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Could intracranial tumor volume predict prognosis of patients with brain metastases from esophageal carcinoma?

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Abstract

Purpose: A previous study demonstrated that intracranial tumor volume had some correlation with gastrointestinal cancer patients' outcome. The aim of this study was to analyze patients with esophageal carcinoma (EC) and brain metastases to investigate if intracranial tumor volume would be a predictor of these patients' survival.

Methods: A total of 52 patients with brain metastases from esophageal squamous cell carcinoma or esophageal adenocarcinoma were retrospectively reviewed. Patients without images of brain metastases in the hospital information system were eliminated.

Results: The median follow-up time duration was 8.4 months (interquartile range 4.0–15.2). The median overall survival (OS) from time of brain metastases diagnosis was 8.0 months for all cases. Median OS of patients with small and large cumulative intracranial tumor volume (CITV) (<6.65 cm^3, ≥6.65 cm^3) was 11.23 and 7.4 months, respectively. Median OS of patients with large and small largest intracranial tumor volume (LITV) (≥7.75 cm^3, <7.75 cm^3) was 6.4 and 10.6 months, respectively. Univariate analysis demonstrated that CITV (hazard ratio [HR] 1.255, 95% confidence interval [CI] 0.673–2.342, $p = 0.475$) or LITV (HR 1.037, 95% CI 0.570–1.887, $p = 0.904$) was not significantly associated with improved OS. Multivariate analysis demonstrated that CITV and LITV were not significantly associated with improved OS.

Conclusion: EC patients with small intracranial tumor volume may have longer OS than those with large intracranial tumor volume, but this difference did not reach statistical difference. Future studies with a larger sample size may validate the correlation of intracranial tumor volume and patient survival.

KEYWORDS
brain metastases, esophageal carcinoma, intracranial tumor volume, overall survival

INTRODUCTION

Esophageal carcinoma (EC) is one of the most common malignancies in the world, and these patients often have poor prognosis. Brain metastasis is rare in patients with EC.[1-7] Prognosis for patients with EC and brain metastases is much poorer, with reported median overall survival (OS) of 6 months approximately.[2-5,7] In clinical practice, common treatment methods include surgery, radiotherapy, and systemic therapy. Our previous study showed that the median OS was 7.6 months for 66 patients with esophageal squamous cell carcinoma (ESCC).[7] Receipt of locoregional treatment, including brain surgery and radiotherapy, was associated with improved survival. For patients who received locoregional treatment, median OS was 10.9 months, while for patients without locoregional treatment, median OS was only 3.0 months.

In addition to treatment modalities, common factors affecting the survival of patients with brain metastases include the number of brain metastases, absence of extracranial

metastases, and Karnofsky performance score (KPS). The graded prognostic assessment (GPA) index, as a more objective, quantitative, prognostic index, used some variables, including age, KPS, the number of brain metastases, and absence/presence of extracranial metastases, to estimate expected OS for patients with brain metastases.[8] In recent years, some studies have demonstrated that intracranial tumor volume may have some correlation with patient outcome and should be added into the diagnosis-specific GPA (DS-GPA) index, which is commonly reported in patients with lung cancer, breast cancer, melanoma, renal cell carcinoma, and so on.[9–15] Joshi et al. analyzed 718 patients with gastrointestinal cancer treated with stereotactic radiosurgery (SRS) for brain metastases.[9] The study demonstrated that cumulative intracranial tumor volume (CITV) was an important prognostic variable in these patients and it also augmented the prognostic accuracy of the gastrointestinal-specific GPA index. The results have some heterogeneity, however, because it does not collect information on the specific gastrointestinal cancer histology (e.g. esophageal or colon). In this study, we analyzed patients with EC and brain metastases to investigate if intracranial tumor volume is a predictor of these patients' survival.

