Prognostic Factors and Independent Validation of a Risk Stratification Model in Octogenarian Patients Irradiated for Brain Metastases

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Abstract. Background/Aim: This study aimed at validation of a prognostic model, originally developed by Rades *et al.*, in an age-restricted, particularly vulnerable subgroup of patients with brain metastases, because international variations in clinical practice and survival outcomes may impact on the performance of survival prediction tools. Materials and Methods: Retrospectively, data from a single institution were analyzed. The study included 50 patients managed with palliative whole-brain radiotherapy. The Rades *et al.* score was assigned and the resulting 3 prognostic strata compared. Results: The 3-month survival rates for the 3 strata were 0, 35 and 41%, respectively (p<0.001 pooled over all strata, log-rank test for Kaplan-Meier curves). However, the prognostic impact of extracranial metastases suggested by Rades *et al*., together with performance status and number of brain metastases in their study of 94 patients, was absent. In contrast, cancer type (better survival for breast and melanoma) and lack of steroid treatment were significant in the present study. Conclusion: The original Rades *et al.* score is a useful prognostic model in our validation database. However, additional factors appear to play a role and might therefore be considered when performing future large-scale studies.

While brain metastases may cause clinical symptoms with potentially serious consequences for patients' ability to carry out activities of daily living irrespective of chronological age, their impact on self-care and cognitive functioning is often more pronounced in the geriatric cancer patient population (1, 2). Due to age, frailty and comorbidity even moderate additional deficits may result in immobilization, hospitalization, need for nursing home care, termination of systemic anticancer treatment etc. There is also concern about the side effects of brain-directed radiotherapy, in particular whole-brain irradiation (WBRT), in the geriatric population (3, 4). Despite increasing utilization of focal radiotherapy, mainly stereotactic radiosurgery (SRS), not all patients are optimal candidates for such treatment. Factors such as number of brain metastases and presence of meningeal spread may still cause clinicians to prefer WBRT, a treatment which is able to provide worthwhile symptom palliation (5). In case of very limited life expectancy, symptom palliation may be too short-lived and possibly overshadowed by other medical issues to result in a clear net benefit. Under such circumstances best supportive care (BSC) without brain-directed treatment should be considered (6-8).

In previous studies evaluating prognostic factors only a minority of patients were ≥80 years old. It is therefore relevant to perform separate analyses, which inform decision-making and result in optimized selection criteria for brain-directed radiotherapy. In addition to already validated survival prediction models, such as recursive partitioning analysis (RPA) classes, diagnosis-specific graded prognostic assessment (DS-GPA) and LabBM score (9-12), which all can be recommended for clinical implementation, Rades *et al.* suggested a new model that was derived from a dedicated study of irradiated patients aged ≥80 years (13). Their score was developed in 94 patients

undergoing WBRT. Dose fractionation, treatment period, age, sex, Eastern Cooperative Oncology Group (ECOG) performance score (PS), tumor type, count of brain lesions, metastases outside the brain, and interval tumor diagnosis to radiotherapy were retrospectively evaluated. Independent predictors of survival were used for the score. Based on individual scoring points obtained from 3-month survival rates, prognostic groups were designed. ECOG-PS, number of brain metastases and presence of extracranial metastases were independent prognostic factors. Three groups were created with 3-month survival of 6%, 25%, and 67% (p <0.001), respectively. The median survival was 2.0 months in the cohort of 94 patients. For the three groups, corresponding figures were 1.0, 2.0, and 6.5 months, respectively. The purpose of the present study was to provide external validation of these results in an independent cohort.

