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A New Diagnosis-Specific Survival Score for Patients to be Irradiated for Brain Metastases from Non-small Cell Lung Cancer

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Abstract

Introduction Personalized treatment helps one achieve optimal outcomes in patients with non-small cell lung cancer (NSCLC). Understanding patients' survival prognoses in a palliative situation like intracerebral metastases is critical. A new survival score, the WBRT-30-NSCLC, was developed for patients with intracerebral metastases from NSCLC.

Methods Eight factors were investigated in 157 patients receiving 10 × 3 Gy of whole-brain radiotherapy (WBRT) including age, gender, Karnofsky performance score (KPS), interval from diagnosis of NSCLC to WBRT, pre-WBRT systemic treatment, primary tumor control, number of intracerebral metastases, and metastasis outside the brain. Factors significant ($p < 0.05$) or showing a trend ($p < 0.08$) on multivariate analysis were used for the WBRT-30-NSCLC. Patient scores were derived by adding factor scores (6-month survival rates divided by 10). WBRT-30-NSCLC was compared to other scores for intracerebral metastases from NSCLC.

Results On multivariate analysis, age ($p = 0.005$), KPS ($p < 0.001$), systemic treatment ($p = 0.018$), and metastasis outside the brain ($p < 0.001$) were significant; number of intracerebral metastases ($p = 0.075$) showed a trend. Four groups were designed (912, 1317, 1820, and 22 points) with 6-month survival rates of 3, 26, 65, and 100%. Positive predictive value (PPV) to predict death ≤ 6 months after WBRT was 97% (updated DS-GPA classification 86%, Rades-NSCLC 88%), and PPV to predict survival ≥ 6 months was 100% (updated DS-GPA 78%, Rades-NSCLC 74%).

Conclusions The WBRT-30-NSCLC appeared very precise in identifying patients with intracerebral metastases from NSCLC dying ≤ 6 months or surviving ≥ 6 months. It appeared more precise than previous scores and can support physicians developing personalized treatment regimens.

Keywords Non-small cell lung cancer · Intracerebral metastases · Whole-brain radiotherapy · Survival prognoses · Disease-specific survival score

Introduction

Non-small cell lung cancer (NSCLC) is the most common primary tumor type found in patients with intracerebral metastases [1]. The vast majority of these patients receive radiotherapy, either as whole-brain radiotherapy (WBRT) alone, local therapy (stereotactic radiosurgery or fractionated stereotactic radiotherapy), or as a combination of WBRT and local therapy [2–4]. Despite the increasing use of local therapies, WBRT alone is still administered to a considerable number of patients with intracerebral metastases from NSCLC, particularly for patients with multiple lesions or a markedly reduced performance status [2, 3]. For WBRT of intracerebral metastases, different dose-fractionation schedules are used including short-course (e.g., 5 × 4 Gy over 1 week) and longer-course (e.g., 10 × 3 Gy over 2 weeks and 20 × 32 Gy over 4 weeks) WBRT schedules.

The selection of the WBRT schedule should take into account the patients' survival prognoses. Since 5 × 4 Gy in 1 week was shown non-inferior to longer-course WBRT with respect to intracerebral control and survival in patients with limited survival prognoses of up to 3 months, 5 × 4 Gy appears a good choice for these patients [5]. In contrast,

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for those patients with longer expected survival times of more than 6 months, longer-course WBRT schedules including lower doses per fraction appear a better option in terms of improved long-term intracerebral control and less late WBRT-related toxicity [6, 7].

Thus, to select the optimal WBRT schedule, treating physicians should be able to estimate a patient's remaining lifespan precisely. This goal can be achieved with survival scores that would ideally be available for each primary tumor type to account for different biologies and prognoses. For patients with intracerebral metastases from NSCLC, two scoring instruments do already exist, the disease-specific graded prognostic assessment (DS-GPA) classification and our previous score (Rades-NSCLC) [8, 9]. These scores were created in cohorts of patients heterogeneously treated for their intracerebral metastases. The patients used for building the DS-GPA received different WBRT schedules plus/minus a radio-sensitizer, chemotherapy, or stereotactic radiosurgery, and the patients used for building our previous score received different WBRT schedules [8, 9]. Therefore, hidden selection biases might have been introduced when creating the scoring tools due to different treatment regimens. To reduce the risk of bias, a scoring tool (WBRT-30) was created in a homogeneously treated series; all patients received 10×3 Gy of WBRT alone [10]. However, the WBRT-30 was developed in a series of patients with intracerebral metastases from many different primary tumor types. To be more specific and provide the best possible level of personalization of the treatment, a WBRT-30 score was created in this study particularly for patients with intracerebral metastases from NSCLC (WBRT-30-NSCLC) and compared to the existing scoring instruments.

