09
Siewert type I	2.72 (1.48–5.01)	0.001	2.44 (1.31–4.54)	0.005
Siewert type II	1 (reference)		1 (reference)	
Tumor differentiation				
Well/moderate	1 (reference)			
Poor	0.77 (0.47–1.29)	0.33		
Signet ring cell carcinoma				
No	1 (reference)			
Yes	0.88 (0.43–1.82)	0.75		
Baseline T category				
T1/2	1 (reference)		1 (reference)	
T3/T4	6.34 (1.98–20.4)	0.0019	2.62 (0.74–9.26)	0.13
Baseline N category				
N0	1 (reference)		1 (reference)	
N1/N2/N3	5.20 (2.46–11.0)	< 0.0001	3.32 (1.48–7.47)	0.003
Baseline clinical stage				
I/II	1 (reference)			
III/IVA	16.99 (2.33–123.7)	0.005		
IVB	18.41 (2.44–138.8)	0.005		

CI confidence interval, *OR* odds ratio

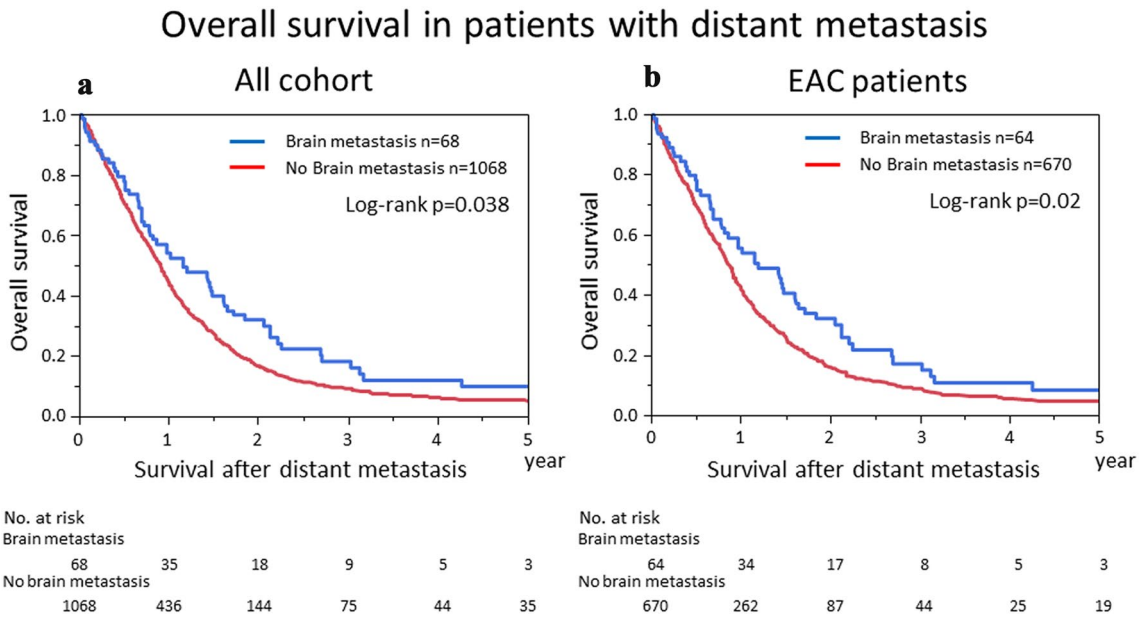

Fig. 2 Kaplan–Meier analysis of overall survival in patients with distant metastasis, categorized by presence of brain metastases. **a** Kaplan–Meier curves for the cohort as a whole. **b** Kaplan–Meier curves for patients with esophageal and gastroesophageal junction adenocarcinoma (EAC)

Table 4 Brain metastases characteristics and patient survival ($n=68$)

	n	Median survival time; years (95% CI)
Number of brain meta		
1	37	1.43 (0.54–2.21)
2	8	0.41 (0.15–1.58)
≥ 3	22	0.20 (0.10–0.70)
N/A	1	-
Metastases pattern when diagnosed		
Brain only	41	1.20 (0.61–1.48)
First metastatic site with other distant metastasis	19	0.32 (0.14–0.72)
Metastases after other distant metastases	8	0.26 (0.07–0.51)
Metastasis site during follow up		
Brain only	34	1.09 (0.50–1.58)
With lung	9	0.51 (0.08–1.86)
With liver	10	0.22 (0.08–0.32)
With bone	14	0.25 (0.13–0.62)
With distant lymph node	23	0.27 (0.18–0.62)
With others	7	
Treatment		
Resection	31	1.47 (0.81–2.21)
Stereotactic radiosurgery	8	1.12 (0.38–3.11)
Whole brain radiation	23	0.18 (0.08–0.25)
N/A	6	0.33 (0.14–0.86)

OS after distant metastasis to other organs. (Median OS, 1.2 vs 0.87 years; Fig. 2b).

Median OS and 95% confidence intervals among patients with BRM is shown in Table 4, according to several clinical strata. For patients with solitary BRM, OS was significantly longer than for patients who had multiple BRM (Fig. 3a). For patients who had BRM with no other distant metastases, OS was significantly longer than for those with extracranial metastases (Fig. 3b). For patients who underwent surgery or stereotactic radiosurgery, OS was significantly longer than for patients who underwent whole-brain radiation (Fig. 3c).

