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Remaining Lifespan of Patients Aged ≥65 Years Receiving Whole-brain Irradiation for Metastases from Cancer of Unknown Primary

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Abstract. *Background/Aim: Personalized therapies may improve outcomes in elderly patients with brain metastases from cancer of unknown primary (CUP). To contribute to this strategy, an instrument for judging their survival time was designed. Patients and Methods: This retrospective study included 53 patients, aged ≥65 years and treated with whole-brain irradiation (WBI) for brain metastases from CUP. The WBI-program, age, gender, Karnofsky performance score (KPS), number of brain metastases and non-cerebral metastases were analyzed. Results: KPS≤60 (p<0.001) and presence of non-cerebral metastases (p=0.003) were significantly associated with unfavorable survival. These factors formed the basis for the prognostic implement; patient-scores of zero (n=23), one (n=21) or two points (n=9) were obtained. Corresponding survival rates at 6-months were 0%, 19% and 56% (p<0.001). Conclusion: With this instrument, it is easier to judge the remaining survival time of elderly patients with brain metastases from CUP. This information should be used when selecting individual treatment- and WBI-programs.*

In approximately 6% of patients who present to a radiation oncologist for irradiation of cerebral metastases, the primary tumor is unknown (1, 2). Many of these have unsatisfying outcomes. Improvement may not only be achieved with the involvement of novel technologies and drugs, but also with the relatively new strategy of offering the patients individualized treatment concepts (1). Particularly elderly patients with often markedly reduced organ function, resulting in less tolerance regarding multimodal therapies, may benefit from individualized approaches (3). To provide an optimally tailored treatment program, several aspects need to be considered including the patient's social situation, living condition, and also his life expectancy. If this is quite short, the radiotherapy should be short as well (1). In case of a more protracted survival, late treatment-related adverse events and long-term control of the disease are gaining importance. Thus, it is desirable to know a patient's prognosis most precisely, which can be facilitated with the use of scores. Physicians generally agree that separate instruments for each tumor entity would be optimal to provide the best possible individualization of treatment. This applies also to the technique and fractionation of radiotherapy, when a patient is referred to a radiation oncology department for treatment of brain metastases (1). Moreover, beyond the type of primary tumor, the patient's age also plays an important role. Children, young adults and elderly should be regarded as specific groups. The present study focused on patients who were at least 65 years old and assigned to whole-brain irradiation (WBI) for brain metastases from cancer of unknown primary (CUP).

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Key Words: Cancer of unknown primary, brain metastases, patients aged ≥65 years, whole-brain irradiation, remaining lifespan.

Patients and Methods

This retrospective study included 53 patients with CUP aged 65 years or older, who were treated with WBI alone. The current study was approved by the responsible ethics committee (University of Lübeck, AZ19-011A). The WBI-program and other factors were investigated with respect to 3- and 6-month survival (Table I). The other factors were the age at the first day of WBI (≤73 years compared to ≥74 years, median: 73 years), gender (females compared to males), the Karnofsky performance score (KPS≤60 compared to KPS≥70, median KPS: 60), number of brain metastases (<4 compared to ≥4) and non-cerebral metastases at the first day of WBI (absence compared to presence).

Table I. *Distribution of the WBI-regimens and the other potential prognostic factors.*

Factor	Number of patients (%)
WBI-program	
4 Gy × 5	16 (30)
3 Gy × 10	26 (49)
2.5 Gy × 14/2 Gy × 20	11 (21)
Age at first day of WBI	
≤73 Years	27 (51)
≥74 Years	26 (49)
Gender	
Female	18 (34)
Male	35 (66)
Karnofsky performance score	
≤60	33 (62)
≥70	20 (38)
Number of brain metastases	
<4	18 (34)
≥4	35 (66)
Non-cerebral metastases	
No	19 (36)
Yes	34 (64)

WBI: Whole-brain irradiation.

Table II. *Three-month and 6-month survival rates after whole-brain irradiation.*

	3 months (%)	6 months (%)	*p*-Value
WBI-program			
4 Gy × 5	69	25	0.06
3 Gy × 10	38	15	
2.5 Gy × 14/2Gy × 20	18	0	
Age at first day of WBI			
≤73 Years	37	11	0.31
≥74 Years	50	23	
Gender			
Female	33	17	0.48
Male	49	17	
Karnofsky performance score			
≤60	30	3	**<0.001**
≥70	65	40	
Number of brain metastases			
1-3	56	17	0.53
≥4	37	17	
Non-cerebral metastases			
No	74	32	**0.003**
Yes	26	9	

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

Analyses were performed using the Kaplan–Meier method. Afterwards, the differences between the corresponding Kaplan–Meier curves for each potential prognostic factor were calculated by applying the log-rank test. Significant factors ($p<0.05$) were incorporated into the scoring instrument. For each factor that achieved significance, zero points or one point were assigned in case of a less favorable or a more favorable outcome, respectively. The sum-scores for each patient (patient-scores) were obtained after adding the points from all significant factors.

