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ORIGINAL ARTICLE

Stereotactic radiosurgery for the treatment of esophageal carcinoma brain metastases

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Summary

Purpose: *The authors evaluated the results of stereotactic radiosurgery (SRS) for the treatment of metastatic brain tumors from esophageal carcinoma.*

Methods: *We retrospectively analyzed the clinical characteristics and treatment outcomes in 21 patients with metastatic brain tumors from esophageal carcinoma who underwent SRS between July 2011 and February 2019.*

Results: *21 patients (25 SRS procedures) of a total of 88 tumors underwent Gamma knife SRS. Tumor histology was adenocarcinoma in 6 patients (28.6%) and squamous cell carcinoma in 15 patients (71.4%). The median age was 66 years (range 58-73). Eleven patients (52.4%) presented with multiple metastases (range 2-11), and 10 (47.6%) with a single metastasis. The median tumor volume was 0.55 cm^3 (range 0.004-44.64 cm^3). No complications related to radiosurgical treatment were identified. The local tumor control rate in this group was 94.2 %. The median survival time from the diagnosis of esophageal cancer was 22 months and the median survival from SRS was 16 months. Higher Karnofsky Performance Scale (KPS) at the time of procedure was associated with increased survival (p=0.003). After SRS, 4 patients had subsequent SRS (1 for boost therapy, 3 for new metastatic deposits), 1 patient underwent craniotomy due to tumor progression. Of the 19 patients who have died, 17 (89.5%) succumbed to systemic disease progression and 2 (10.5%) had neurologic deaths.*

Conclusion: *SRS is an effective and minimally invasive treatment that can prolong survival. Accordingly, SRS could be used as the initial treatment modality, if possible, even in patients with multiple metastases.*

Key words: *stereotactic radiosurgery, gamma knife, esophageal carcinoma, brain metastases*

Introduction

As compared to lung and breast cancer, esophageal carcinoma rarely metastasizes to the brain, In the available literature, the incidence of brain metastasis is constant at 0%-5% [1,2]. Current treatment options are mainly based on local therapy approaches such as neurosurgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or a combination of them [3-7]. In the past decades, SRS has become a well-established treatment modality for local control for a number of tumor subtypes [8,9]. The typically spherical, well-circumscribed morphology of brain metastases provide ideal targets for SRS. Recent studies have shown a favorable response to SRS with better local control and improved survival in brain metastases secondary to esophageal carcinoma.

Because of the rarity of these metastases, there are no firm guidelines with respect to treatment that should be undertaken in these patients. Randomized treatment evaluations specific to this his-

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tology are not possible due to the small number of patients. We therefore performed a retrospective review of our institution using SRS for treating brain metastases secondary to esophageal carcinoma, with a focus on identifying predictors of response to achieve local control and correlates of survival, as well as a description of the treatment modalities and their outcomes.

Methods

Patients and setting

We retrospectively reviewed the medical records of patients with brain metastases from esophageal carcinoma treated by SRS at our institution between July 2011 and February 2019. This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. Signed written informed consents were obtained from all participants before the study entry.

Table 1. Patient characteristics and radiosurgical parameters

Characteristics	*Number of patients*
Age (years)	
Median	66
Range	58-73
Gender	
Male	18
Female	3
Histology	
Adenocarcinoma	6
Squamous cell carcinoma	15
Metastasis treated (patients)	
Single	10
Multiple	11
Other metastatic sites	
Liver	4
Lung	2
Other	1
KPS	
Median	80
Range	60-100
RTOG RPA class	
I and II	17
III	4
Tumor size in volume (cm^3)	
Median	0.55
Range	0.004-44.64
Marginal does prescribed (Gy)	
Median	15.0
Range	10.0-22.0

Stereotactic radiosurgery protocol

SRS was performed using the Leksell Gamma Knife (Elekta AB, Stockholm, Sweden) model Perfexion. The expanded technical elements of this procedure have been detailed in our previous publications [10]. On the day of treatment, the Leksell frame G was applied under local anesthesia. A high resolution and volumetric adolinium-enhanced magnetic resonance image was obtained for dose planning. The radiosurgery isodose and marginal dose prescribed are usually determined on the basis of the Radiation Therapy Oncology Group (RTOG) 90-05 dosing guidelines with modifications [11]. At the conclusion of treatment, all patients received 40 mg of intravenous methylprednisolone. The final prescription dose expressed as a marginal dose, isodose line and other associated treatment parameters are summarized in Table 1. Clinical and imaging follow-up (MRI when possible) was requested at 3-month intervals after SRS. If the intracranial disease burden increased as a result of new metastases or tumor growth, a repeat SRS procedure was recommended.