Discussion

This is the largest cohort assessing the incidence of BRMs from UGC, and it uncovered several novel findings. First, the highest risk of developing BRMs was with adenocarcinoma histology than with squamous cell carcinoma histology (EAC, 4.3%; ESCC, 1.2%.) and the primary tumor located more proximally from the esophagogastric junction (proximal EAC, 4.8%; Siewert type I, 5.9%; Siewert type II, 2.2%; Siewert type III, 0.7%; stomach cancer, 0%). Second, Siewert type I and presence of lymph node metastases were risk factors for BRMs in patients with EAC. Third, patients with solitary BRM could have favorable prognoses.

We found that BRMs were more common in patients with EAC than those with GAC. Several reports have assessed BRMs from esophageal cancer. Our institute previously reported that incidence of BRM was 1.7% among 1512 patients with esophageal cancer and 3.9% among 518 patients with esophageal cancer who received trimodal treatment [7, 10]. Welch et al. reviewed 583 patients with esophageal cancer and identified BRMs in 22 patients (3.8%) [6]. These incidence rates are consistent with our data (2.9%).

We hypothesized that esophageal cancer histology types could correlate with BRMs. We showed that the incidence of BRMs from ESCC was 1.2%, which is consistent with some Asian studies [11, 12]. Ogawa et al. showed that incidence of BRMs was 1.4% among 2554 patients with ESCC [11]. Song et al. showed that BRMs incidence was 1.6% among 1612 patients with ESCC [12]. Combined with our data, these findings show the incidence rates for BRMs from ESCC to be significantly lower than from EAC. The BRMs incidence has also been shown to vary by histology in lung cancers. Cagney et al. evaluated SEER data and showed that the incidence of BRMs from lung cancer was 14.4%

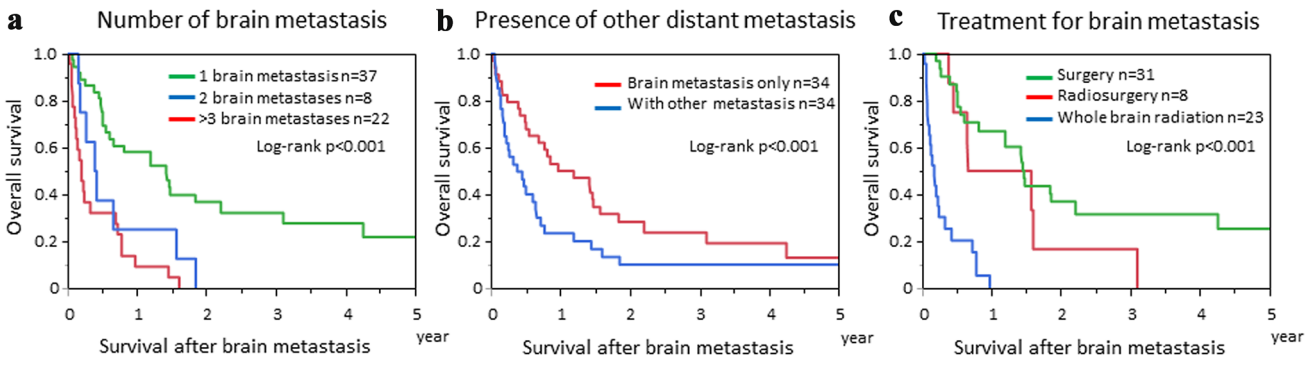

Fig. 3 Kaplan–Meier analysis of overall survival for patients with brain metastasis. **a** Kaplan–Meier curves by numbers of brain metastases. **b** Kaplan–Meier curves by presence of other distant metastases. **c** Kaplan–Meier curves by treatment for brain metastases

from adenocarcinoma, compared with 5.3% from squamous cell carcinoma [4]. However, why adenocarcinoma is more likely to develop BRMs is unclear.

The molecular mechanisms by which cancer cells can migrate to and grow in the brain remain unclear [13]. The molecular features of EAC and GAC overlap [14], but few GAC developed BRMs in this study. Moreover, HER2 expression have been found to be associated with BRMs [15, 16]. However, even GAC with HER2 positive did not have higher frequency of BRMs. Microenvironment of the brain differs from that of other organs. Complexity in the brain is conferred by blood brain barrier, and microglia, or astrocytes. These findings suggest that further basic research needed to discover mechanism of BRMs.

Our data showed that median OS after BRMs was 1.16 years, which is longer than other reports about esophageal cancer (3.8–5.0 months) [4–6, 10]. Moreover, longer survival in patients with single BRM is consistent with previous reports [5, 10]. As especially reported for lung cancer [17], our data demonstrates the contribution of resection to prolonging survival. The treatment choice for a solitary BRM is excision or stereotactic radiosurgery, whereas treatment for multiple BRMs is limited to radiation or chemotherapy only. Thus, our data indicate that identifying early-stage BRM improves chances for resection, and for improved survival.

Our study has some limitations. First, this is a retrospective study. Second, a few patients were lost to the follow-up. Third, because only patients who had symptoms of BRMs underwent evaluation, we might have missed some asymptomatic BRMs. To overcome these limitations, a prospective observational study would be ideal.

In conclusion, BRMs are rare in UGC, but patients with proximally located EAC or with lymph node metastases should be carefully monitored for BRMs.

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Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to disclose.

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