Results

In all 53 patients, median post-WBI survival was 3 months; survival at 3 and 6 months was 43% and 17%, respectively. KPS≤60 ($p<0.001$) and presence of non-cerebral metastases at the first day of WBI ($p=0.003$) were significantly associated with a worse outcome (Table II). These two factors formed the basis for the design of the predictive instrument. The following scoring points were assigned: 0 points for KPS≤60 and presence of extra-cerebral metastases, and 1 point each for KPS≥70 and absence of non-cerebral metastases. Thus, the patient-scores were either 0 points (n=23), 1 point (n=21) or 2 points (n=9). Three-month survival rates related to these patient-scores were 13%, 62% and 78%, and the 6-month rates were 0%, 19% and 56% ($p<0.001$, Figure 1).

Discussion

Although many patients with metastases from CUP experience quite unfavorable outcomes, less research focused on this group compared to other tumors (4-9). More studies are required that will particularly address metastatic CUP. One potential option to improve the situation of patients with metastatic CUP is the novel concept of treatment personalization that should always consider an individual subject's survival-time. Prognostic factors and survival scores have already been presented for patients of any age with brain metastases from CUP and for another palliative situation, namely spinal cord compression (SCC) (5-7). For SCC, a score for elderly patients, who should be considered a specific group, is already available (8). What has been missing for patients with metastatic CUP is an implement designed for elderly patients with brain metastases. This study has been performed to close this gap. Based on two significant factors, namely KPS and non-cerebral metastases, a scoring instrument ranging from zero to two points has been developed for elderly patients with CUP assigned to WBI.

The survival of patients with zero points was very poor; the median survival time was only 1 month, the 3-month survival rate was only 13%, and no patient survived longer than 5 months. Taking into account this very poor prognosis, patients of this group appear good candidates for WBI with 4 Gy × 5. In a previous study, this regimen was not inferior to 3 Gy ×

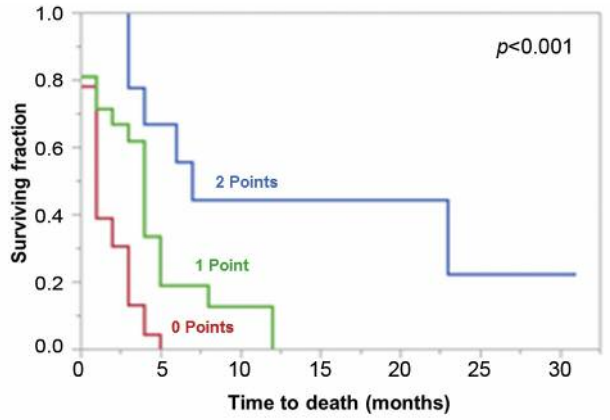

Figure 1. *Kaplan–Meier curves of the prognostic groups, zero points (n=23), one point (n=21) and two points (n=9), for survival after whole-brain irradiation.*

10 with respect to intracerebral control and survival (10). Patients of the zero-points group in the present study may even be considered for best supportive care (generally corticosteroids) without WBI. In a randomized trial of patients with brain metastases from non-small cell lung cancer and poor prognoses, the addition of WBI to best supportive care did not significantly improve survival or quality of life (11).

The patients of the current study with one point had a median survival time of 4 months, and 62% of the patients survived for at least 3 months. However, the 6-month survival rate was only 19%. Thus, their survival prognosis may be called poor to intermediate, and these patients may be good candidates for short-course WBI with 4 Gy × 5. Patients of the two-points group had the best survival prognoses with a median survival time of 7 months and a 6-month survival rate higher than 50%. These patients should receive longer-term WBI, since in a previous study of patients with quite favorable survival prognoses, WBI with higher total doses resulted in improved rates of survival and freedom from new or recurrent brain metastases (12). Therefore, these patients should be treated with 3 Gy × 10 or even total doses >30 Gy, *i.e.* regimens such as 2.5 Gy × 14 or 2 Gy × 20. Patients of the two-point group with a very limited number of brain lesions may also be considered for a local therapy, either alone or combined with WBI (1, 5). When taking these recommendations into consideration, one should be aware of the retrospective study-design always bearing the risk of hidden selection biases.

In conclusion, with this new instrument, it has become easier to judge the remaining survival time of elderly patients with brain metastases from CUP. This information should be used during the process of selecting individual treatment- and WBI-programs.

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

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

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