Patients and Methods

In this study, the data of 471 patients with NSCLC who were treated with 30 Gy in 10 fractions of WBRT alone for intracerebral metastases between 1998 and 2017 were retrospectively analyzed. This patient cohort mainly represents an unselected series, since 30 Gy in ten fractions was the institutional standard dose-fractionation regimen of WBRT for many years. In this cohort, eight clinical pre-treatment factors were investigated for potential associations with survival. Median values were chosen for designing the subgroups for each factor to be compared. The investigated pre-treatment factors were age (≤62 vs. ≥63 years, median age = 62 years), gender, Karnofsky performance score (KPS < 70 vs. = 70 vs. > 70, median KPS = 70), interval from diagnosis of NSCLC to the first fraction of WBRT (≤1 vs. ≥2 months, median interval = 1 month), pre-WBRT systemic treatment (no vs. yes), control of the primary tumor (no vs. yes), number of intracerebral lesions (13 vs. ≥4, median number = 4 lesions), and metastasis outside the brain prior to or at WBRT (no vs. yes) (Table 1).

These eight factors were included in the univariate analysis which was performed with the Kaplan–Meier method plus the log-rank test [11]. The factors that reached significance on univariate analysis ($p < 0.05$) were evaluated for independent associations with survival in a multivariate analysis (Cox proportional hazard model). The factors that were significantly associated with survival ($p < 0.05$) or showed a strong trend ($p < 0.08$) in the Cox proportional hazard analysis were incorporated in the WBRT-30-NSCLC. The scores for each of these factors (factor scores) were calculated by dividing the corresponding 6-month survival rate (in %) by 10. The scores for each patient (patient scores) were derived by adding the factor scores. Prognostic groups were designed by considering the 6-month survival rates of the patient scores.

In addition, the new WBRT-30-NSCLC was compared to other disease-specific survival scores for patients with intracerebral metastases from NSCLC with respect to positive predictive values (PPVs) for correct identification of

Table 1 Distribution of the eight investigated potential prognostic factors

Factor	Number of patients	Proportion (%)
Age (years)		
≤62	238	51
≥63	233	49
Gender		
Female	183	39
Male	288	61
Karnofsky Performance Score		
<70	179	38
=70	115	24
>70	177	38
Interval from diagnosis of NSCLC to WBRT		
≤1 month	296	63
≥2 months	175	37
Pre-WBRT systemic treatment		
No	303	64
Yes	168	36
Control of the primary tumor		
No	302	64
Yes	169	36
Number of intracerebral metastases		
1–3	198	42
≥4	273	58
Metastasis outside the brain		
No	162	34
Yes	309	66

patients who die within 6 months and those patients who survive 6 months or longer following WBRT. The other scores were the updated DS-GPA classification for NSCLC and our previous score (Rades-NSCLC) (Tables 2 and 3) [8, 9]. Furthermore, the WBRT-30-NSCLC and the other three tools were compared for the discriminations between the different prognostic groups within each scoring system (Chi-square test).

