Received: 6 July 2021 | Accepted: 10 September 2021

DOI: 10.1111/1759-7714.14167

ORIGINAL ARTICLE

WILEY

Clinicopathological characteristics and prognosis of brain metastases in elderly patients with esophageal carcinoma

Yi Wang[1†] | Linlin Xiao[1†] | Jiandong Zhang[2] | Xiaoyan Lv[1] | Feng Cao[1] | Min Zhao[3] | Fengpeng Wu[1] | Shaowu Jing[1] | Jun Wang[1]

[1]Department of Radiation Oncology, Fourth Hospital of Hebei Medical University, Shijiazhuang, China

[2]Department of Radiation Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan, China

[3]Department of Oncology, Hebei Chest Hospital, Research Center of Hebei Lung Cancer Prevention and Treatment, Shijiazhuang, China

Correspondence
Jun Wang, Department of Radiation Oncology, Fourth Hospital of Hebei Medical University, Jiankang Road #12, Shijiazhuang, Hebei 050011, China.
Email: wangjunzr@163.com

Funding information
Medical Science Research Key Projects of Hebei Provincial Department, Grant/Award Number: ZD20140060; the 2016 Beijing Hope Marathon Fund of China Cancer Foundation, Grant/Award Number: LC2016W10

Abstract

Background: Brain metastases (BM) from esophageal carcinoma (EC) is clinically rare and has not yet been reported in elderly patients. This study aimed to investigate the clinicopathological characteristics, outcomes and prognostic factors of BM in elderly patients with EC, in order to provide guidance for clinical practice.

Methods: A total of 20 EC patients older than 65 years who were diagnosed with BM were identified from the fourth Hospital of Hebei Medical University between January 1, 2009 and December 31, 2018. Survival was evaluated by the Kaplan–Meier method and Cox proportional hazards models.

Results: The median time from diagnosis of EC to BM was 11.8 months (0–249.2 months). The median overall survival (OS) was 4.8 months (1.13–23.3 months), with 20% of patients achieving the 1-year survival rate. Patients with KPS score of ≥70 had a significantly better OS than those with KPS score<70 (8.4 vs. 3.9 months, $p = 0.033$). Compared to patients without brain radiotherapy, patients with brain radiotherapy showed better outcomes in both median OS (8.4 vs. 2.9 months) and 1-year survival rate (23.1% vs. 14.3%, $p = 0.043$). The median OS of patients with radiotherapy combined with chemotherapy and/or targeted therapy and radiotherapy alone was 9.7 months (3.4–23.3 months) and 7.2 months (1.7–18.4 months), respectively, with no significant difference between the two groups ($p = 0.215$).

Conclusions: Brain radiotherapy provided clinically meaningful survival benefit for elderly patients with BM from EC. Thus, active treatments for those patients might be required.

KEYWORDS
brain metastases, elderly patients, esophageal carcinoma, prognosis, radiotherapy

INTRODUCTION

Esophageal cancer (EC) is the seventh most common cancer and the sixth most common cancer cause of death worldwide.[1] In China, the mortality rate of EC ranks fourth, accounting for 50% of the global mortality.[2] The incidence of EC increases with patients' ages. Among patients with brain metastases (BM), statistical reports show that the proportion of patients over 70 years of age can reach 30% to 40%.[3]

In China, 70% of EC patients are in the middle to late stages, with the common distant metastasis sites of EC including the liver, bone and lung, yet rarely the brain. The incidence of BM among EC patients has been reported to be only 1.2%–1.7% in previous studies.[4–7] Compared to squamous cell carcinoma, patients with adenocarcinoma are more likely to have BM, with an incidence of 12.2% versus 0.49%–1.4%.[7,8] In addition, the clinical manifestations of BM in elderly patients may be more atypical or lack regularity due to their insensitivity to the physical conditions, conferring difficulties in the diagnosis and treatment. At present, most domestic and foreign

[†]Yi Wang and Linlin Xiao contributed equally to this study.

literature on BM from EC are case reports[9–11] and few studies have analyzed a large number of cases.[8] In particular, no research on BM from elderly EC patients has been reported to date.

Thus, we collected the data of BM from EC patients older than 65 years in our hospital over the last 10 years and aimed to explore their clinicopathological characteristics and prognosis, in order to assist in modifying their clinical management.