MATERIALS AND METHODS

Patient population

In this study, consecutive patients with EC treated at the Fourth Hospital of Hebei Medical University between January 1, 2009 and May 31, 2020 were identified in an institutional tumor registry through a protocol approved by the institutional review board with waiver of informed consent. All included patients had no history of other malignant tumors, and diagnosis was pathologically confirmed as EC. The primary tumor in esophagus was restaged according to the eighth edition of the American Joint Committee on Cancer TNM staging classification for carcinoma of the esophagus and esophagogastric junction.[16] All included patients were diagnosed as brain metastases by contrast-enhanced computerized tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) or positron emission tomography- CT scans. Patients without images of brain metastases in the hospital information system were eliminated. Patients with esophageal small cell carcinoma were eliminated. The intracranial tumor volume was determined from thin-slice (1-mm) axial and coronal T1-weighted contrast-enhanced MRI or (3-mm) axial radiotherapy localization contrast-enhanced CT. All patients were followed to October 30, 2021 by outpatient clinical visit and/or telephone.

Statistical analysis

Outcome data was analyzed by SPSS 21.0 statistical software. OS was defined as the time from the diagnosis of brain metastases until death or last follow-up, with patients censored at date of last follow-up. The cut-off for CITV or largest intracranial tumor volume (LITV) was defined as the CITV/LITV that maximized sensitivity and minimized 1-specificity on the receiver-operating characteristic (ROC) curve with 6 months survival as the end point. The Kaplan–Meier

TABLE 1 Characteristics of patients

Clinical factors	Number of cases (%)
Gender	
Male	42 (80.8)
Female	10 (19.2)
Age	
<65	33 (63.5)
≥65	19 (36.5)
Pathological type	
Squamous cell carcinoma	46 (88.5)
Adenocarcinoma	5 (9.6)
Adenosquamous carcinoma	1 (1.9)
Lesion site	
Upper thoracic esophagus	5 (9.6)
Middle thoracic esophagus	24 (46.2)
Lower thoracic esophagus	23 (44.2)
Stage at initial diagnosis	
II	7 (13.5)
III	26 (50)
IV	19 (36.5)
Number of brain metastases	
1	33 (63.5)
2–3	14 (26.9)
>3	5 (9.6)
Extracranial metastases	
Yes	28 (53.8)
No	24 (46.2)
KPS	
<70	12 (23.1)
70–90	40 (76.9)
Gastrointestinal-specific GPA score[17]	
0–1	27 (51.9)
2–3	25 (48.1)
Control of primary lesion	
Yes	38 (73.1)
No	14 (26.9)
Treatment for brain metastases	
Locoregional and systematic treatment	20 (38.5)
Locoregional treatment alone	20 (38.5)
Systematic treatment alone	8 (15.3)
Symptomatic alone	4 (7.7)

Abbreviations: GPA, graded prognostic assessment; KPS, Karnofsky performance score.

method was used to estimate OS, and curves were compared by log-rank test. Cox proportional hazard regression analysis was used to perform the univariate analysis and multivariate analysis. All statistical tests were two-sided with $p = 0.05$.

RESULT

Patient characteristics

Fifty-two patients with brain metastases from EC were included in this study. The median time from diagnosis of EC to diagnosis of brain metastases was 12.0 months (range 0–136 months). There were 46 (88.5%) patients with ESCC, five (9.6%) with esophageal adenocarcinoma, and one (1.9%) with adenosquamous carcinoma. Thirty-three (63.5%) patients had single brain metastatic lesion and 19 (36.5%) patients had multiple brain metastatic lesions. Most patients had advanced stage at initial diagnosis, including 26 (50%) patients with stage III disease and 19 (36.5%) patients with stage IV disease. There were 28 (53.8%) patients with extracranial metastases, including lung, bone, liver, lymph node and soft tissue. Twenty (38.5%) patients received locoregional and systematic treatment for brain metastases, 20 (38.5%) locoregional treatment alone (including radiotherapy and surgery), eight (15.3%) systematic treatment alone, and four (7.7%) symptomatic treatment alone. Primary lesion was controlled in 38 (73.1%) patients. Patient characteristics are summarized in Table 1.

