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A Scoring Tool to Estimate the Survival of Elderly Patients With Brain Metastases from Esophageal Cancer Receiving Whole-brain Irradiation

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Abstract. *Background/Aim: Elderly patients with metastatic esophageal cancer may benefit from individualized therapies. A tool to predict the survival of such patients with brain metastases was created. Patients and Methods: In 11 elderly patients (≥65 years) receiving whole-brain irradiation (WBI) for brain metastases from esophageal cancer, age, gender, performance status, number of brain metastases, metastases outside the brain, time between cancer diagnosis and WBI, and WBI regimen were evaluated for survival. Results: On univariate analyses, age ≥73 years (p=0.046) and time between diagnosis of esophageal cancer and WBI ≤6 months (p=0.046) were significantly associated with poorer survival. On multivariate analysis, both showed a trend. Based on these two factors, the following points were assigned: age ≤72 years=1 point, age ≥73 years=0 points; time between cancer diagnosis and WBI >6 months=1 point, and ≤6 months=0 points. Three prognostic groups were thus formed: 0, 1 and 2 points. Survival rates of these groups at 6 months were 0%, 0% and 40% (p=0.012), respectively. Conclusion: This new tool allows estimation of survival and treatment individualization in elderly patients irradiated for brain metastases from esophageal cancer.*

Patients with brain metastases from esophageal cancer are rare (1). Esophageal cancer accounts for approximately 1% of all types of cancer and fewer than 0.5% of patients with brain metastases. A considerable number of these patients are elderly patients, a group that is rapidly increasing in developed countries due to demographic changes (2). It is generally agreed that this age group must be considered a specific group of patients with cancer due to their generally slower metabolism, reduced organ function and concomitant diseases. To achieve the best possible treatment results in terms of efficacy and feasibility, these patients likely benefit from individualization of their cancer therapy (3). An individualized treatment program ideally considers various aspects of a patient's situation including their remaining lifespan. Prognostic tools can be very useful for estimating a patient's survival time. In the present study, we aimed to create a tool specifically for elderly patients with brain metastases from esophageal cancer who received whole-brain irradiation (WBI), the most common type of radiation treatment administered to this particular group (4).

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Key Words: Elderly patients, brain metastases, esophageal cancer, whole-brain irradiation, survival, scoring tool.

Patients and Methods

This retrospective study included 11 elderly patients, aged 65 years or older (2,6), who received WBI alone for brain metastases from esophageal cancer. Nine of these patients had more than three intracerebral lesions. Some of the patients were included in prior studies (3, 5). The present study received approval from the local Ethics Committee (University of Lübeck, 19-011A). It aimed to create a scoring tool that estimates the survival prognoses of these patients. To achieve this goal, we investigated six pre-treatment factors for potential associations with survival. These factors were age (≤72 *vs.* ≥73 years), gender, Karnofsky performance score (KPS ≤70 *vs.* >70), number of brain metastases [1 or 2 (limited) *vs.* 4 or more (multiple), no patient had 3 lesions], metastases outside the brain (no *vs.* yes), and time between diagnosis of esophageal cancer and WBI (≤6 *vs.* >6 months). In addition to these factors, the radiation regimen was investigated (20 Gy/5 fractions *vs.* 30 Gy/10 fractions *vs.* 35-40 Gy/14-20 fractions). The distributions of all seven factors are summarized in Table I.

Univariate analyses of survival following WBI were performed with the Kaplan–Meier method and the log-rank test. Factors significantly ($p<0.05$) associated with survival on univariate analyses were additionally included in a multivariate analysis (Cox regression). Those factors that showed at least a trend ($p\leq0.15$) for

an association with survival were used to create the scoring tool. For each of these factors, scoring points of 0 (worse survival) and 1 (better survival) were assigned (factor scores). For each patient, the scoring points were added to obtain the patient score.

