

Brain metastases from esophageal cancer

A retrospective analysis of the outcome after surgical resection followed by radiotherapy

Pantelis Stavrinou, MD^a, Lars Plambeck^a, Martin Proescholdt, MD^c, Markus Ghadimi, MD^b, Roland Goldbrunner, MD^a, Stefan Grau, MD^{a,*}

Abstract

Brain metastases deriving from esophageal cancer are very rare with scarce data available concerning these patients' outcome. We, therefore, evaluated outcome after surgical resection followed by radiotherapy of brain metastasis from esophageal cancer.

A retrospective analysis was conducted on consecutive patients undergoing resection of brain metastasis from esophageal cancer in 2 neuro-oncological centers between 2008 and 2018. Clinical and demographic data were retrieved from electronic patient charts. Post-treatment survival was calculated using Kaplan–Meier estimates.

Twenty-five patients were identified. Treatment for primary disease comprised neo-adjuvant radio-chemotherapy followed by surgery (64.0%), surgery and adjuvant radio-chemotherapy (8.0%), radio-chemotherapy only (24.0%), and 1 patient receiving esophageal stenting only. Median time interval since initial diagnosis was 16 (range 0–110) months. All but 1 brain lesion were neurologically symptomatic and median Karnofsky performance score improved postoperatively from 70 to 80. After resection of brain metastases patients received whole-brain (n=13 (52.0%)) or local fractionated (n=9 (36.0%)) radiotherapy. In 2 patients adjuvant treatment was impeded by clinical deterioration; 1 patient refused radiotherapy. By the time of analysis 22 patients had died. Median survival after brain metastasis was 6 (95% CI 0.5–11.6) months.

Survival after resection of metastasis from esophageal cancer is poor compared to other tumor entities. Nevertheless, resection of symptomatic brain metastases may improve clinical status in the context of a palliative concept.

Abbreviations: BM = brain metastasis, EC = esophageal cancer, KPS = Karnofsky performance score, RPA = recursive partitioning analysis.

Keywords: brain metastasis, esophageal cancer, neurosurgery, survival

1. Introduction

While esophageal cancers (EC) frequently metastasize to the lung, liver, bone and lymph nodes,^[1] cerebral disease is a rare finding, and most publications can only provide a small number or represent case reports.^[2] A recent large cohort study reported a prevalence of 3.4% of brain metastases (BM) among patients with EC, and the histological subtype (adeno vs squamous cell carcinoma) influenced the probability of brain metastases.^[3] Only scarce data are available regarding the manifestation pattern of BM from EC, with most studies describing solitary

metastases in the majority of the cases; however these caused neurological symptoms in all patients described. Until now, patients with gastrointestinal tumors do not undergo regular screening for BM according to current guidelines.

While treatment algorithms for brain metastases of some solid tumors are under modification due to a growing number of targetable driver mutations, this is not the case for most gastrointestinal tumors, including esophageal carcinoma,

Traditionally, standard treatment for large, single or solitary and/or symptomatic BM is surgery followed by local or whole-brain radiotherapy, although radiosurgical techniques have replaced radiotherapy to a large extent, also in cases of multiple metastases.^[4] While for some tumor entities (e.g., melanoma or MSCLC) medical targeted treatments are available also with presumed activity in brain disease, the treatment of BM in EC still focuses on local regimens.

In this context different treatments such as surgical resection, local, or whole-brain radiation therapy or radiosurgery have been reported.^[5–7]

Due to the limited information and rarity of this disease, we retrospectively analyzed treatment outcomes of consecutive patients with surgically treated brain metastasis from esophageal cancers (ECBM).

2. Methods

2.1. Study design and patient data

This study was approved by the local ethical committees at both university hospitals (approval Nr. Regensburg 14-101-0298, Cologne 18-089).

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^a University Hospital of Cologne, Center for Neurosurgery, Department of General Neurosurgery, ^b University Hospital of Cologne, Department of General and Visceral surgery, University of Cologne, ^c Department of Neurosurgery, University of Regensburg, Germany.

