

A Specific Survival Score for Patients Receiving Local Therapy for Single Brain Metastasis from a Gynecological Malignancy

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Abstract. *Background/Aim: Personalization of the treatment of brain metastases considering patient's overall survival (OS) prognosis is gaining importance. This study was conducted to develop an OS score particularly for patients receiving local therapies for single brain metastasis from gynecological malignancies. Patients and Methods: In 11 patients, the following factors were retrospectively analyzed for associations with OS: Age, Karnofsky performance score (KPS), tumor type, extra-cranial metastatic sites, and time from diagnosis of gynecological malignancy to treatment of brain metastasis. Factors showing at least a strong trend were used for the score. Results: A KPS of 80-90% resulted in a significantly better OS than a KPS of 50-70% ($p=0.008$). Absence of extra-cranial metastases showed a strong trend ($p=0.052$). For the score, the following points were used: KPS 50-70%=0, KPS 80-90%=1, presence of extra-cranial metastatic sites=0, absence=1. Patients' scores were 0, 1 or 2 points. OS rates at both 6 and 12 months were 0%, 67% and 100%, respectively ($p=0.020$). Conclusion: This specific score can be used to estimate OS in patients receiving local therapies for single brain metastasis from gynecological malignancies and personalize their care.*

Patients with a single brain metastasis from a gynecological malignancy are quite rare and account for less than 0.5% of adult patients with brain metastases from a solid tumor (1). The majority of patients with single brain metastasis receive

a local therapy, either alone or in combination with whole-brain irradiation (WBI) plus/minus a radiation boost to the metastatic site (2). The overall survival (OS) prognoses of patients with a single brain metastasis can vary considerably between a very few months and much longer than one year. The OS prognosis should be considered when tailoring the treatment regimen to a patient. Patients with a poor expected OS time should preferably receive a short palliative regimen with consuming as little of the patients' remaining lifespan as possible. In patients with a longer expected OS time, the goals of treatment should be more on intracerebral control, prolonging of survival and avoidance of late treatment-related morbidities (2). Therefore, it would be very helpful if an OS score was available giving physicians a better idea of an individual patient's OS prognosis. Since solid tumors vary with respect to prognosis and biological behavior, specific OS scores for different tumor types associated with brain metastases would be ideal to choose the best personalized treatment for each patient (3-6). Furthermore, the prognoses and treatment of patients with a single brain metastasis differ from those patients with oligometastatic disease and multiple brain metastases (7-9). Therefore, specific scores for each of these three categories appear reasonable. In addition to a previous score developed in patients with brain metastases from a gynecological malignancy, of whom 80% received WBI alone and 70% had more than one lesion, this subgroup analysis was performed to create a specific OS score particularly for patients who received a local therapy for a single brain metastasis (10).

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Key Words: Gynecological malignancies, single brain metastasis, local therapies, survival score, personalized care.

Patients and Methods

Eleven patients with a single brain metastasis from a gynecological malignancy who received a local therapy as part of their treatment between 2000 and 2016 were included in this retrospective study, which represents a subgroup analysis of a previous study (10). Local therapies included 15-25 Gy of stereotactic radiosurgery or 3x10 Gy of fractionated stereotactic radiotherapy alone ($N=6$) and neurosurgical resection followed by 10x3 Gy or 20x2 Gy of whole-

brain irradiation plus/minus a sequential boost to the resection cave ($N=5$). Patients had either ovarian cancer ($N=8$), cervical cancer ($N=1$), uterine cancer ($N=1$) or vulvar cancer ($N=1$). In this cohort, the following factors were investigated for an association with OS: Age (≤ 65 vs. >65 years, median=65), Karnofsky performance score (KPS) (50-70% vs. 80-90%, median=70), primary tumor type (ovarian cancer vs. other malignancies), extra-cranial metastatic sites (no vs. yes) and time from diagnosis of the gynecological malignancy to treatment of the brain metastasis (<36 vs. ≥ 36 months, median=36). The distribution of these factors is shown in Table I.

For the statistical analyses of OS, the Kaplan–Meier method and the log-rank test were applied (11). p -Values from the log-rank test of <0.05 were considered significant, and p -values of <0.06 nearly significant (=strong trend). Factors showing at least a strong trend were used for the creation of the survival score.

Results

A KPS of 80-90% resulted in significantly better OS than a KPS of 50-70% ($p=0.008$). In addition, absence of extra-cranial metastatic sites showed a strong trend ($p=0.052$). Therefore, these two factors were incorporated in the OS score. The OS rates at 6 and 12 months following treatment of the single brain metastasis of all investigated factors are summarized in Table II.

With respect to the OS score, the following scoring points were used: KPS of 50-70%=0 points, KPS of 80-90%=1 point, presence of extra-cranial metastatic sites=0 points, absence of extra-cranial metastatic sites=1 point. After adding these points, the score for a patient was either 0 ($N=4$), 1 ($N=3$) or 2 ($N=4$) points. For these scores, the OS rates at 6 months were 0%, 67% and 100%, respectively, and the OS rates at 12 months were also 0%, 67% and 100%, respectively ($p=0.020$, Figure 1).

Discussion

Since patients with brain metastases from a gynaecological malignancy are rare, there is a lack of data regarding this particular group. The majority of these patients present with multiple cerebral lesions and usually receive WBI alone (2). Patients with only a single lesion often have a considerably better OS prognosis than those patients with multiple lesions and could, therefore, benefit from employment of local therapies such as neurosurgical resection and stereotactic radiosurgery/radiotherapy (2, 7-9).