Intracranial tumor volume

The median CITV and LITV were 13.04 cm³ (range 0.2–92.9 cm³) and 11 cm³ (range 0.2–92 cm³), respectively.

According to the ROC curves, the cut-off values for CITV and LITV were 6.65 cm³ and 7.75 cm³, respectively. According to the cut-off values, patients were divided into a large CITV group and a small CITV group, a large LITV group and a small LITV group.
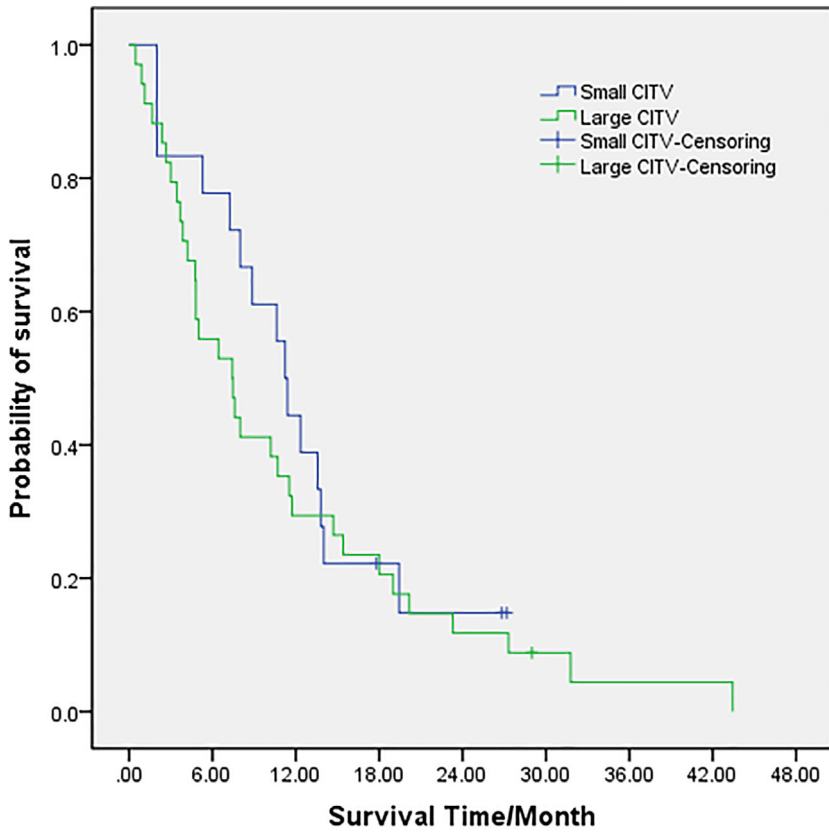
Survival

The median follow-up time duration was 8.4 months (interquartile range 4.0–15.2). At last follow-up, 48 patients were dead and four patients were alive. The median OS from time of brain metastases diagnosis was 8.0 months (95% confidence interval [CI] 4.278–11.722) for all cases, and survival rates at 6 and 12 months were 63.5% and 34.6%, respectively (Figure 1).