Results

For the entire cohort, the survival rates at 3 and 6 months after WBI were 45% and 18%, respectively, and the median survival time was 3 months. On univariate analyses, age ≥73 years (p=0.046) and a time between diagnosis of esophageal cancer and WBI of ≤6 months (p=0.046) were significantly associated with poorer survival (Table II). In the additional multivariate analysis, both age (risk ratio=2.96, 95% confidence interval=0.67-13.8; p=0.150) and the time between diagnosis of esophageal cancer and WBI (risk ratio=2.96, 95% confidence interval=0.67-13.8; p=0.150) showed a trend for association with survival. Therefore, these two factors were used for creation of the scoring tool. The following points were assigned: age ≤72 years=1 point, age ≥73 years=0 points, time between cancer diagnosis and WBI >6 months=1 point, and time between cancer diagnosis and WBI ≤6 months=0 points. Thus, three prognostic groups were formed, *i.e.* 0 points (n=4), 1 point (n=2) and 2 points (n=5). The corresponding survival rates for these groups at 3 months were 0%, 100% and 60%, respectively, and the survival rates at 6 months were 0%, 0% and 40%, respectively (p=0.012, Figure 1). When combining patients with 0 and 1 points (n=6), the 3- and 6-month survival rates were 33% and 0%, respectively (Figure 2).

Discussion

Several pre-clinical and clinical studies have been performed during recent years to improve the often poor survival prognoses of patients with advanced esophageal cancer (7-14). Many elderly patients with brain metastases from esophageal cancer have very poor prognoses and may particularly benefit from individualized therapies taking into account their survival time. Individualization of the treatment may help avoid unnecessary toxicity due too aggressive treatments in patients with poor prognoses and suboptimal outcomes due to too little treatment in those patients with more favorable prognoses. When aiming to design a treatment program based on the patient's lifespan, scoring tools are helpful and can be easily applied prior to the start of treatment. Such tools have already been developed specifically for several tumor types metastasizing to the brain (15-19). The development of such specific tools is reasonable because tumor types can differ considerably regarding their biological behavior. Moreover, for elderly patients with cancer, who are considered a separate and important group, one would ideally also have specific tools

Table I. *Distribution of the investigated factors.*

Characteristic	Number of patients	Proportion (%)
Radiation regimen		
20 Gy in 5 fractions	1	9.1
30 Gy in 10 fractions	4	36.4
35-40 Gy in 14-20 fractions	6	54.5
Age		
≤72 Years	6	54.5
≥73 Years	5	45.5
Gender		
Female	3	27.3
Male	8	72.7
Karnofsky performance score		
≤70	6	54.5
>70	5	45.5
Number of brain metastases		
Limited	2	18.2
Multiple	9	81.8
Metastases outside the brain		
No	4	36.4
Yes	7	63.6
Time from diagnosis of esophageal cancer to WBI		
≤6 Months	5	45.5
>6 Months	6	54.5

WBI: Whole-brain irradiation.

Table II. *Univariate analyses of survival.*

Characteristic	Survival rate (%)		p-Value
	At 3 months	At 6 months	
Radiation regimen			
20 Gy in 5 fractions	0	0	0.773
30 Gy in 10 fractions	50	25	
35-40 Gy in 14-20 fractions	50	17	
Age			
≤72 Years	67	33	**0.046**
≥73 Years	20	0	
Gender			
Female	0	0	0.058
Male	63	25	
Karnofsky performance score			
≤70	33	17	0.434
>70	50	20	
Number of brain metastases			
Limited	50	0	0.886
Multiple	44	22	
Metastases outside the brain			
No	75	25	0.121
Yes	29	14	
Time from diagnosis of esophageal cancer to WBI			
≤6 Months	20	0	**0.046**
>6 Months	67	33	

WBI: Whole-brain irradiation, bold: significant p-values.

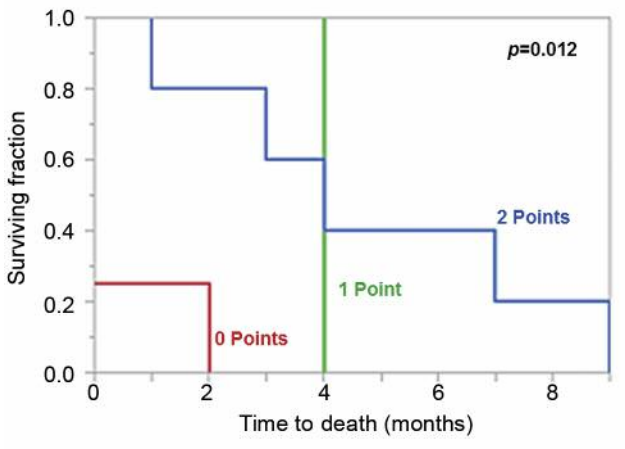

Figure 1. *Kaplan–Meier curves for survival of the three prognostic groups with 0 points (n=4), 1 point (n=2) and 2 points (n=5). The p-value was obtained from the log-rank test.*