* Correspondence: Stefan Grau, University Hospital of Cologne, Department of Neurosurgery, Kerpener Str. 67, 50937 Cologne, Germany (e-mail: Stefan.grau@uk-koeln.de).

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In this retrospective bi-centric study all adult (>18 years) patients with intracerebral metastasis from esophageal cancer undergoing resection between March 2008 and July 2018 at 2 University hospitals (University of Cologne and Regensburg) were identified. Patients' characteristics (age, gender, Karnofsky performance score (KPS) pre- and post-treatment), tumor parameters (first diagnosis, disease stage, type and number of metastatic tumors, local and systemic treatment) were analyzed.

The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) groups were calculated pre- and postoperatively. This classification has been demonstrated to predict the further course of patients with BM based on age, the neurological status (KPS), the number of BM and the systemic disease status at the time of BM diagnosis.^[8]

Surgery was performed via an osteoplastic craniotomy with the aid of intraoperative neuronavigation and/or ultrasound guidance. In cases of proximity to eloquent regions, intraoperative cortex stimulation was implemented. The extent of resection was assessed using an early cranial magnetic resonance imaging (cMRI) within 48 hours after surgery.

2.2. Statistical analysis

Descriptive statistics are provided as median and range or frequency and percentage. Post-surgical survival after BM resection, overall survival (since initial diagnosis) and potential influence of prognostic factors (age, pre- and postoperative Karnofsky Score (KPS), extra-cranial disease and RPA class) were calculated using the Kaplan–Meier method and log-rank test. Ordinal parameters were compared using a Wilcoxon test. *P* values <.05 were considered significant. Statistical analyses were performed using SPSS Statistics software (Release 22.0.0, SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline and clinical characteristics

Twenty-five patients were identified. The median age at diagnosis of brain metastasis (BM) was 61 (48–76) years. Twenty-one (84%) patients were male. Cancer subtypes were adenocarcinoma (*n*=19 (76%)) and squamous cell carcinoma (*n*=6 (25%)).

Allocation to Union for International Cancer Control (UICC) at the time of primary diagnosis is shown in Table 1. At the time of brain metastasis, all patients were assigned to class IVb.

Treatment of the primary tumor comprised neoadjuvant radio-chemotherapy followed by surgical resection (64.0%), surgery followed by radio-chemotherapy (8.0%), and definitive radio/chemotherapy (24%). One patient received esophageal stenting only.

Brain metastases were diagnosed using MRI (*n*=23) or cranial CT (*n*=2), which were performed due to neurological symptoms (23/25) or conspicuous findings on staging chest CT adjacent to the skull base (*n*=2). Brain lesions were single or solitary in 23 patients; 2 patients had oligometastatic disease with 2 or 3 metastases. Tumor location was supratentorial in 18 and infratentorial in 6 patients; 1 patient had supra- and infratentorial tumors. The median tumor diameter was 3.8 cm (range 2.1–4.7).

The median time interval between primary treatment and the development of BM was 16 (range 0–110) months. Four patients showed synchronous metastases (≤3 months since initial tumor diagnosis). Tumors were symptomatic in 23/25 patients.

Table 1

Demographic and clinical characteristics of esophageal cancer patients treated for brain metastases. (RPA = recursive partitioning analysis).

Parameter	N (25)
Gender (male/female)	21/4
Histology (n;%)	
Adenocarcinoma	19 (76)
Squamous cell carcinoma	6 (24)
Tumor diameter (cm, median; range)	3.8 (2.1–4.7)
UICC classification at primary diagnosis (n=20)	
I	4
II	3
III	5
IVb	8
Treatment of primary tumor (%)	
Neo-adjuvant radio-chemotherapy & surgery	64.0
Surgery & radio-chemotherapy	24.0
Radio-chemotherapy	8.0
Symptomatic only	0.4
Symptoms (n;%)	
Headache	6 (24)
Hemiparesis	7 (28)
Aphasia	4 (16)
Nausea/vomiting	7 (28)
Vertigo	9 (36)
Ataxia	9 (36)
Visual disturbance	3 (13)
Seizures	3 (13)
Location	
Supratentorial	18 (72)
Infratentorial	6 (24)
both	1 (4)
Karnofsky performance score	
Pre-operative	70 (40–100)
Post-operative	80 (0–100)
RPA	
Preoperative/postoperative	
Class 1	9/10
Class 2	13/12
Class 3	3/3

Recursive partitioning analysis (RPA) preoperatively assigned 9 patients (36.0%) to class I, 13 (52.0%) patients to class II and 3 (12.0) to class III.