METHODS

Data resources and study population

This study reviewed more than 2000 elderly patients with EC in the Fourth Hospital of Hebei Medical University from January 2008 to December 2017. EC patients who were diagnosed with BM were retrospectively analyzed. All patients identified had no history of other malignant tumors. The primary EC lesion was confirmed by histopathological examination. The BM were identified and diagnosed by imaging examinations including computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT). Clinicopathological data and treatment methods were collected from medical records or via telephone follow-ups. The time of follow-up was calculated from the BM diagnosis to death or December 30, 2019. The overall survival (OS) was defined as the time from the BM diagnosis until death or the end of follow-up.

The patients were scored by special diagnostic evaluation prognostic scale (diagnosis-specific graded prognostic assessment, DS-GPA) standard. The prognosis of patients with BM from digestive-tract tumor was usually graded only according to the Karnofsky score (KPS);[12] patients with KPS ≤ 70 received one point, KPS equal to 80 received two points, 90 received three points and 100 received four points.

Statistical analysis

All statistical analysis was performed by SPSS 21.0 statistical software. The Fisher's exact test was used for comparison of clinicopathological data between patients in different groups. The Kaplan–Meier method was used to estimate OS and perform univariate analysis, and curves were compared by log-rank test. Cox proportional hazard regression analysis was used to perform the multivariate analysis. $p < 0.05$ was considered statistically significant.

RESULTS

In total, there were 20 EC elderly patients diagnosed with BM, of which 18 patients had esophageal squamous cell carcinoma and two had adenocarcinoma. Three cases were located in the upper thoracic segment, 12 in the middle thoracic segment, and five in the lower thoracic segment. Most patients had solitary BM (90%). Eight patients had one or more extracranial metastasis at the same time, including four with liver metastasis, four with lung metastasis, two with distant lymph-node metastasis and one with soft-tissue metastasis. In this study, five patients had a DS-GPA score of 0 points, five patients had one point, nine patients had two points, and one patient had three points (see Table 1 for details).

TABLE 1 Characteristics of brain metastases in patients

Clinical factors	Number of cases(%)
Gender	
Male	13 (65%)
Female	7 (35%)
Pathological type	
Squamous cell carcinoma	18 (90%)
Adenocarcinoma	2 (10%)
Lesion site	
Upper thoracic esophagus	3 (15%)
Middle thoracic esophagus	12 (60%)
Lower thoracic esophagus	5 (25%)
Brain metastases	
Single	18 (90%)
Multiple	2 (10%)
Extracranial metastases	
Yes	8 (40%)
No	12 (60%)
KPS score	
≥70	13(65%)
<70	7(35%)
DS-GPA score	
0–1	10 (50%)
2–3	10 (50%)
Treatment	
Radiotherapy alone	9 (45%)
Chemoradiotherapy	4 (20%)
Chemotherapy alone	1 (5%)
Symptomatic alone	6 (30%)

Therapeutic modalities

Among the 20 patients, 13 patients received brain radiotherapy, one received systemic therapy alone, and six received supportive care alone. Among the 13 patients who received brain radiotherapy, nine cases were treated with radiotherapy alone, and four cases were treated with chemotherapy and/or targeted therapy. One patient was treated with stereotactic radiosurgery (SRS) and 12 patients received conventionally fractionated radiotherapy to the lesion(s) and (or) whole brain radiotherapy (WBRT) (Table 2).

TABLE 2 Clinicopathological characteristics of EC patients with or without brain radiotherapy

Clinical factors	Patients with brain radiotherapy	Patients without brain radiotherapy	*p*-value
Gender			0.329
Male	7	6	
Female	6	1	
Primary lesion site			0.356
Middle thoracic esophagus	9	3	
Other thoracic esophagus	4	4	
Brain metastases			1.000
Single	12	6	
Multiple	1	1	
Extracranial metastases			1.000
Yes	5	3	
No	8	4	
KPS score			
≥70	9	4	0.651
<70	4	3	
DS-GPA score			1.000
0–1	6	4	
2–3	7	3	

Patient outcomes

At the last follow-up, all patients had died. The median time from the diagnosis of EC to BM was 11.8 months (0–249.2 months). The median OS was 4.8 months (1.13–23.3 months), with 20% of patients achieving the 1-year survival rate. Compared to patients without brain radiotherapy, patients with brain radiotherapy showed better outcomes in both median OS (8.4 vs. 2.9 months) and 1-year survival rate (23.1% vs. 14.3%, $p = 0.043$) (Table 3, Figure 1). The median OS of patients with radiotherapy combined with chemotherapy and/or targeted therapy and radiotherapy alone was 9.7 months (3.4–23.3 months) and 7.2 months (1.7–18.4 months), respectively, with no significant difference between the two groups ($p = 0.215$). Multivariate analysis showed that no variate was significantly associated with improved OS.

