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Evaluation of Five Survival Scores in a Cohort of Elderly Patients With Cerebral Metastasis from Non-small Cell Lung Cancer

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Abstract. *Background/Aim: Survival scores are important for treatment personalisation. A score for older patients with cerebral metastasis from non-small cell lung cancer (NSCLC) was generated. Patients and Methods: Dose-fractionation of whole-brain irradiation, age, gender, general condition, histology, count of cerebral lesions, extra-cerebral metastatic spread and time between NSCLC-diagnosis and whole-brain irradiation were analysed for survival in 285 patients. Independent prognostic characteristics were utilised for the score, which was compared against five others. Results: Based on general condition (p<0.001) and extra-cerebral spread (p=0.003), three groups were generated according to the score, 2 (n=49), 4-6 (n=206) and 7 (n=30) points. Positive predictive values (PPVs) to predict death ≤6 months and survival for ≥6 months were 100% and 52%, respectively. PPVs of other scores were 88-98% and 60-63%. Conclusion: The accuracy of the new score to predict death within ≤6 months was optimal, whereas its accuracy to predict survival for ≥6 months was lower when compared to the other low PPVs of existing scores.*

Lung cancer is by far the most common primary tumor in patients with cerebral metastases and accounts for about half of patients suffering brain metastases (1, 2). About 75 to 80% of patients with cerebral metastasis from lung cancer have non-small lung cancers (NSCLC), mainly adenocarcinomas. A considerable number of these patients are 65 years or older. This group is constantly increasing because of the demographic change and the fact that patients with NSCLC live longer due to more successful treatments of the primary tumor and extra-cerebral metastases including novel systemic therapies (3). Many patients with cerebral metastases from NSCLC have already multiple intracerebral lesions when the brain metastases are diagnosed (4-6). Most of these patients are assigned to whole-brain irradiation, which can be performed with several dose-fractionation schedules including shorter programs lasting about one week (*e.g.* 4 Gy × 5) and longer programs generally lasting two to four weeks (*e.g.* 3 Gy × 10 and 2 Gy × 20) (2, 6). When aiming to choose the optimal dose-fractionation-schedule, the patient's survival prognosis is important. In cases with poor expected survival, shorter-course irradiation is appropriate, since it results in similar cerebral control and survival as longer schedules in poor-prognosis patients but is generally less burdensome (7). Moreover, the patients preserve their limited lifespan for personal matters. In older patients with cerebral metastasis from NSCLC who are expected to live considerably longer, late treatment-related morbidity and long-term control of the cerebral metastases are more relevant (8). Thus, it is important to precisely estimate a patient's survival prognosis prior to irradiation to select the ideal dose-fractionation-schedule. Therefore, a new score was designed specifically for older patients requiring whole-brain irradiation for cerebral metastasis from NSCLC. This score was compared against four existing scores for accuracy in predicting both death within ≤6 months and survival for ≥6 months (4, 6, 9, 10).

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Patients and Methods

In a cohort of 285 older (≥65 years) NSCLC patients who received whole-brain irradiation (total doses of 30 to 40 Gy) for cerebral metastases between 1998 and 2019, eight characteristics were analysed with respect to OS. This study had received approval from the responsible local Ethics Committee. The eight characteristics included dose-fractionation-schedule (3 Gy × 10 compared to 2 Gy × 18-20), age (≤72 compared to ≥73 years), gender, histology (adenocarcinoma compared to squamous cell carcinoma and

anaplastic carcinoma), patient's general condition assessed using the performance score of the Eastern Cooperative Oncology Group [ECOG-PS (11)] (0-1 compared to 2 and 3-4, lower scores represent a better general condition), count of the cerebral lesions (1 to 3 compared to more than 3), extra-cerebral metastatic spread (presence compared to absence of extra-cerebral spread), and the time period between initial diagnosis of NSCLC and first day of whole-brain irradiation (≤1 compared to >1 month) (Table I).

These characteristics were examined by univariate analysis applying the Kaplan-Meier-method plus the log-rank test. Significant characteristics (p-value less than 0.05) and those achieving borderline significance (p-value less than 0.07) were subsequently evaluated for independence with the Cox proportional hazard model. If significance was achieved in both analyses, the characteristic qualified for integration into the new score. For each of these characteristics, a score was created; points were calculated by dividing the OS-rates at 6-months by 10. The points of the characteristics were added to obtain the total scores for each patient.