Clinical and demographic data are summarized in Table 1.

3.2. Surgical and adjuvant treatment of brain metastasis

The indication for surgery as well as the adjuvant treatment concept was decided within an interdisciplinary tumor board in 23/25 patients. In these patients, surgery was indicated in cases of single or solitary metastases, or large, symptomatic tumors even in the presence of other metastases with a palliative intention as well as to enable further treatment. In 2 patients surgery was necessary due to acute symptoms and/or tumor-associated hemorrhage.

Gross total resection was achieved in 23/25 patients; in 2 patients adhesion of the tumor to cerebral vessels hindered radical resection.

Surgical complications occurred in 2 patients: 1 developed a sinus thrombosis and died in the early postoperative period, and in a second patient superficial wound infection required surgical intervention.

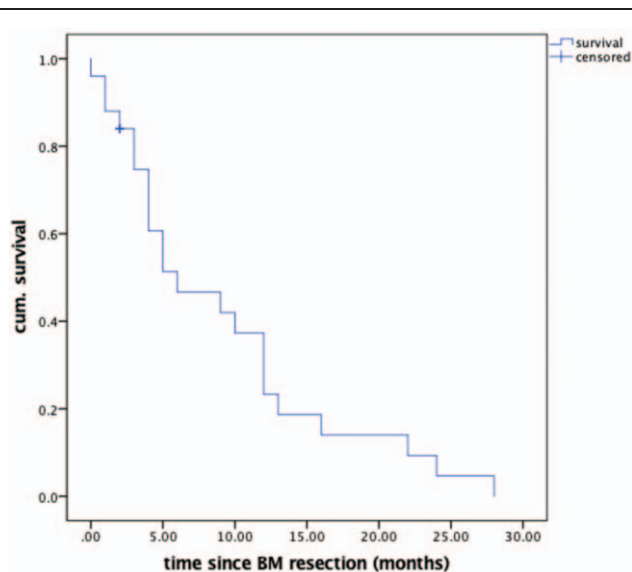


Figure 1. Kaplan–Meier survival curve for esophageal cancer patients surgically treated for brain metastases. The median survival was 6 (95% CI 0.5–11.6) months.

Median KPS was 70 (60–100) before surgery and 80 (80–100) at discharge, a difference that was statistically significant ($P = .03$, Wilcoxon test).

After resection of brain metastases patients received whole-brain (WBRT; $n = 13$ (54.2%)) or local fractionated ($n = 8$ (33.3%)) radiotherapy. In 2 patients adjuvant treatment was planned but not conducted due to clinical deterioration before the start of treatment.

3.3. Survival outcome

By the time of analysis 22 patients had died. Median survival after surgical removal of brain metastasis was 6 (95% CI 0.5–11.6) months (Fig. 1), overall survival since initial tumor treatment was 31 (95% CI 16.7–45.3) months. Nineteen patients died from systemic disease, 2 patients died from cerebral progressive disease, and in 1 patient the cause of death was unknown.

During their further course, 2 patients developed cerebral tumor recurrence, which was treated by radiosurgery.

Survival was not significantly influenced by tumor type (adenocarcinoma vs squamous cell carcinoma, $P = .214$), KPS (≥ 70 vs < 70 , $P = .381$) or age ≥ 70 ($P = .438$). The presence of extracranial metastases at the time of metastectomy also did not influence survival ($P = .211$). The number of BM (single/solitary vs oligo) was not decisive either ($P = .485$).

In consequence, recursive partitioning analysis (RPA) classes did not correlate with survival ($P = .36$).

The time interval since initial diagnosis did not influence post-BM survival. Patients with early metastases (≤ 6 months) showed a median survival of 5.5 months, while patients with later diagnosis of BM survived 6.3 months ($P = .981$) after BM resection.