Patients and Methods

For this retrospective analysis, a continuously maintained and updated database was employed, which provides data from consecutively irradiated patients with brain metastases since 2006 (real world cohort, complete and incomplete radiotherapy courses, treatment before June 2022, follow-up through October 2022). The database was originally created to allow for regional quality-of-care analyses, has already been utilized (5, 7, 8, 12) and does not require additional approval by the local Ethics Committee (REK Nord). Patients managed with BSC or neurosurgical intervention rather than WBRT were excluded. Radiotherapy fractionation was selected by the physician in charge at the time of first consultation and treatment planning. Other anti-cancer therapy (endocrine, chemotherapy etc.) was tailored to disease burden and biology, organ function and patient preferences. Steroids were prescribed as needed

to control neurological symptoms. Staging of extracranial metastases consisted of computed tomography (CT). If clinically relevant, other modalities such as ultrasound og magnetic resonance imaging (MRI) were added to clarify the overall distribution of metastases. Contrast-enhanced MRI was the prevailing method of brain metastases detection, unless contraindicated. In the latter case, CT was employed.

Rades *et al.* assigned 6 points for single and 3 for multiple brain metastases (13). Extracranial metastases resulted in 3 points (brain only: 6 points). ECOG PS 3 resulted in 1 point (PS 0-2: 4 points). Patients with highest point sum, *i.e.* 13-16, were allocated to the best prognostic group (sum 10: intermediate, sum 7: short survival). We did not change this method of score assignment. Overall survival from the start of radiotherapy was calculated employing the Kaplan–Meier method (SPSS 28; IBM Corp., Armonk, NY, USA). Log-rank tests were employed to compare actuarial survival curves. Multivariate forward stepwise Cox regression was employed to assess the correlation between survival and baseline parameters. Only one patient was still alive (9.5 months after radiotherapy) at the time of data analysis.

Results

The present study included 50 patients aged 80-90 years, median 82. Their median overall survival was 2.1 months, 95% confidence interval 1.4-2.8 months, mean 5.6 months. Six patients had been unable to complete radiotherapy. Additional baseline parameters are shown in Table I. Point sum distribution was poorly balanced (sum 7: 1 patient, sum 10: 17 patients, sum 13: 26 patients, sum 16: 6 patients), but showed a trend towards statistical significance as prognostic factor for survival with p=0.08 in univariate Cox regression for continuous variables. Figure 1 shows the Kaplan-Meier

survival curves for the final three-tiered score. Three-month survival was 0, 35 and 41%, respectively. Further details are displayed in Table II.

In univariate log-rank tests, presence of extracranial metastases was not associated with survival, p=0.74. In contrast, patients with single brain metastasis survived longer than those with 2 or more (median 5.5 vs 2.1 months, p=0.08). ECOG PS was highly significant, p<0.001. Among other baseline parameters (all displayed in Table I were tested), additional systemic anticancer treatment showed a trend (p=0.06), while lack of steroid treatment (p=0.015, median 6.3 vs 1.7 months) and favorable cancer type (p=0.008, median 5.5 in breast/melanoma vs 1.9 months in all others) were significant. In multivariate Cox regression, lack of steroid treatment evolved as the most relevant predictor of survival (p=0.02), followed by ECOG PS (p=0.06) and cancer type (p=0.11).

Discussion

This study was performed to provide the first independent validation of the prognostic factors and resulting score proposed by Rades *et al.* (13). We followed the same selection criteria and methods to make sure both studies are easy to compare. Overall survival was almost identical (median 2.0 and 2.1 months, respectively). These survival outcomes are relatively disappointing and shorter than commonly reported in studies of WBRT in unselected populations (all-comers irrespective of age) (14-16). It is well known that many octogenarians are poor candidates for standard anticancer treatment, including systemic drug therapy and surgery, and therefore unfavorable outcomes are not uncommon in this age-group (17-19). On the other hand, limited survival is not synonymous to limited benefit in terms of symptom palliation. The latter

is the most relevant endpoint in the current setting of palliative radiotherapy. As seen in both original and validation study, survival beyond 1 year can be achieved in a minority of patients, meaning that withholding treatment in all octogenarians cannot be recommended. The issue of cognitive deterioration after WBRT is clearly relevant in the subset of patients surviving for more than 2-3 months.

