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An Instrument to Guide Physicians when Estimating the Survival of Elderly Patients With Brain Metastasis from Gynecological Cancer

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Abstract. *Background/Aim: For treatment personalization in elderly cancer patients, survival prognoses should be considered. We developed an instrument to estimate survival of elderly patients with brain metastasis from gynecological cancer. Patients and Methods: In 15 patients, whole-brain radiotherapy regimen, tumor site, age, Karnofsky performance score (KPS), number of brain metastases, extra-cerebral metastases and interval from diagnosis of gynecological cancer until radiotherapy were retrospectively evaluated for survival. Characteristics found significant on multivariate analysis were used for the instrument. Results: In the multivariate analysis, KPS ≥70% (hazard ratio=3.71, p=0.0499) and an interval ≥28 months (hazard ratio=3.71, p=0.030) were significantly associated with better survival. Based on these characteristics, patients received 0 (n=6), 1 (n=3) or 2 points (n=6). Six-month survival rates of the groups 0-1 and 2 points were 0% and 50%, respectively (p=0.007). Conclusion: This instrument helps estimating survival in elderly patients with brain metastases from gynecological cancer and contributes to personalization of their treatment.*

Very few cancer patients with brain metastases have a gynecological malignancy (1). Some of them are elderly patients, generally defined as ≥65 years of age (2, 3). Elderly patients are a specific group that is viewed separately. Many of them have significant co-morbidities, and their ability to withstand aggressive anti-cancer therapy is often limited (4). Therefore, this group may benefit from treatment personalization, a strategy that has gained increasing attention in oncology during recent years. The strategy takes into account several patient-specific aspects including the survival prognosis. Estimation of survival and treatment personalization can be facilitated with prognostic instruments (5-8). Ideally, such instruments would be available specifically for each tumor entity, since primary tumor types show considerably different biological behaviors. This study aimed to develop a specific instrument that allows predicting the survival of elderly patients irradiated for brain metastases from a gynecological cancer.

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Patients and Methods

The data of 15 elderly patients, who were diagnosed with brain metastases from a gynecological malignancy, were analyzed in this retrospective study. Elderly was defined as aged ≥65 years, based on the definition of the World Health Organization (3). The patients had received whole-brain irradiation (WBI) with 20 Gy in 5 fractions (n=5), 30 Gy in 10 fractions (n=7) or 35 Gy in 14 fractions (n=3). Twelve patients (80%) had multiple (*i.e.* ≥3) brain metastases. Primary tumor sites were ovary in 9 patients, uterus in 3 patients, uterine cervix in 2 patients and vulva in 1 patient, respectively. Some patients were evaluated in previous studies (4, 9, 10). This study was approved by the ethics committee of the University of Lübeck (reference number 19-011A). The fractionation regimen, the primary tumor site (ovary *vs.* other sites) and five additional characteristics were evaluated with respect to 6-month survival following WBI (Table I). Additional characteristics included age at start of WBI (≤71 *vs.* ≥72 years, median=71 years), Karnofsky performance score=KPS (≤60% *vs.* ≥70%, median=70%), number of brain metastases (1-2 *vs.* ≥4, no patient had 3 metastases), presence of extra-cerebral metastases (no *vs.* yes), and the interval from first diagnosis of gynecological cancer until start of WBI (≤27 *vs.* ≥28 months, median=27 months).

Initially, all seven characteristics were analyzed in a univariate manner using the Kaplan–Meier method supplemented by the log-rank test. Those characteristics that showed a significant association with survival following WBI ($p<0.05$) were additionally analyzed in a multivariate manner using the Cox proportional hazard model). The characteristics that were significant ($p<0.05$) on both univariate and multivariate analysis, formed the basis of this prognostic instrument. Points of 0 (worse prognosis) and 1 (better prognosis) were assigned to each significant characteristic. For each patient,

Table I. *Summary of the seven analyzed characteristics.*

Characteristic	Number of patients (%)
Fractionation regimen	
20 Gy in 5 fractions	5 (33.3)
30 Gy in 10 fractions	7 (46.7)
35 Gy in 14 fractions	3 (20.0)
Age at start of WBI	
≤71 Years	8 (53.3)
≥72 Years	7 (46.7)
Primary tumor site	
Ovary	9 (60.0)
Others	6 (40.0)
Karnofsky performance score	
≤60%	7 (46.7)
≥70%	8 (53.3)
Number of brain metastases	
1-2	3 (20.0)
≥4	12 (80.0)
Extra-cerebral metastases	
No	3 (20.0)
Yes	12 (80.0)
Interval from diagnosis of gynecological cancer until WBI	
≤27 Months	8 (53.3)
≥28 Months	7 (46.7)

WBI: Whole-brain irradiation.

Table II. *Six-month survival rates after whole-brain irradiation (univariate analyses).*

	At 6 months (%)	*p*-Value
Fractionation regimen		
20 Gy in 5 fractions	20	0.738
30 Gy in 10 fractions	14	
35 Gy in 14 fractions	33	
Age at start of WBI		
≤71 Years	13	0.632
≥72 Years	29	
Primary tumor site		
Ovary	33	0.353
Others	0	
Karnofsky performance score		
≤60%	0	**0.003**
≥70%	38	
Number of brain metastases		
1-2	33	0.967
≥4	17	
Extra-cerebral metastases		
No	67	0.110
Yes	8	
Interval from diagnosis of gynecological cancer until WBI		
≤27 Months	0	**0.002**
≥28 Months	43	

WBI: Whole-brain irradiation; bold: significant *p*-values.

the points of these characteristics were added, and the patient score was obtained.