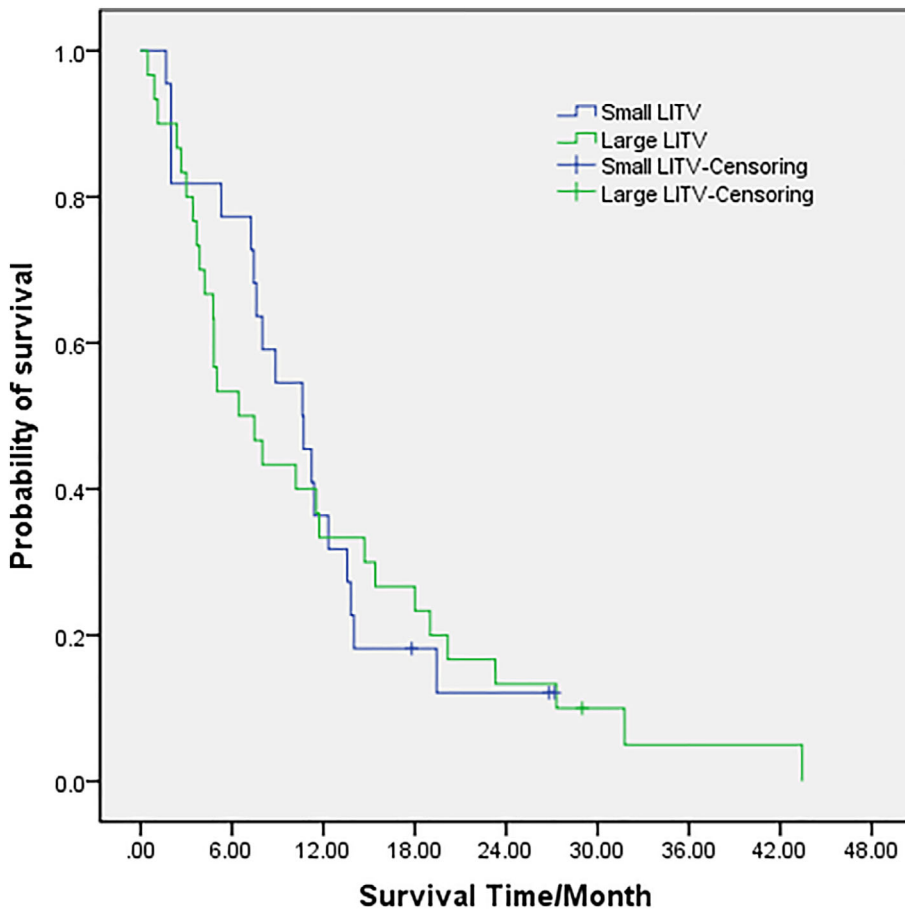For patients with small CITV (<6.65 cm³), median OS was 11.23 months (95% CI 9.629–12.831), and survival rates at 6 and 12 months were 77.8% and 44.4%, respectively. For patients with large CITV (≥6.65 cm³), median OS was 7.4 months (95% CI 3.716–11.144), and survival rates at 6 and 12 months were 55.9% and 29.4%, respectively. Univariate analysis demonstrated that CITV was not significantly associated with improved OS (hazard ratio [HR] 1.255, 95% CI 0.673–2.342, $p = 0.475$) (Figure 2). Multivariate analysis demonstrated that CITV was not
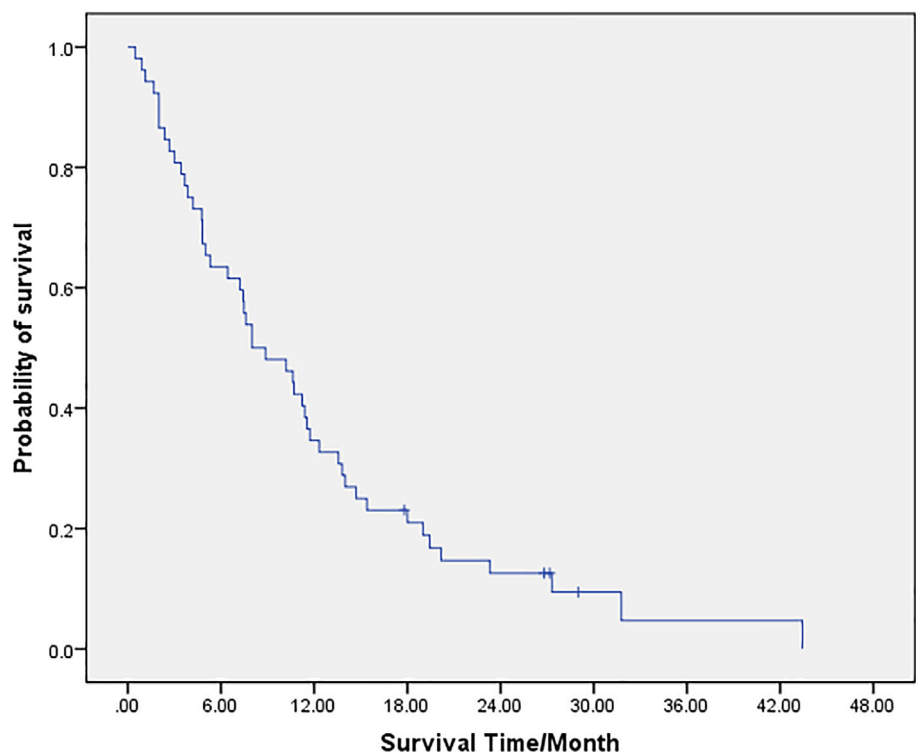
FIGURE 1 Kaplan–Meier estimates of survival from the time of diagnosis of brain metastases among all the patients