In a second step, our new score was assessed against five existing scores. Of the other scores, three were diagnosis-specific, *i.e.* updated diagnosis-specific graded prognostic assessment (DS-GPA) for NSCLC, Rades-NSCLC and WBRT-30-NSCLC (4, 9, 10). The fourth score (Evers-Score) was designed for older patients with cerebral metastases, irrespective of the primary cancer site (6). All five scores were evaluated for the positive predictive values (PPVs) to accurately predict death within ≤6 months and survival for ≥6 months following irradiation. PPVs were calculated by dividing the number of true positives by the number of all patients (true positives plus false positives).

Results

Follow up periods were 2 months (range=0-54 months) in all 285 patients and 9 months (range=0-25 months) in patients alive at the last contact. On univariate analysis, female gender (p=0.025), better general functional status (p<0.0001) and absence of extra-cerebral spread (p=0.001) were positively correlated with OS (Table II). In addition, age ≤72 years (p=0.069) and histology of adenocarcinoma (p=0.059) showed a trend (borderline significance). These five characteristics were additionally included in the Cox proportional hazard model, where better general condition (p<0.0001) and absence of extra-cerebral metastatic spread (p=0.003) maintained their significant correlation with OS (Table III). The points assigned to these characteristics (based on the 6-month OS-rates) are summarized in Table IV.

From these scoring points, patient-scores of 2 (n=49), 4 (n=104), 5 (n=89), 6 (n=13), and 7 (n=30) points were received. The corresponding 3-month OS-rates were 2%, 23%, 41%, 46% and 63%, respectively, and the 6-month OS-rates were 0%, 10%, 28%, 31% and 53%, respectively (p<0.001). Taking into account the 6-month OS-rates, three groups were formed, which were 2 points (n=49), 4 to 6 points (n=206) and 7 points (n=30). The 3-month OS-rates were 2%, 33% and 63%, respectively, and the 6-month OS-rates were 0%, 19% and 53%, respectively (p<0.001). The Kaplan-Meier curves for OS of these groups are shown in Figure 1.

Table I. *Summary of the characteristics evaluated for inclusion in the new score.*

Characteristic	Number of patients (%)
Dose-fractionation-schedule	
3 Gy × 10	163 (57.2)
2 Gy × 18-20	122 (42.8)
Age	
≤72 Years	151 (53.0)
≥73 Years	134 (47.0)
Gender	
Female	98 (34.4)
Male	187 (65.6)
Histology of carcinoma	
Adeno	193 (67.7)
Squamous cell	48 (16.8)
Anaplastic	22 (7.8)
Not specified	22 (7.8)
ECOG-PS	
0-1	119 (41.8)
2	104 (36.5)
3-4	62 (21.8)
Count of cerebral metastases	
1 to 3	119 (41.8)
More than 3	166 (58.2)
Extra-cerebral spread	
Presence	229 (80.4)
Absence	56 (19.6)
Time between diagnosis of NSCLC and irradiation	
≤1 Month	165 (57.9)
>1 Month	120 (42.1)

ECOG-PS: Performance score of the Eastern Cooperative Oncology Group.

Four patients of the entire cohort were alive at the last contact but had a follow up period of less than 6 months. The calculations of the PPVs regarding death within ≤6 months and survival for ≥6 months were performed in the remaining 281 patients. When applying our new score, the PPV of the group with the worst OS (2 points) to correctly predict death within ≤6 months was 100%. This PPV was higher than those achieved with the other four scores (4, 6, 9, 10), where the PPVs ranged between 88% and 98% (Table V). When aiming to correctly predict survival for ≥6 months, the PPV achieved with the new score was the lowest of all five scores, *i.e.* 52% compared to 60-63% (Table V) (4, 6, 9, 10). The highest PPV was achieved when applying the Evers-Score (6).