DISCUSSION

In this cohort study, the clinical characteristics and prognosis of elderly EC patients with BM over the last 10 years in our hospital were statistically analyzed. This is the first study to explore the BM from EC in elderly patients. In previous studies, Go et al.[4] analyzed the data of seven EC studies and found that the interval between the diagnosis of EC and the occurrence of BM was 5.6–12.3 months. Song et al.[8] revealed the median age of 73 esophageal squamous cell carcinoma patients was 58 years (17–82 years), and the median interval was 7.13 months (0–30.54 months). Our study focused on elderly patients with BM from EC, and the median time from diagnosis of EC to BM was 11.8 months, which was longer than that of nonelderly patients in the above study. The reason may be that the disease progressed slowly, or the metabolic function of elderly patients was too poor to detect their symptoms in time.

Elderly patients who develop EC also suffer from loss of physiological function because of their age and other complications, such as hypertension, diabetes and cardiovascular disease. As a result, their ability to resist external trauma, drugs, radiation and other lethal stress is poor and they are prone to decline in immunity, organ dysfunction, with slow self-healing after treatment. Thus, for elderly patients, regular comprehensive review during treatment and follow-up is very important. Caution should be taken with regard to rare metastasis appearing in organs such as the brain to avoid the possibility that the symptoms caused by metastases are being hidden by senile diseases. The optimal therapeutic modalities should be treated individually. At present, the clinical treatment of BM mainly includes surgery, radiotherapy and chemotherapy. Most of these therapeutic modalities are suitable for patients accompanied with single BM with good general condition and no extracranial metastasis. Up to 90% of patients had single BM in this study; however, no patients were treated surgically. Elderly patients often have underlying diseases and poor physique, and they cannot tolerate surgical treatment, such as craniotomy. In addition, eight of the 20 patients had accompanying extracranial metastasis except for BM and about 40% had multiple organ metastases. Surgical treatment was limited, and most patients underwent symptomatic conservative treatment. The number of cases receiving radiotherapy to the brain was also low. Among the seven patients who did not receive brain radiotherapy, three had low KPS score which were 20, 30, 50 and were unable to tolerate radiotherapy. Two patients had complications with liver or lung metastasis at the same time, and receiving brain radiotherapy alone may not improve patient survival. Two refused to continue their treatment because of family reasons. For patients with advanced cancer, participation in local treatment may not be ideal in the real world.

Brain radiotherapy is the standard treatment for BM. Song et al.[7] retrospectively analyzed 26 patients with BM from EC (including 12 patients with single BM and 14 with multiple metastasis), and the results showed that the overall median survival time was 4.2 months (7.0 months in the surgery group vs. 4.0 months in the radiotherapy group vs. 1.8 months in the chemotherapy group). Notably, all five patients received WBRT after surgery. Song et al.[8] retrospectively analyzed 73 patients with BM from esophageal squamous cell carcinoma: a total of 48 patients received simple brain radiotherapy, and 21 did not receive local treatment. Results showed that the median OS was 7.13 months in the radiotherapy group and 3.4 months in the nonradiotherapy group. Xiangqun et al.[10]

TABLE 3 Univariate analysis of prognosis

Median	Patients number	Median survival (month)	X^2 value	*p*-value
Sex			0.657	0.418
Male	13	4.8		
Female	7	7.2		
Pathological type			0.004	0.948
Squamous cell carcinoma	18	4.8		
Adenocarcinoma	2	6.4		
Primary lesion site			1.727	0.422
Upper thoracic esophagus	3	7.2		
Middle thoracic esophagus	12	4.8		
Lower thoracic esophagus	5	4.2		
Extracranial metastasis			3.451	0.063
Yes	8	4.2		
No	12	8.4		
Brain metastases			0.161	0.688
Single	18	4.8		
Multiple	2	2.3		
Location			2.684	0.261
Supratentorial	14	6.4		
Infratentorial	4	3.4		
Supra- and infratentorial	2	3.9		
KPS score			4.547	0.033
≥70	13	8.4		
<70	7	3.9		
DS-GPA score			0.814	0.367
0–1	10	3.4		
2–3	10	7.2		
Brain radiotherapy			4.080	0.043
Yes	13	8.4		
No	7	2.9		

also found that postoperative radiotherapy could significantly prolong the median OS (65.5 months vs. 17.7 months) in EC patients with single BM. As for our study, the median OS in patients with brain radiotherapy was 8.4 months compared to 2.9 months in patients without brain radiotherapy ($p = 0.043$). The results indicated that even for elderly patients with EC, the median OS in patients with radiotherapy was nearly three times higher than those without. Moreover, active radiotherapy for craniocerebral metastasis significantly prolonged the survival of patients.