Statistics

Survival analyses were performed for time to progression of individual metastatic lesions. Overall survival estimates were determined using the Kaplan-Meier method. Exploratory univariate Cox proportional hazards regression analysis was used to identify independent variables associated with survival. Given the limitations of the sample size, multivariate regression analysis was not performed. All analyses were performed using SPSS version 17 (SPSS, Inc., Chicago, IL, USA). P value <0.05 was considered statistically significant.

Results

Patient population and dosimetry parameters

All 21 patients were treated with SRS at our institution between 2011 and 2019. During this period a total of 856 patients underwent SRS for intracranial brain metastases. This patient cohort underwent 25 SRS procedures with a total of 88 tumors treated. The histologic esophageal cell of origin were adenocarcinoma in 6 patients (28.6%) and squamous cell carcinoma in 15 (71.4%). Three females (14.3%) and 18 males (85.7%) were included in this study. The median age was 66 years (range 58-73). The initial presentation of these patients included the development of a neurological deficit in 8 patients (38.1%). Five patients had limb weakness, two patients presented with gait disorders and one patient had aphasia. The other presentations included headache in six patients (28.6%) or onset of seizures in three (14.3%).

In this patient series, there was a median time interval of 8 months between primary diagnosis and presentation with intracranial metastases. Five patients (23.8%) had a synchronous diagnosis.

Eleven patients (52.4%) presented with multiple metastases (range 2-11), and 10 (47.6%) presented with a solitary metastasis. Extracranial metastases were present in 5 patients at the time of SRS.

The median Karnofsky performance status (KPS) score was 80 (range 60-100). Stratification by recursive partitioning analysis (RPA) devised by the Radiation Therapy Oncology Group's (RTOG) [12] showed class I in 5 patients (23.8%), class II in 12 patients (57.1%) and class III in 4 patients (19.1%). The median follow-up was 16 months (range 4-54). The median prescription dose was 15 Gy (range 10-22). The median tumor volume was 0.55 cm^3 (range 0.004-44.64).

Outcome and prognostic analysis

The local tumor control rate was 94.2% at 3 months after SRS as assessed in 86 tumors (98.8% of the tumors treated) with imaging response follow-up. Complete regression occurred in 11 tumors (12.8%), partial regression occurred in 55 tumors (64.0%), no change was evident in 15 tumors (17.4 %), and continued tumor growth occurred in 5 tumors (5.8%).

During the follow-up period, one patient received boost radiosurgery one month later because of its big tumor volume and low marginal dose (10Gy) at the first time of SRS. Three patients subsequently developed new metastases that required repeat SRS, one patient underwent a craniotomy 6 months after initial SRS due to tumor progression and refractory peri-tumoral edema. Eighteen patients experienced improvement of neurological symptoms at 3 months follow-up. No complications related to the radiosurgical treatment were identified. Nineteen of the 21 patients have died and two were alive at the end of follow-up. Seventeen (89.5%) succumbed to systemic disease progression and 2 (10.5%) due to neurologic reasons.

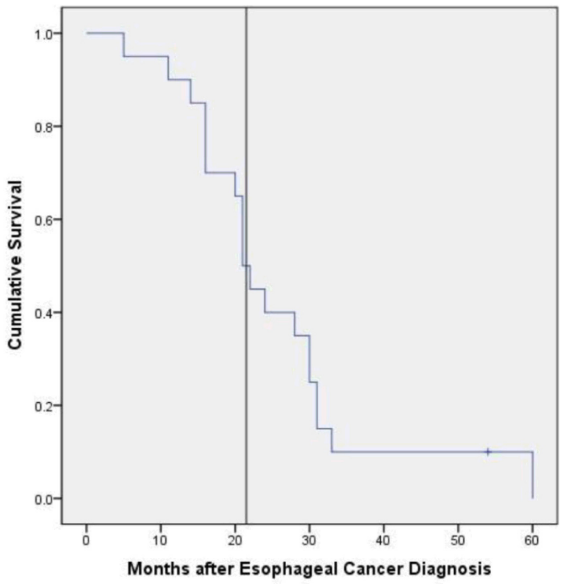

Figure 1. Kaplan-Meier curve depicting survival from the date of esophageal cancer diagnosis. The vertical line represents the time of 50% survival.