Discussion

Many patients with only few cerebral metastases of limited size are considered for local therapies such as neurosurgery and radiosurgery, either alone or in combination with whole-brain irradiation. Moreover, local therapies may be combined with novel systemic agents that are able to cross the blood-

Table II. *Post-irradiation survival rates at 3 and 6 months (univariate analyses).*

Characteristic	At 3 months (%)	At 6 months (%)	*p*-Value
Dose-fractionation-schedule			0.49
3 Gy × 10	29	18	
2 Gy × 18-20	33	22	
Age			0.069
≤72 Years	34	23	
≥73 Years	26	15	
Gender			**0.025**
Female	33	25	
Male	29	16	
Histology of carcinoma			0.059
Adeno	35	23	
Squamous cell	24	15	
Anaplastic	23	9	
ECOG-PS			**<0.0001**
0-1	46	33	
2	29	15	
3-4	3	0	
Count of cerebral metastases			0.19
1 to 3	33	23	
More than 3	29	17	
Extra-cerebral spread			**0.001**
Presence	27	15	
Absence	46	35	
Time between diagnosis of NSCLC and irradiation			0.54
≤1 Month	31	19	
>1 Month	30	19	

ECOG-PS: Performance score of the Eastern Cooperative Oncology Group, bold *p*-values were significant.

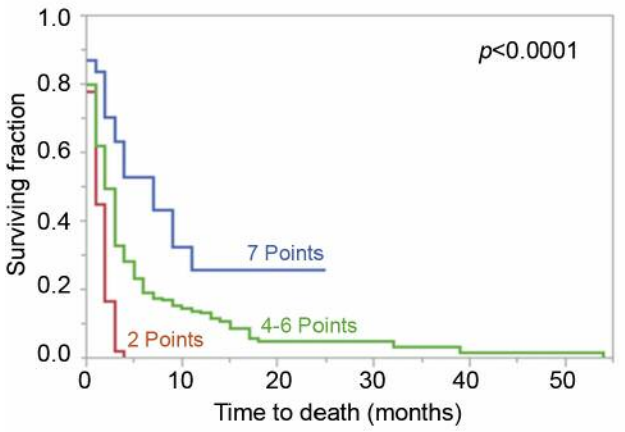

Figure 1. *Kaplan–Meier curves for post-irradiation OS of the patients with 2 points (n=49), 4 to 6 points (n=206) and 7 points (n=30).*

Table III. *Results of the multivariate analysis with the Cox proportional hazard model.*

Characteristic	Hazard ratio	95% confidence interval	*p*-Value
Age	1.15	0.89-1.50	0.29
Gender	1.17	0.88-1.56	0.28
Histology of carcinoma	1.13	0.92-1.37	0.25
ECOG-PS	1.51	1.2-1.81	**<0.0001**
Extra-cerebral spread	1.64	1.18-2.33	**0.004**

ECOG-PS: Performance score of the Eastern Cooperative Oncology Group, bold *p*-values were significant.

brain-barrier. These agents include immuno-therapeutic drugs and targeted therapy particularly for EGFR- or ALK-positive adenocarcinomas (12-16). However, patients with these mutations are generally younger than the current cohort (17). Moreover, a considerable number of older patients cannot tolerate local therapies and systemic immunotherapies. Therefore, many older patients with a limited number of cerebral metastases from NSCLC receive whole-brain irradiation alone (1, 4, 10). This applies also to the vast majority of older patients with multiple cerebral lesions. For this type of radiation therapy, various dose-fractionation-schedules can be employed with overall treatment times ranging from one to four weeks (1). To select the optimal schedule for an older patient, several aspects need to be considered, one of them being the patient's remaining lifespan. For short-term survivors, each day without receiving cancer treatment is important. Therefore, 4 Gy × 5 administered on five consecutive working days, appears the best option. This schedule has been compared to a two-week schedule (3 Gy × 10) with respect to intracerebral control and OS in patients with limited survival prognoses (7). At 6 months following irradiation, intracerebral control rates were 50% and 37%, respectively (p=0.07), and OS-rates were 24% and 27%, respectively (p=0.29). Longer-term survivors appear not adequately treated with 4 Gy × 5 and should receive whole-

Table IV. *Characteristics independently associated with survival and related points.*

Characteristic	6-month OS (%)	Points
ECOG-PS		
0-1	33	3
2	15	2
3-4	0	0
Extra-cerebral spread		
Presence	15	2
Absence	35	4

OS: Overall survival; ECOG-PS: performance score of the Eastern Cooperative Oncology Group.