Results

The median survival time after WBI was 4 months in the entire cohort, and the 6-month survival rate was 20%. A KPS ≥70% (p=0.003) and an interval from first diagnosis of gynecological cancer until start of WBI of ≥28 months (p=0.002) were significantly associated with more favorable survival prognoses on univariate analyses (Table II). In the analysis with the Cox proportional hazard model, both KPS (hazard ratio=3.71, 95% confidence interval=1.00-14.58, p=0.0499) and the interval from diagnosis of gynecological cancer until WBI (hazard ratio=3.71, 95% confidence interval=1.00-14.58, p=0.030) maintained significance. Based on these two characteristics, the scoring instrument was designed. Patients with a KPS of ≤60% received 0 points, and patients with a KPS of ≥70% received 1 point. Patients with an interval from diagnosis of gynecological cancer until WBI of ≤27 months received 0 points, and patients with an interval of ≥28 months 1 point. Thus, the patients received 0 points (n=6), 1 point (n=3) or 2 points (n=6). The corresponding 6-month survival rates associated with these points were 0%, 0% and 50%, respectively (p<0.001). Since the 6-month survival rates of both patients with 0 points and 1 point were 0%, these patients were combined to one prognostic group. The 6-month survival rates of the prognostic groups 0-1 points and 2 points were 0% and 50%, respectively (p=0.007, Figure 1).

Discussion

The prognoses of many patients with locally advanced or metastatic gynecological malignancies are quite unfavorable and require improvement. Besides experimental, translational and clinical research, the patients may benefit from the novel strategy of treatment personalization (11-15). This is particularly important for elderly patients who may not tolerate aggressive systemic therapies (4). Since personalized treatments should take into account a patient's remaining lifespan, it would be important to have a precise idea of the patient's survival prognosis prior to the start of treatment. Estimation of the remaining survival time can be facilitated with the help of prognostic instruments. In this study, a new instrument was created particularly for elderly patients with a gynecological malignancy who developed brain metastases. Two independent prognostic factors for survival, namely the KPS and the interval from first diagnosis of gynecological cancer until start of WBI, were identified. The performance

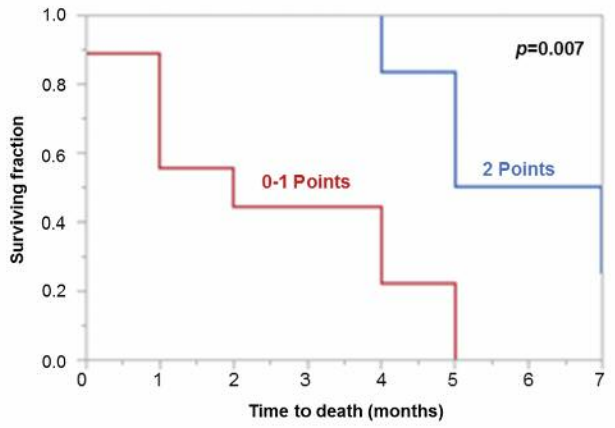

Figure 1. *Kaplan–Meier curves for survival following WBI of the prognostic groups 0-1 points (n=9) and 2 points (n=6). The p-value was calculated using the log-rank test.*

status was also predictive of survival in a previous study of patients treated with WBI alone for brain metastases from gynecological cancers of any age (median age=59 years) (10). However, the interval from the first diagnosis of gynecological cancer until start of WBI was not significantly associated with survival in the previous study. This difference supports the idea of creating specific scores for elderly patients.

Based on the survival data of the two independent prognostic factors, we formed two prognostic groups, namely 0-1 points and 2 points. No patient of the 0-1 points group survived longer than 5 months following WBI, and the median survival time after WBI was only 2 months. These patients appear good candidates for a WBI-regimen with a short overall treatment time such as 20 Gy in 5 fractions administered over 5 consecutive working days. In a previous study of 442 patients treated with WBI alone for multiple brain metastases and with comparably poor survival prognoses, cerebral control and survival were not significantly different after 20 Gy in 5 fractions and 30 Gy in 10 fractions (overall treatment time=2 weeks) (16). Since 67% of the patients with 0 points died within 1 month following WBI, these patients may be considered for best supportive care (BSC) including dexamethasone alone. This strategy has already been suggested for patients with very poor survival and brain metastases from non-small cell lung cancer. In a randomized trial, there was no significant difference in survival, overall quality of life or dexamethasone use between patients receiving BSC plus dexamethasone alone and those patients receiving the same regimen plus WBI with 20 Gy in 5 fractions (17). Moreover, the difference between the mean quality-adjusted life-years was only 4.7 days (41.7 *vs*. 46.4 days).

In the current study, patients with 2 points had a 6-month survival rate of 50% and a median survival time of 6 months. Since a previous study has shown that patients with more favorable survival prognoses can benefit from WBI with higher total doses in terms of better cerebral control and survival, these patients may be good candidates for longer-course WBI such as 30 Gy in 10 fractions or 35 Gy in 14 fractions (18). Moreover, lower doses per fraction were reported to result in less pronounced neurocognitive deficits than higher doses per fraction (19). When choosing a WBI-regimen for an individual patient, one should keep in mind that the risk of experiencing neurocognitive deficits increases with survival time. When considering our recommendations, the small sample size (due to the rarity of these patients) and the retrospective study design should be taken into account.

In conclusion, this new instrument helps physicians estimate the survival prognoses of elderly patients with brain metastases from gynecological cancer and, therefore, contributes to the personalization of their treatment.

Conflicts of Interest

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

Authors' Contributions

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

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