Efforts have been made to improve the results of the primary treatment of gynecological malignancies including novel surgical approaches and systemic drugs (12-18). An improvement of the primary treatment often results in a better prognosis and a prolonged lifetime. Since the risk of developing metastases increases with lifetime the number of patients with brain metastases from a gynaecological malignancy will likely increase, too. For these patients,

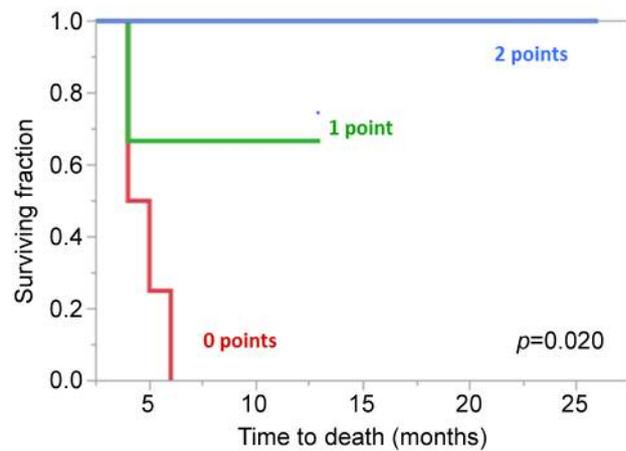


Figure 1. Kaplan-Meier curves of survival for 0, 1 and 2 scoring points. The p -value was obtained using the log-rank test.

Table I. Distribution of the factors potentially associated with survival.

	Number of patients
Age at the time of treatment	
≤ 65 years	6
>65 years	5
Karnofsky performance score	
50-70%	6
80-90%	5
Primary tumor type	
Ovarian cancer	8
Other malignancies	3
Extra-cranial metastatic sites	
No	6
Yes	5
Time from diagnosis of the gynecological malignancy to treatment brain metastasis	
<36 months	5
≥ 36 months	6

personalized treatment regimens are required to achieve optimal results in terms of palliation, disease control and reduction of treatment-related side effects. Besides other factors, personalized treatment should also consider the patient's OS prognosis. Therefore, it would be of great value for the treating physicians to have a more precise idea of the patient's remaining lifespan. OS scores assist them with this matter (3-6). Taking into account that primary tumors are different in many aspects, specific scores should be available for different tumor types to allow best possible personalization of the treatment. Furthermore, since the treatment of brain metastases also depends on the number of lesions, *i.e.* one vs. limited number of vs. multiple lesions, separate OS scores for the different categories of the

Table II. Freedom from new cerebral metastases (univariate analysis).

Factor	Survival		<i>p</i> -Value
	At 6 months (%)	At 12 months (%)	
Age at the time of treatment			
≤65 years	50	50	
>65 years	60	60	0.87
Karnofsky performance score			
50-70%	17	17	
80-90%	100	100	0.008
Primary tumor type			
Ovarian cancer	50	50	
Other malignancies	67	67	0.70
Extra-cranial metastatic sites			
No	83	83	
Yes	20	n.a	0.052
Time from diagnosis of the gynecological malignancy to treatment brain metastasis			
<36 months	40	40	
≥36 months	67	67	0.42

n-a-: Not available; bold *p*-values=significant or nearly significant.

numbers of lesions would be desirable (2, 7-9). The present study aimed to create an OS score specifically for patients treated with local therapies for a single brain metastasis from a gynaecological malignancy. This study represents a subgroup analysis of a previous study that included patients with gynecological malignancies who belonged to all three categories regarding the number of brain metastases (one lesion, limited number of lesions, multiple lesions) (10). Moreover, 80% of the patients of the previous study received WBI alone and no local therapy. And 70% of the patients in the previous study had a very poor performance score (3-4 according to the Eastern Cooperative Oncology Group, which is similar a KPS of 50% or less) (10). In the present study, only one patient had a KPS of 50% and no patient had a KPS of less than 50%. Therefore, the aim to create a specific OS score particularly for patients receiving local therapies for a single lesion is justified. In the present study, two factors were included in the OS score, KPS and extra-cranial metastatic sites. Three prognostic groups were identified with significantly different OS rates at both 6 and 12 months. Of the patients of the 0-point group, no patient survived 6 months or longer. Therefore, these patients should receive the least stressful treatment possible, *e.g.* lower-dose (to keep the time patients have to lie under the tight head mask short) single-fraction stereotactic radiosurgery (*e.g.* 12-15 Gy), or short-course local 3-D conformal radiotherapy (2). Neurosurgical resection should be avoided in this group. In the 1-point group and the 2-point group, 67% and 100% of the patients survived for 12 months or longer following treatment. Taking into account these favorable prognoses,

improvement of intracerebral control and OS with acceptable late toxicity should be the goals of treatment. These patients appear suitable candidates for neurosurgical resection, higher-dose stereotactic radiosurgery (*e.g.* 20-25 Gy) or fractionated stereotactic radiotherapy (*e.g.* 3×10-12 Gy in three days), either alone or supplemented by WBI (19-22). However, taking into account the retrospective design of this study and the small size of the patient cohort, these recommendations are preliminary and await validation in a larger population.

In conclusion, given the limitations of the study, this very specific score can support physicians when they attempt to estimate the OS of patients planned to receive a local therapy for a single brain metastasis from a gynecological malignancy and can enhance the personalization of treatment for this particular patient group.

Conflicts of Interest

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

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Received March 19, 2018
Revised March 30, 2018
Accepted April 2, 2018