The vast majority of reports anatomically categorize brain metastases as supratentorial or infratentorial.[13] In this study, we also divided patients into supratentorial, infratentorial and supratentorial and infratentorial groups. The results showed that the median survival time was 6.4, 3.4 and 3.9 months, respectively ($X^2 = 2.684$, $p = 0.261$). The median survival time of patients with supratentorial metastasis may be longer than those with infatentorial metastasis, suggesting that the prognosis of patients with infratentorial metastasis is poor. These results are consistent with other studies.[14,15] As the loss of imaging data for some patients and the small sample may deviate the results, we did not analyze the effect of tumor volume on the prognosis of patients with brain metastasis in this study. We will analyze it in a larger sample in the future.

Chemotherapy is a controversial treatment for BM. Due to the existence of the blood–brain barrier, the effect of chemotherapy alone is unsatisfactory. Among the 13 patients who received brain radiotherapy, nine were treated with radiotherapy alone, and four were treated with chemotherapy and/or targeted therapy. The results showed that compared with radiotherapy alone, combined therapy brought clinical survival benefit by 2.5 months (9.7 months vs. 7.2 months). This revealed that active and effective systematic treatment simultaneously conducted with radiotherapy might benefit the survival of patients. No statistical difference existed between the two groups, which might be due to the low number of cases. Moreover, among the 20 patients, only five received systematic treatment,

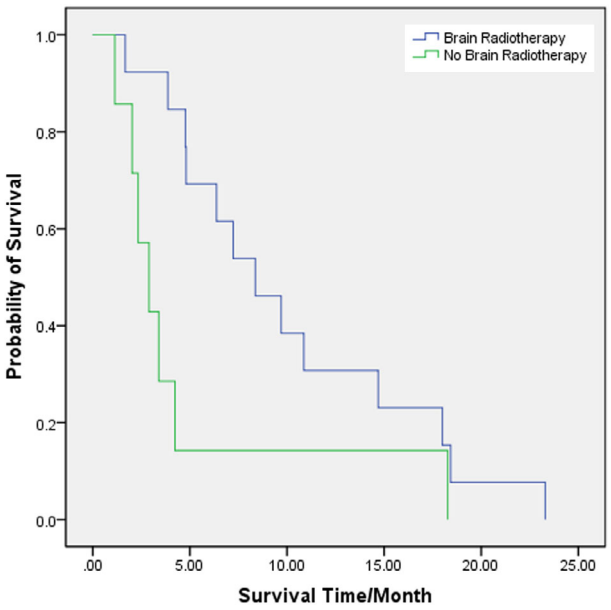

FIGURE 1 Effect of brain radiotherapy on the survival of patients

accounting for only 25%. Thus, to a certain extent, effective systemic treatment for elderly patients with EC was seriously inadequate. Based on the survival curve, the benefit of radiotherapy to patients with BM from EC was primarily reflected in the first year. Because of the lack of systemic therapy, local radiotherapy is hard to improve the long-term survival of patients.

We used the DS-GPA grading system to stratify the prognosis of EC patients with BM.[4] Some studies have shown that KPS score is the prognostic factor of DS-GPA grading standard for BM from digestive tract tumors.[16] It is also a factor affecting the prognosis and survival of EC patients with BM.[7,8,12] Accordingly, we used DS-GPA based on KPS score, but no correlation was found between the DS-GPA score and prognosis of patients. The nonstatistical difference was primarily due to the small samples. Various studies have shown that good KPS score had a statistically significant impact on survival in patients with EC and brain metastases.[6,7] We also found that patients with KPS score of ≥70 had a significantly better OS than those with KPS score<70 (8.4 vs. 3.9 months, $p = 0.033$). It also indicted that poor prognosis in elderly patients with EC might result from their generally poor condition.

However, the OS was still unsatisfactory in our study, and the longest survival time of patients was only 23.3 months. A large sample prospective group study is needed to further analyze the survival benefits of radiotherapy combined with chemotherapy, targeting, immunity and other treatments, as well as the local control and survival rates of different modes of radiotherapy to provide guidance for clinical treatment. We found none of the patients with BM were treated by surgery. Previous studies have shown that the surgical treatment of single intracranial metastasis could prolong survival.[17] The effects of surgical treatment of BM in patients with good physical condition also needs to be followed up and compared in future studies to provide individualized treatment advice to elderly EC patients with BM. However, in the real world, the rate of BM from esophageal squamous cell carcinoma is lower; that is, only 0.49%–1.4%. In China, squamous cell carcinoma is the main type of EC, accounting for about 90% of all patients. The difficulty of enrollment is the primary limitation in future relevant prospective studies.