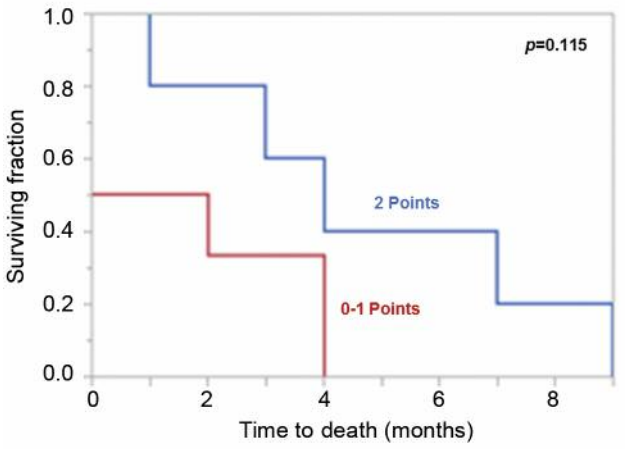

Figure 2. *Kaplan–Meier curves for survival of the prognostic groups with 0-1 points (n=6) and 2 points (n=5). The p-value was obtained from the log-rank test.*

(2, 6). Therefore, the current study was conducted to create a scoring tool that helps predict the survival of elderly patients irradiated for brain metastases from esophageal cancer. All patients included in this study received WBI alone, which is the most common treatment for patients with multiple cerebral lesions or poor general condition (4). Therefore, the risk of a selection bias due to the type of radiotherapy was reduced. In this study, two factors were significantly associated with survival on univariate analyses, namely age and the time between diagnosis of esophageal cancer and WBI. These factors were different from those showing significant associations with survival in a previous study of radiotherapy for brain metastases from esophageal cancer including patients of any age (5). In that study, survival was associated with KPS, number of brain metastases and metastases outside the brain. This finding supports the development of a scoring tool specifically for elderly patients.

In the present study, three groups were formed with significantly different survival rates. No patient with 0 points survived for 3 months following WBI. Therefore, these patients appear good candidates for short-course WBI. In a previous retrospective study of 442 patients with brain metastases and poorer estimated survival, WBI with 20 Gy in 5 fractions over 1 week was not inferior to 30 Gy in 10 fractions over 2 weeks regarding local control and survival (20). Patients with 1 point achieved a 3-month survival rate of 100%, but no patient survived longer than 4 months. Therefore, patients with 0 points and 1 point may me combined to one group that appears well treated with 20 Gy in 5 fractions (20). On the other hand, patients with 2 points had a more favorable prognosis, with a survival rate of 40% at 6 months. Therefore, these patients would appear to be better treated with 30 Gy in 10 fractions or even WBI programs with total doses beyond 30 Gy and lower doses per fraction. WBI with doses >30 Gy can result in better local control and survival in patients with brain metastases and favorable survival prognoses (21). Moreover, doses per fraction of <3 Gy were reported to be associated with a lower risk of WBI-induced neuro-cognitive deficits (22). However, when considering these treatment recommendations, one has to be aware of the retrospective nature of this study, including the risk of hidden selection biases and the small sample size, which is due to the fact that elderly patients with brain metastases from esophageal cancer are very rare.

In summary, this new scoring tool helps estimate of the survival prognosis of elderly patients irradiated for brain metastases from esophageal cancer. Its use allows rational treatment individualization for such patients.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

T.N., T.B., S.E.S and D.R. participated in the design of the study. T.N. and D.R. provided the data that were analyzed by S.E.S. and D.R. S.E.S and D.R. drafted the article, which was reviewed and approved by all Authors.

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