Predicting Overall Survival in Patients with Brain Metastases from Esophageal Cancer

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Abstract. *Aim: To identify survival predictors and develop a survival score for patients with brain metastases from esophageal cancer. Patients and Methods: In 16 patients, seven factors were analyzed including age, gender, Karnofsky performance score (KPS), time from diagnosis of esophageal cancer to irradiation, number of brain metastases, histology, and presence of extracerebral metastases. Results: Improved survival was significantly associated with KPS ≥80 (p<0.001), the presence of one brain metastasis (p=0.007), and no extra-cerebral metastases (p=0.002). These factors were included in the final score. Factor scores were calculated by dividing 6-month survival rates by 10. Total survival scores represented the sums of factor scores and were 2, 7, 10, 19 or 24 points. Six-month survival rates by score were 0%, 0%, 0%, 67% and 100%, respectively. Two groups were formed, those of patients with 2-10 points and those with 19-24 points; 6-month survival was 0% and 88%, respectively (p<0.001). Conclusion: This new score facilitates the selection of individual therapies for patients with brain metastases from esophageal cancer.*

A considerable proportion of patients with cancer develop brain metastases during their disease (1). Most patients have a limited remaining life time of only a few months when the diagnosis of brain metastasis is made. The prognosis of these patients needs to be improved. On the other hand, potentially burdensome overtreatment must be avoided, particularly in patients with a short expected survival. Thus, the therapeutic strategy for each patient should follow a very individualized approach that also takes into account the patient's survival prognosis. The prognosis may be estimated with the help of prognostic factors and scores. Several survival scores for patients presenting with brain metastases already exist, often derived from data including many different primary tumor types (2-5). However, the biology and course of disease can vary considerably between different primary tumor types. Therefore, separate scores for each tumor entity, taking into account the specific prognostic factors of each primary tumor type, are important to optimally tailor the treatment to the individual patient's needs. This is the first study to focus particularly on metastasis to the brain from esophageal cancer. The major goals of the present study were the identification of predictors for overall survival and the development of a survival score for this rare group of patients in order to help in providing the most appropriate treatment approach for each individual patient.

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Materials and Methods

Patients. The data of 16 patients who had received radiation therapy for brain metastases from esophageal cancer were included in this retrospective analysis. Nine patients had more than one brain lesion and were treated with whole-brain irradiation (WBI) alone, either with 20 Gy in five fractions (N=4) or 30 Gy in 10 fractions (N=5). Seven patients had a single intracerebral lesion and were treated either with radiosurgery alone (N=2) or with resection of the metastasis followed by WBI (N=7).

For the entire cohort, a total of seven factors were analyzed regarding their potential association with overall survival. These factors were age (≤63 *vs.* ≥64 years; median age=63.5 years), gender, Karnofsky performance score (KPS ≤70 *vs.* ≥80), time interval from the first diagnosis of esophageal cancer to radiation therapy (≤12 *vs.* >12 months), number of brain metastases (1 *vs.* ≥2), histology (squamous cell carcinoma *vs.* adenocarcinoma) and extracerebral metastases (absence *vs.* presence). Patients' characteristics are shown in Table I.

Statistical analyses. The analysis of overall survival was performed with the Kaplan–Meier method (6) and the log-rank test. The factors that were significantly associated with overall survival ($p<0.05$) were included in a survival score. The score for each significant factor (factor score) was calculated by dividing the associated 6-month overall survival rate (as a percentage) by 10. The total survival score for each patient represented the sum of the scores for the significant factors.

Table I. *Patients' characteristics*.

	No. of patients	Proportion (%)
Age		
≤63 years	8	50
≥64 years	8	50
Gender		
Female	1	6
Male	15	94
Karnofsky performance score		
≤70	8	50
≥80	8	50
Time from cancer diagnosis to radiotherapy		
≤12 months	10	63
>12 months	6	38
Number brain metastases		
1	7	44
≥2	9	56
Histology		
Squamous cell carcinoma	5	31
Adenocarcinoma	11	69
Extracerebral metastases		
No	9	56
Yes	7	44

Table II. *Analysis of overall survival*.