Rades *et al.* were able to identify 3 groups with distinct 3-month survival of 6%, 25%, and 67%, respectively. The corresponding figures were 0%, 35% and 41% in our study. Thus, congruence was best in the poor prognosis group (7 points, median survival 1.0 month). This group consisted of 17 patients (18% of the cohort) in the Rades *et al.* study, but only 1 patient (2%) in our study. Given our longstanding research focus on overtreatment and patient selection for BSC (7, 8), we were probably more reluctant to start WBRT in poor-prognosis patients. In light of the short survival reported by Rades *et al.*, we now feel even more confident to prefer BSC in patients with 7 points.

In both studies, survival outcomes were heterogeneous in the intermediate group (10 points), with <40% alive at 3 months in both studies. This means that some of these patients failed to survive long enough to really benefit from WBRT. Interestingly, most patients (32 of 50, 64%) were assigned to the best prognostic group (only 26% in the Rades *et al.* study). Due to their increasing likelihood to survive beyond 3 months, this group might benefit from focal radiotherapy (SRS or other types of partial brain irradiation), or advanced WBRT techniques that preserve cognitive function better than standard WBRT, so-called hippocampus-avoidance WBRT (20, 21). It should also be noted that systemic therapy is relevant in the context of decision-making, because

many patients harbour active extracranial disease, and failure to control these lesions will result in limited survival (22). Also in the present study, additional systemic therapy was associated with better survival.

Our study was limited by its retrospective design and the smaller size compared to Rades *et al.* (13). This resulted in smaller subgroups and lower likelihood of achieving statistical significance. Nevertheless, group size cannot explain the difference in parameters that were found to impact survival. With a *p*-value of 0.74, extracranial metastases were not even close to a trend (3-month survival rate 40% and 36%, respectively), in contrast to single brain metastases, p=0.08. PS has long been a well-appreciated parameter that is part of many traditional survival prediction models (9, 10). According to our results, primary tumor type might impact survival (not significant in the original study) together with steroid medication (not examined by Rades *et al.*). In patients with breast cancer or melanoma, a clinically important survival advantage was observed (median 5.5 vs 1.9 months). Similar differences were present for steroid treatment (median 6.3 vs 1.7 months, the number one prognostic factor in multivariate analysis). These 2 parameters might facilitate decision-making in patients with 10-16 points. In conclusion, the original Rades *et al.* score is a useful prognostic model in our validation database. However, additional factors appear to play a role and might therefore be considered when performing future large-scale studies.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Figure 1. Actuarial overall survival for three different strata according to the Rades *et al.* score, $p<0.001$ (pooled over all strata).