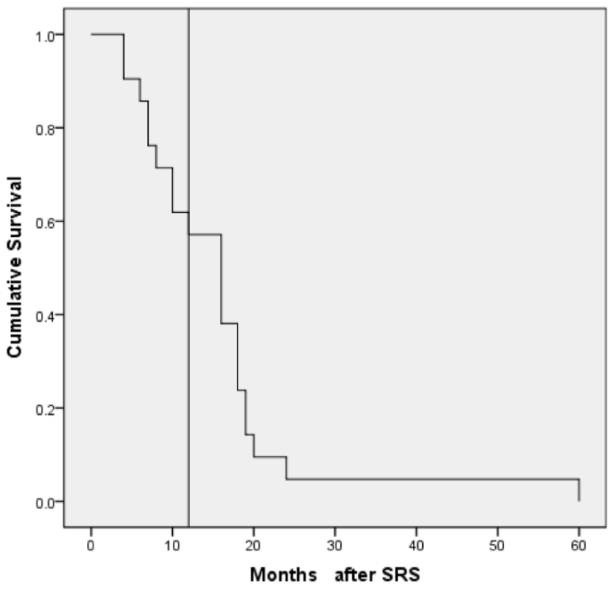

Figure 2. Kaplan-Meier curve depicting survival from the date of SRS. The vertical line represents the time of 50% survival.

Table 2. The results of statistical analyses for overall survival

	Univariate Cox proportional hazards regression analyses		
	HR	*95%CI*	*p value*
Age (>66 years)	1.390	0.572-3.380	0.467
Female gender	0.796	0.226-2.798	0.796
Tumor histologic subtypes	0.695	0.261-1.852	0.467
Karnofsky performance status (>70)	0.038	0.005-0.312	0.002
RTOG RPA I and II versus III	0.096	0.022-0.421	0.002
Single versus multiple	0.640	0.252-1.626	0.348

The median overall survival time after esophageal cancer diagnosis was 22 months (range 5-60). The 1-year survival rate after diagnosis was 90%, after 2 years was 40%, after 3 years was 10%, and after 5 years was 5% (Figure 1). The median overall survival after SRS was 16 months (range 4-54). This corresponded to a 6 months survival rate of 90% and a 12 months survival rate of 60% (Figure 2). A higher KPS at SRS was associated with increased survival time (p=0.002). RPA analysis demonstrated a median survival after SRS of 18 months in class I, 16 months in class II and 8 month in class III. Survival time decreased as the RPA class increased (p=0.002). A higher number of brain metastasis (p=0.348), the gender (p=0.796), increasing age (p=0.467) and tumor histological subtypes (p=0.467) were not correlated with survival. The results of the statistical analyses are summarized in Table 2.

Discussion

Brain metastases from esophageal carcinoma are very rare, but their incidence is rising in recent years due in part to prolonged survival associated with more effective systemic treatments [1,13]. In our series, the incidence was 2.64% (20/756). The most common histology in both primary tumor and brain metastases is adenocarcinoma in Western countries, whereas the most common histology in China and other Asian countries is squamous cell carcinoma. In our series, tumor histology was squamous cell carcinoma in 14 patients and adenocarcinoma in 6 patients. We found that tumor histologic subtypes were not associated with patient survival. This finding was also in agreement with the previously cited studies [1,14].

SRS has proven to be effective and a low risk management for a wide variety of patients with brain metastases. Some previously studies have demonstrated a high local control rate of 84-92% in patients with brain metastases from gastroesophageal cancer [15-17]. In this study, the local tumor control rate was 94.2%. No complications related to the radiosurgical treatment were identified, and 90% of patients experienced improvement of neurological symptoms at 3 months follow-up. All of our patients underwent SRS as initial treatment for intracranial esophageal metastasis. There was a lot of Level I evidence revealing no difference in local tumor control between the SRS alone and WBRT with or without SRS [18,19]. Three patients developed distant metastases and one patient showed tumor progression that required treatment. This supports the need for frequent clinical and imaging observations of the patients.

In this study, the median survival after diagnosis of the primary esophageal cancer was 21.5 months. This was similar with a previous research of 18 months after diagnosis [17]. The median survival after SRS for brain metastasis was 16 months compared with 3.8-4.2 months after the SRS reported by other authors [2,14,17,20]. These previous studies included some patients who had previous WBRT or surgery for brain metastasis. The results also illustrated that SRS, as the sole or principal therapeutic strategy, achieves excellent results. There were retrospective randomized studies in patients with gastrointestinal cancer evaluated WBRT and SRS versus SRS alone that found no evidence of improved overall survival with the addition of WBRT [21]. A higher KPS score at the time of SRS is correlated with increased survival. This finding is also supported by the existing literature [2,17,20]. A lot of studies had suggested that higher RPA class is associated with worse outcome among patients with all types of brain metastasis [12,22]. In the present study, although a trend was evident supporting a correlation between RPA classification and survival duration, no statistical significance was obtained. Decreasing survival as the RPA class increased trended toward significance without reaching it. The low patient numbers may be the most likely cause. Furthermore, age, number of brain metastases and total tumor volume were also not prognostic factors for patient survival, which is consistent with previous studies regarding multiple metastases [17,23,24].