	Overall survival at 6 months (%)	*p*-Value
Age		
≤63 years	50	
≥64 years	38	0.80
Gender		
Female	0	
Male	47	0.24
Karnofsky performance score		
≤70	0	
≥80	88	<0.001
Time from cancer diagnosis to radiotherapy		
≤12 months	40	
>12 months	50	0.54
Number brain metastases		
1	71	
≥2	22	0.007
Histology		
Squamous cell carcinoma	40	
Adenocarcinoma	45	0.25
Extracerebral metastases		
No	78	
Yes	0	0.002

Results

Median overall survival was 4 months (range=1-37 months). According to the analysis of overall survival, the KPS ($p<0.001$), the number of brain metastases ($p=0.007$), and extra-cerebral metastases ($p=0.002$) were significant predictors and, therefore, were included in the survival score. The results of the analysis of overall survival are given in Table II. The 6-month survival rates according to the three significant prognostic factors and the corresponding factor scores are summarized in Table III.

The addition of the three factor scores for each patient resulted in total survival scores of 2 points (N=5), 7 points (N=2), 10 points (N=1), 19 points (N=3) and 24 points (N=5). The 6-month overall survival rates by score were 0%, 0%, 0%, 67% and 100%, respectively. Based on the 6-month overall survival rates, two prognostic groups were formed, those with 2-10 points and and those with 19-24 points. Six-month survival rates of these two groups were 0% and 88%, respectively ($p<0.001$, log rank test).

Table III. *6-Month survival rates and the corresponding factor scores*.

	Overall survival at 6 months (%)	Score
Karnofsky performance score		
≤70	0	0
≥80	88	9
Number brain metastases		
1	71	7
≥2	22	2
Extracerebral metastases		
No	78	8
Yes	0	0

Discussion

Despite novel therapeutic approaches, the treatment results achieved in patients with brain metastases are often disappointing and require improvement (1). The latter may be achieved with more individualized therapies. In order to choose the best treatment for a patient, it is important to know his or her survival prognosis. Prognostic factors and scores can help estimate the prognosis of an individual patient with brain metastases. In the present study, for the first time, we aimed to identify predictors for overall survival and to develop a survival score for patients with brain metastases from esophageal cancer.

According to the results of this study, improved overall survival was significantly associated with a good performance status (KPS ≥80), presence of only one brain metastasis, and absence of extracerebral metastatic lesions. The small sample size and the retrospective design of the

study must be considered when interpreting these findings. However, since esophageal cancer is extremely rare in patients with brain metastases, accounting for fewer than 1% for this group, a larger cohort of such patients cannot be expected in the near future (1).

The prognostic significance of the performance status and of extracerebral lesions has also been recognized in four survival scores based on the data of more than 1,000 patients with brain metastases from different types of primary tumor (2-5). In 1997, Gaspar *et al*. presented the Recursive Partitioning Analysis (RPA) classification developed from the data of 1,200 patients (2). In 2008, two scoring systems were presented, the Graded Prognostic Assessment (GPA) index (N=1,906) and the first Rades Score (N=1,085) (3,4). In 2011, the second Rades Score, which also estimated the risk of an intracerebral recurrence in a series of 1,797 patients, was published (5). The third significant prognostic factor in the present study of esophageal cancer, the number of brain metastases, had been described only in the GPA index and the second Rades Score (4,5). This finding supports the idea that primary tumors leading to brain metastasis exhibit different biological behaviors. The idea of developing separate survival scores for different tumor types is also supported by Sperduto *et al*., who presented disease-specific GPA indices for non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), melanoma, renal cell carcinoma (RCC), gastrointestinal (GI) cancer without further specification, and breast cancer (7). The prognostic factors significantly associated with overall survival were different for these tumor entities. In patients with NSCLC or SCLC, overall survival was significantly associated with age, KPS, the number of brain metastases, and the presence of extracerebral metastases. In patients with melanoma or RCC, overall survival was significantly associated with KPS and number of brain metastases; and in patients with GI cancer or breast cancer, with KPS. In our own preceding study of patients with brain metastases from NSCLC, overall survival was associated with gender, performance status and the presence of extracerebral metastases (8). In another study of patients with SCLC, KPS, the number of brain metastases, and presence of extracerebral metastases were significant predictors (9). In a study of patients with breast cancer with brain metastases, overall survival was significantly associated with KPS and the presence of extracerebral metastases (10). The fact that each tumor type has a specific profile of significant predictors for overall survival demonstrates the importance of developing separate survival scores for each entity, in order to provide the best tailored treatment for each patient presenting with brain metastases.

In summary, overall survival of patients with brain metastases from esophageal cancer was significantly associated with KPS, number of brain metastases, and the presence of extracerebral metastases. Based on these three factors, a specific survival score for this group of patients was developed. This new survival score facilitates the choice of the best available therapy for each patient with brain metastases from esophageal cancer.

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