4. Discussion

Currently, treatment paradigms for several tumors metastasizing to the brain, such as malignant melanoma or lung cancer, are

changing substantially due to novel therapies.^[9–12] For example, conventional WBRT is giving way to local radiotherapeutic and radiosurgical concepts to an increasing degree^[13] and medical treatments are on the rise.^[14]

Extensive data regarding various treatment concepts and their outcomes are available for the tumors most frequently causing brain metastases. However, due to the rarity of esophageal cancer and the very low incidence of cerebral metastasis no reliable data concerning treatment outcomes for these tumors exist. Previous reports demonstrated different modalities such as surgery alone, surgery combined with WBRT or radiosurgery with low numbers for each modality.

Despite the small number, this series may provide an insight into these patients' course after a surgical resection followed by focal or whole-brain radiotherapy.

In this cohort, survival after diagnosis of ECBM was comparable to other gastrointestinal tumors with brain metastases, but short compared to some other solid tumors, where higher post-resection survival rates are reported (e.g., for melanoma, breast, and lung cancer). However, other reported survival data for BMEC differ strongly: Yoshida published a series of 17 patients (with surgical resection in 10 patients) showing a median survival of 26.2^[7] months, while Weinberg et al reported a series of 27 patients surviving only 3.9 months^[5], which is similar to survival rates reported by Ogawa et al^[6] In a recent report Li et al found a post-metastectomy survival of 14.4 months.^[15] The data presented here may thus fit more into the range of the latter studies.

Due to the rarity of ECBM and the small cohort sizes reported above, the differing survival rates may thus reflect the heterogeneity of these patients as well as a significant bias in all these studies including the present one. This bias may particularly be seen in a neurosurgical focus on cerebral disease, disregarding the systemic disease course, which most probably defines the patient's further course to a greater extent than brain metastases do. This theory is supported by unchanged survival rates despite cerebral local control by postoperative radiotherapy or radiosurgery^[16–18] and—in this study—the vast majority of systemic deaths. Furthermore, the median time interval between initial diagnosis and treatment of the brain metastases was already in the upper range of reported overall survival rates^[1] of patients suffering from EC, thus the appearance of brain metastases may indicate the beginning of systemic progression, perhaps the earliest sign due to its associated neurological symptoms.

Alternatively, in the light of the poor prognosis associated with esophageal cancer, a survival rate of 6 months after BM resection may be considered relevant, since the resection of brain metastasis frequently offers the chance of symptom improvement thus fitting surgery into a palliative concept. An improvement of the neurological status by resection of brain metastases has been analyzed previously^[19] and was also observed in this study. The surgical complication rate was within the range of previously reported data, making surgery for BM in esophageal cancer comparable with other cancer types.

Due to the lack of targeted treatment options, the resection of symptomatic BM followed by radiotherapy may, therefore, represent a valuable treatment path besides radiosurgical modalities, which have not been analyzed with a focus on esophageal cancer metastases.

In accordance with a recent study^[3], the vast majority of tumors were an adenocarcinoma subtype, indicating a particular

tendency for these tumors to metastasize to the brain. This may lead to paying more attention to potential metastatic brain disease in these patients.

5. Limitations

This study carries all the limitations of a retrospective analysis and addresses a relatively low number of patients. Furthermore, the presented cohort could not be compared to a conservatively treated population with BM from EC. However, with respect to the rarity of the disease larger numbers are difficult to generate and prospective trials investigating BM in EC will be difficult to conduct.

Author contributions

Conceptualization: Pantelis Stavrinou, Stefan Grau.

Data curation: Lars Plambeck.

Formal analysis: Markus Ghadimi, Stefan Grau.

Investigation: Lars Plambeck, Martin Proescholdt.

Project administration: Roland Goldbrunner.

Supervision: Stefan Grau.

Writing – original draft: Pantelis Stavrinou.

Writing – review & editing: Markus Ghadimi, Roland Goldbrunner, Stefan Grau.

Stefan Grau orcid: 0000-0002-9742-527X.

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