Table V. *Positive predictive values of the evaluated scores for identification of death within ≤6 months and survival for ≥6 months. Evaluated scores were the new score, updated DS-GPA classification (9), Rades-NSCLC score (4), WBRT-30-NSCLC score (10) and Evers-Score (6).*

Prognosis	New score	Updated DS-GPA	Rades-NSCLC	WBRT-30-NSCLC	Evers-score
Worst prognosis					
Points	2	0.0-1.0	5-9	9-12	3-6
Death ≤6 months (PPV)	100% (49/49)	88% (181/206)	91% (165/181)	98% (101/103)	98% (89/91)
Best prognosis					
Points	7	2.5-3.0	15	18-20	13
Survival ≥6 months (PPV)	52% (15/29)	60% (9/15)	60% (6/10)	60% (15/25)	63% (5/8)

PPV: Positive predictive value.

brain irradiation with doses of 30 Gy or beyond, depending on the OS time. In a retrospective study that compared 3 Gy × 10 (n=109) to 2 Gy × 20 (n=75) in patients with very favorable survival prognoses, 2 Gy × 20 resulted in increased 1-year rates of OS (61% *versus* 50%, p=0.007) and intracerebral control (44% *versus* 28%, p=0.064) (8). These data underline that it is important to be aware of a patient's survival prognosis before assigning a dose-fractionation-schedule. To support treating radiation oncologists in this matter, a new score was developed for estimating the 6-month OS probability of older patients with cerebral metastases from NSCLC. This new instrument consisted of three groups, 2 points, 4-6 points and 7 points, with 6-month OS rates of 0%, 19% and 53%, respectively. Patients of the 2-points group appear good candidates for irradiation with 4 Gy × 5 (7). As these patients had a very poor prognosis with a median OS time of only 1 month and a 3-month OS-rate of only 2%, they may be also considered for best supportive care alone. In a randomized trial, the benefit of adding whole-brain irradiation to best supportive care was small; mean quality-adjusted life-time was 46.4 days in irradiated patients compared to 41.7 days with best supportive care alone (5). A confirmatory study from Norway showed that in patients with more favorable features, the addition of whole-brain irradiation resulted in longer OS (18). Patients with 4 to 6 points had a poor to intermediate survival prognosis with a median OS time of 2 months and 3- and 6-month OS-rates of 33% and 19%, respectively. Therefore, these patients may be considered for 4 Gy × 5 or 3 Gy × 10. Patients of the 7-points group had the best survival prognosis with a median OS time of 7 months and a 6-month OS-rate of 53%. These patients appear good candidates for longer-course irradiation with 3 Gy × 10 or a schedule with a higher dose such as 2 Gy × 20 (8). To reduce the risk of radiation-induced cognitive deficits, these patients should also be considered for a hippocampal sparing technique and administration of memantine (19). When using the new score, the fact that it was built from retrospective data should be regarded.

Since several prognostic tools had already been developed to estimate the survival prognoses of patients with cerebral metastases from NSCLC, one may question whether an additional score is really necessary and useful? To answer this question, the new score was compared to existing tools for accuracy in predicting death within ≤6 months and survival for ≥6 months following irradiation. The evaluated existing scores included the updated DS-GPA classification for NSCLC, the Rades-NSCLC score, the WBRT-30-NSCLC score and the non-diagnosis specific Evers-Score for elderly patients (4, 6, 9, 10). The accuracy of our new score to correctly predict death within ≤6 months was optimal, *i.e.* 100%, and higher than that of the other scores (4, 6, 9, 10). The WBRT-30-NSCL and the Evers-Score each achieved an accuracy of 98%, which was very close to the new score (6, 10). With respect to correct prediction of survival for ≥6 months, the accuracy of the new score was only 52%. Of the other scores, the Evers-Score achieved the highest accuracy with a PPV of 63% (6). However, the PPVs of all five scores evaluated in the present study were unsatisfyingly low, and an additional score is necessary to identify patients who live ≥6 months following treatment with adequate precision (4, 6, 9, 10).

In summary, this new score was very precise in identifying patients who died within ≤6 months following irradiation and achieved the highest PPV of the evaluated scores. However, our new score did not have adequate precision when aiming to predict OS of ≥6 months. Also, the accuracy of the other scores, of which the Evers-Score achieved the highest PPV, regarding the identification of patients surviving ≥6 months was disappointing, and an additional score is required.

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 this study. T.N., S.J., M.T.K. and D.R. collected the data, which were analysed by D.R. and S.E.S. The draft of this article was written by D.R. and S.E.S, and the article subsequently reviewed and approved by all Authors.

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