FIGURE 2 Kaplan–Meier estimates of survival from the time of diagnosis of brain metastases among patients with small CITV (blue line) and patients with large CITV (green line). CITV, cumulative intracranial tumor volume

FIGURE 3 Kaplan–Meier estimates of survival from the time of diagnosis of brain metastases among patients with small LITV (blue line) and patients with large LITV (green line). LITV, largest intracranial tumor volume

significantly associated with improved OS (HR 1.439, 95% CI 0.717–2.885, $p = 0.306$).

For patients with small LITV (<7.75 cm^3), median OS was 10.6 months (95% CI 6.918–14.342), and survival rates at 6 and 12 months were 77.3% and 36.4%, respectively. For patients with large LITV (≥7.75 cm^3), median OS was 6.4 months (95% CI 2.136–10.724), and survival rates at 6 and 12 months were 53.3% and 33.3%, respectively. Univariate analysis demonstrated that LITV was not significantly associated with improved OS (HR 1.037, 95% CI 0.570–1.887, $p = 0.904$) (Figure 3). Multivariate analysis demonstrated that LITV was not significantly associated with improved OS (HR 1.238, 95% CI 0.595–2.576, $p = 0.567$).

DISCUSSION

The GPA index was originally developed from a database of 1960 patients accrued to four Radiation Therapy Oncology Group (RTOG) protocols for patients with brain metastases.[8] In this study, GPA index was compared with three other indices, including the RTOG recursive partitioning analysis, the score index for radiosurgery (SIR), and the basic score for brain metastases. Of the four indices, the GPA index is the least subjective, the most quantitative, and the easiest to use and remember. Patients with GPA of 4.0 may have the best prognosis. While some scholars thought that patients with brain metastases might be a heterogeneous population so that no duplicate factors were appropriate for all patients. Then, DS-GPA index was developed.[18,19] The DS-GPA index is a valuable tool for clinicians when making treatment decisions, e.g. aggressive treatment or hospice care. It can also be used to conduct stratified analysis in clinical trials so that treatment effects can be analyzed accurately. The adjusted DS-GPA index of different cancers was also different. For example, lung-specific GPA includes some variables for age, KPS, number of brain metastases, and extracranial metastases (presence and absence), melanoma-specific GPA includes some variables of KPS and the number of brain metastases, and gastrointestinal-specific GPA only includes one variable of KPS.