The present study had several limitations. The clinical features of the patients were reviewed retrospectively and our patient sample size was small. In addition, the frequency of brain metastasis from esophageal carcinoma in our series probably underestimates the true frequency. However, considering the rarity of the disease, this study can provide useful information on the management of brain metastases from esophageal carcinoma.

Conclusions

The rarity of intracranial esophageal metastasis has resulted in no firm guidelines with respect to treatment that should be undertaken. This study demonstrates that SRS is an effective and minimally invasive treatment option for local control of brain metastases from esophageal carcinoma. Higher KPS scores were associated with increased survival and SRS could be used as the initial treatment modality, if possible, even in patients with multiple metastases.

Conflict of interests

The authors declare no conflict of interests.

References

1. Welch G, Ross HJ, Patel NP et al. Incidence of brain metastasis from esophageal cancer. Dis Esophagus 2017;30:1-6.
2. Song Z, Lin B, Shao L, Zhang Y. Brain metastases from esophageal cancer: clinical review of 26 cases. World Neurosurg 2014;81:131-5.
3. Sdralis E, Davakis S, Syllaios A, Mpaili E, Lorenzi B, Charalabopoulos A. Minimally invasive esophagectomy for esophageal cancer in octogenarians. Clinical and oncological outcomes. JBUON 2020;25:520-6.
4. Kaneko T, Hirao M, Shimada M et al. [Postoperative brain metastasis from esophageal carcinomas: report of 4 cases]. Kyobu Geka 1991;44:1013-7.
5. Koga H, Mukawa J, Miyagi K et al. Treatment of metastatic brain tumor from esophageal carcinoma--report of four cases. Neurol Med Chir (Tokyo) 1991;31:518-22.
6. Mandard AM, Chasle J, Marnay J et al. Autopsy findings in 111 cases of esophageal cancer. Cancer 1981;48:329-35.
7. Rembish J, Myers P, Kirby N et al. An evaluation of Pencil Beam vs Monte Carlo calculations for intracranial stereotactic radiosurgery. JBUON 2020;25:2731-6.
8. D'Ambrosio AL, DeYoung C, Isaacson SR. Radiosurgical management of brain metastases. Neurosurg Clin N Am 2011;22:45-51.
9. Kondziolka D, Flickinger JC, Lunsford LD. Radiosurgery for brain metastases. Prog Neurol Surg 2012;25:115-22.
10. Xu Q, Wu P, Feng Y, Ye K, Tong Y, Zhou Y. Gamma knife surgery for brain metastasis from hepatocellular carcinoma. PLoS One 2014;9:e88317.
11. Han JH, Kim DG, Kim CY, Chung HT, Jung HW. Stereotactic radiosurgery for large brain metastases. Prog Neurol Surg 2012;25:248-60.
12. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 2000;47:1001-6.
13. Rice TW, Khuntia D, Rybicki LA et al. Brain metastases from esophageal cancer: a phenomenon of adjuvant therapy? Ann Thorac Surg 2006;82:2042-9, 2041-9.
14. Weinberg JS, Suki D, Hanbali F, Cohen ZR, Lenzi R, Sawaya R. Metastasis of esophageal carcinoma to the brain. Cancer 2003;98:1925-33.
15. Da SA, Nagayama K, Schlesinger DJ, Sheehan JP. Gamma Knife surgery for brain metastases from gastrointestinal cancer. J Neurosurg 2009;111:423-30.
16. Hasegawa T, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brain metastases from gastrointestinal tract cancer. Surg Neurol 2003;60:506-14, 514-5.
17. Bowden G, Kano H, Tempel ZJ et al. Gamma knife radiosurgery for management of cerebral metastases from esophageal carcinoma. J Neurooncol 2014;118:141-6.
18. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 1999;45:427-34.
19. Andrews DW, Scott CB, Sperduto PW et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-72.
20. Ogawa K, Toita T, Sueyama H et al. Brain metastases from esophageal carcinoma: natural history, prognostic factors, and outcome. Cancer 2002;94:759-64.
21. Aoyama H, Shirato H, Tago M et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-91.
22. Han JH, Kim DG, Chung HT et al. Stereotactic radiosurgery for brain metastases from hepatocellular carcinoma. J Neurooncol 2013;115:45-51.
23. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys 2006;64:898-903.
24. Lee CC, Yen CP, Xu Z, Schlesinger D, Sheehan J. Large intracranial metastatic tumors treated by Gamma Knife surgery: outcomes and prognostic factors. J Neurosurg 2014;120:52-9.