In summary, because of the poor function of various organs and a variety of coexist chronic diseases in elderly patients diagnosed with BM from EC, the treatment strategies should be distinct from nonelderly patients. The results of this study showed that solitary BM was more common in elderly EC patients compare to multiple metastases. Brain radiotherapy may prolong the survival of elderly EC patients with BM. On this basis, active and effective systematic treatment may to a certain extent bring survival benefits for patients.

ACKNOWLEDGMENTS

The authors sincerely thank Ms Chen-xi Ma from MSD China Medical Affair, for her constructive comments and language instruction during the draft and review of this manuscript. This study was funded by the 2016 Beijing Hope Marathon Fund of China Cancer Foundation (LC2016W10), Medical Science Research Key Projects of Hebei Provincial Department (ZD20140060), and Hebei Clinical Research Center for Radiation Oncology and Oncology Department of Hebei Medical University.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Min Zhao https://orcid.org/0000-0003-3745-9539
Jun Wang https://orcid.org/0000-0002-9733-1433

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32. https://doi.org/10.3322/caac.21338 Epub 2016 Jan 25.
3. Wu M, Van't Veer P, Zhang ZF, Wang XS, Gu XP, Han RQ, et al. A large proportion of esophageal cancer cases and the incidence difference between regions are attributable to lifestyle risk factors in China. Cancer Lett. 2011;308(2):189–96.
4. Go PH, Klaassen Z, Meadows MC, Chamberlain RS. Gastrointestinal cancer and brain metastasis: a rare and ominous sign. Cancer. 2011;117(16):3630–40.
5. Weinberg JS, Suki D, Hanbali F, Cohen ZR, Lenzi R, Sawaya R. Metastasis of esophageal carcinoma to the brain. Cancer. 2003;98(9):1925–33.
6. Ogawa K, Toita T, Sueyama H, Fuwa N, Kakinohana Y, Kamata M, et al. Brain metastases from esophageal carcinoma: natural history, prognostic factors, and outcome. Cancer. 2002;94(3):759–64.

7. Song Z, Lin B, Shao L, Zhang Y. Brain metastases from esophageal cancer: clinical review of 26 cases. World Neurosurg. 2014;81(1):131–5. https://doi.org/10.1016/j.wneu.2013.02.058
8. Song H, Song X, Li H, et al. Prognostic analysis of 73 cases of brain metastasis of esophageal squamous cell carcinoma. Chin J Dig. 2017;37(2):106.
9. Qi H, Wang Z, Zhang X. Occipital brain metastasis of esophageal carcinoma: a case report. Chin J Oncol. 2006;28(2):87.
10. Xiangqun W, Congwen Z, Cheng A. Clinical analysis of 17 cases of postoperative brain metastasis of esophageal carcinoma. J Pract Cancer. 2008;23(4):372–3.
11. Jianhong L, Hongwei L, Hu C. 11 cases of postoperative brain metastasis of esophageal carcinoma. Tumor Res Clin. 2008;20(12):853–4.
12. Nguyen T, Deangelis LM. Treatment of brain metastases. J Support Oncol. 2004;2(5):405–10. discussion 411-6.
13. Kancharla P, Ivanov A, Chan S, Ashamalla H, Huang RY, Yanagihara TK. The effect of brain metastasis location on clinical outcomes: a review of the literature. Neurooncol Adv. 2019;1(1):vdz017.
14. Emery A, Trifiletti DM, Romano KD, Patel N, Smolkin ME, Sheehan JP. More than just the number of brain metastases: evaluating the impact of brain metastasis location and relative volume on overall survival after stereotactic radiosurgery. World Neurosurg. 2017;99:111–7.
15. Cacho-Díaz B, Lorenzana-Mendoza NA, Chávez-Hernandez JD, González-Aguilar A, Reyes-Soto G, Herrera-Gómez Á. Clinical manifestations and location of brain metastases as prognostic markers. Curr Probl Cancer. 2019;43(4):312–23.
16. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70(2):510–4.
17. Kothari N, Mellon E, Hoffe SE, Frakes J, Shridhar R, Pimiento J, et al. Outcomes in patients with brain metastasis from esophageal carcinoma. J Gastrointest Oncol. 2016;7(4):562–9.

How to cite this article: Wang Y, Xiao L, Zhang J, Lv X, Cao F, Zhao M, et al. Clinicopathological characteristics and prognosis of brain metastases in elderly patients with esophageal carcinoma. Thorac Cancer. 2021;12:3005–10. https://doi.org/10.1111/1759-7714.14167