In recent years, some researchers have begun to realize that intracranial tumor volume might affect the prognosis and should be added into the DS-GPA index. We know that the largest lesion volume is one of the prognostic factors for the SIR index. Many studies have explored the correlation of intracranial tumor volume and prognosis in patients with brain metastases, which are commonly reported in patients with lung cancer, breast cancer, melanoma, renal cell carcinoma, and so on. Baschnagel et al.[14] retrospectively reviewed 250 patients with brain metastases who had initially undergone gamma knife surgery and demonstrated that total tumor volume had a much stronger predictive value than the number of metastatic lesions. Tumor volume was associated with patient OS, distant brain failure, and local control, but the number of lesions was not. Marcus

et al.[10] analyzed the data of 365 patients with lung cancer and found that the addition of CITV to the lung-specific GPA index significantly improved its prognostic value. Another study studied 1427 patients undergoing SRS for brain metastases and showed that the number of lesions and the CITV were both important predictors of prognosis.[15] All this research has demonstrated that intracranial tumor volume is a significant prognostic factor and may be an appropriate selection criterion for SRS. Patients with multiple small lesions may also be good candidates for SRS. Intracranial tumor volume may be taken into consideration when predicting the prognosis of and treating patients with brain metastases.

There were also many similar studies as above, but study on gastrointestinal cancer was few. Joshi et al.[9] analyzed the prognostic importance of CITV in 718 patients with gastrointestinal brain metastasis treated with SRS. They used the Net Reclassification Index, integrated discrimination improvement, and the Akaike information criterion to carry out a statistical analysis, and found that a CITV cutoff of 12 cm^3 best augments the prognostic accuracy of gastrointestinal-specific GPA. However, the results have some heterogeneity as the data were collected from three institutions in Japan and America, and did not include information on the specific gastrointestinal cancer histology (e.g. esophageal or colon). In our study, we focused on the correlation of intracranial tumor volume and prognosis of 52 patients with brain metastases from EC, eliminating the partly effect of primary cancer on the prognosis. To the best of our knowledge, this is the first study to explore intracranial tumor volume in EC patients, and it may provide some information for clinical practice. The results showed that patients with small CITV (<6.65 cm^3) or LITV (<7.75 cm^3) had about 4 months longer OS than patients with large CITV (≥6.65 cm^3) or LITV (≥7.75 cm^3), but the results did not achieve statistical difference. Although positive results were obtained in some primary carcinomas with brain metastases (e.g. lung cancer), the conclusion might not be applicable to brain metastasis from EC, but it is very difficult to carry out related clinical research owing to the rare morbidity. Multicenter data collection should be recommended to explore further the relationship between intracranial tumor volume and prognosis of these patients. If intracranial tumor volume might not be an important prognostic factor, we should focus on ameliorating the GPA score of the patients and execute active locoregional treatment based on our previous research.[7]

In previous studies for patients with nongastrointestinal cancer, the optimal threshold of CITV for prognostic difference was often between 2 and 4 cm^3,[10–15] while in the study by Joshi et al.[9] the optimal threshold was 12 cm^3. In our study, the optimal threshold was 6.65 cm^3, thus gastrointestinal cancer might have lager threshold than that of other cancers, and different thresholds might reflect different biological characteristics in various tumors.

There are some limitations in this study. First, this is a retrospective study, and the sample size was very small

compared to previous studies. However, this is the first study to explore the correlation between intracranial tumor volume and prognosis in patients with EC. Second, in our previous study we analyzed the clinical characteristics, treatment modalities, and possible prognostic factors of patients with ESCC and brain metastases. In this study, we only analyzed the correlation of intracranial tumor volume and prognosis. This negative result was not suitable to be added to the DS-GPA index. Finally, as the limitation of data, we did not analyze the correlation of intracranial tumor volume and local tumor control, progression-free survival, and neurocognitive function.

In conclusion, EC patients with small intracranial tumor volume might have longer OS than those with large intracranial tumor volume. Due to the very small sample size, the results were not statistically different. Future studies with a larger sample size may validate the correlation of intracranial tumor volume and patient survival.

CONFLICT OF INTEREST
All the authors declare no conflicts of interest.

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