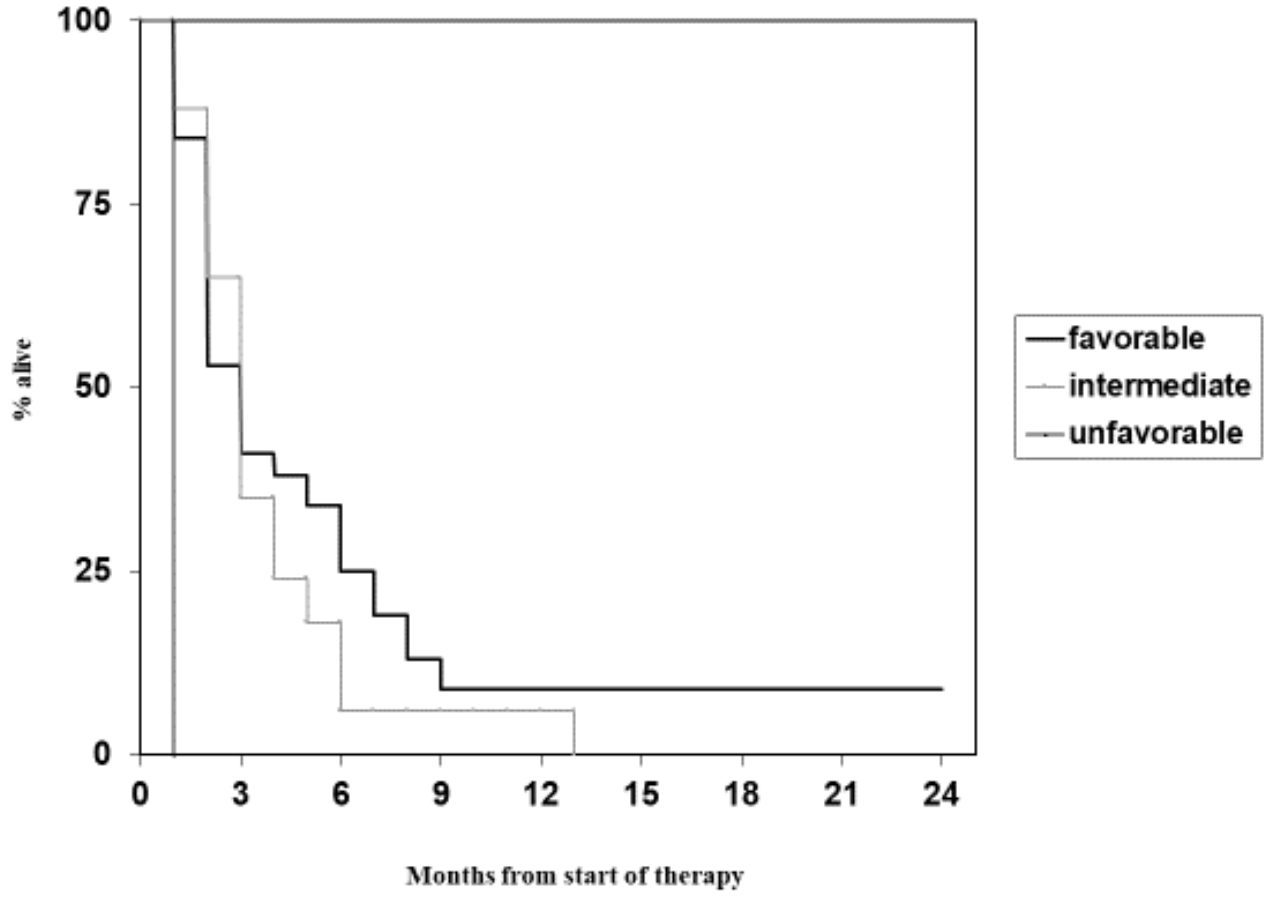

Table I. Baseline characteristics in 50 irradiated patients

Parameter	n	%
Female gender	25	50
Male gender	25	50
Lung cancer, adenocarcinoma	11	22
Lung cancer, small cell	3	6
Lung cancer, others	10	20
Breast cancer	10	20
Colorectal cancer	4	8
Malignant melanoma	4	8
Unknown primary tumor	4	8
Other cancer type	4	8
Controlled primary tumor	23	46
Uncontrolled or unknown primary tumor	27	54
Extracranial metastases	25	50
No extracranial metastases	25	50
No additional systemic cancer therapy	43	86
No steroid treatment at the time of radiotherapy	6	12
Steroid treatment unknown (not recorded)	9	18
Longer course radiotherapy, >10 fractions	9	18
Unable to complete radiotherapy as prescribed	6	12
Performance status 0	3	6
Performance status 1	31	62
Performance status 2	14	28
Performance status >2	2	4
Median values		
Median age, range (years)	82	80-90
Median time interval (cancer diagnosis to radiotherapy, months)	13	0-128
Median total dose, dose per fraction (Gy), number of fractions	30	3, 10

Table II. Survival outcomes in 50 irradiated patients

Point sum	n	% alive at 3 mo	% alive at 12 mo	Mean (mo)
7	1	0	0	0.3
10	17	35	6	3.3
13-16	32	41	9	7.4