Results

In the entire series, the survival rates at 3, 6, 9, and 12 months were 44, 29, 22, and 18%, respectively. On univariate analysis, age ≤ 62 years ($p < 0.001$), female gender ($p = 0.025$), KPS > 70 ($p < 0.001$), systemic treatment prior to WBRT ($p < 0.001$), control of the primary tumor at WBRT ($p = 0.004$), only 1–3 intracerebral metastases ($p < 0.001$), and absence of metastasis outside the brain ($p < 0.001$) showed significant associations with survival (Table 4) and were included in the Cox proportional hazard model. Younger age ($p = 0.005$), higher KPS ($p < 0.001$), systemic treatment prior to WBRT ($p = 0.018$), and absence of metastasis outside the brain ($p < 0.001$) were also significant in this multivariate analysis. In addition, 1–3 intracerebral metastases showed a strong trend ($p = 0.075$). The results of the multivariate analysis are summarized in Table 5. These five predictors of survival were used to design the WBRT-30-NSCLC. After adding the factor scores (Table 6) for each patient, patient scores ranging from 9 to 22 points were obtained. The 6-month survival rates of the different patient scores are illustrated in Fig. 1. Taking into account the 6-month survival rates of the patient scores, four prognostic groups were formed: i.e., 9–12 points ($n = 123$, group A), 13–17 points ($n = 247$, group B), 18–20 points ($n = 89$, group C), and 22 points ($n = 12$, group D). The 6-month survival rates of these groups were 3, 26, 65, and 100%, respectively (Fig. 2, $p < 0.001$). Median survival times were 2, 3, 10, and 19 months, respectively ($p < 0.001$).

Table 2 Updated DS-GPA classification for patients with intracerebral metastases from NSCLC [8]

	Scoring criteria		
	0	0.5	1.0
Age (years)	> 60	50–60	< 50
Karnofsky Performance Score	< 70	70–80	90–100
Extracerebral metastasis	Present	–	Absent
Number of brain metastases	> 3	2–3	1

Prognostic groups: 0.0–1.0 points, 1.5–2.0 points, 2.5–3.0 points, and 3.5–4.0 points

Table 3 Factor scores of the Rades-NSCLC score [9]

	Factor score
Gender	
Female	5
Male	2
Karnofsky Performance Score	
< 70	1
≥ 70	5
Extracranial metastases	
No	5
Yes	2

Prognostic groups: 5–9 points, 11–12 points, and 15 points

The PPV of group A of the present study (worst prognostic group) to identify patients who died ≤ 6 months following WBRT was 97%, which was higher than the corresponding

Table 4 Univariate analyses of survival; *p* values were obtained from the log-rank test

Factor	At 3 months (%)	At 6 months (%)	At 9 months (%)	At 12 months (%)	*p* Value
Age (years)					
≤ 62	55	37	28	23	**< 0.001**
≥ 63	34	21	15	13	
Gender					
Female	48	37	27	24	**0.025**
Male	42	24	18	15	
Karnofsky Performance Score					
< 70	16	6	5	3	**< 0.001**
= 70	50	32	21	13	
> 70	69	50	39	37	
Interval from diagnosis of NSCLC to WBRT					
≤ 1 month	47	31	22	21	0.51
≥ 2 months	40	26	22	13	
Pre-WBRT systemic treatment					
No	40	24	18	14	**< 0.001**
Yes	52	39	29	26	
Control of the primary tumor					
No	41	25	17	16	**0.004**
Yes	50	37	30	23	
Number of intracerebral metastases					
1–3	51	36	28	25	**< 0.001**
≥ 4	40	24	17	14	
Metastasis outside the brain					
No	64	49	39	34	**< 0.001**
Yes	34	19	13	10	
Entire cohort	44	29	22	18	

Bold values indicate statistically significant *p* values

Table 5 Multivariate analyses of survival (Cox proportional hazard model)

Factor	Hazard ratio	95% confidence interval	*p* Value
Age			
≤62 versus ≥63 years	1.34	1.09–1.65	**0.005**
Gender			
Female versus male	1.18	0.96–1.46	0.11
Karnofsky Performance Score			
<70 versus 70 versus >70	0.57	0.50–0.65	**<0.001**
Pre-WBRT systemic treatment			
No versus yes	0.73	0.56–0.95	**0.018**
Control of the primary tumor			
No versus yes	0.95	0.73–1.24	0.72
Number of intracerebral metastases			
1–3 versus ≥4	1.06	0.99–1.14	0.075
Metastasis outside the brain			
No versus yes	1.77	1.41–2.23	**<0.001**

Bold values indicate statistically significant *p* values

Table 6 Six-month survival rates of the factors used to create the WBRT-30-NSCLC and corresponding factor scores

Factor	6-Month survival rate (%)	Factor score
Age (years)		
≤62	37	4
≥63	21	2
Karnofsky Performance Score		
<70	6	1
=70	32	3
>70	50	5
Pre-WBRT systemic treatment		
No	24	2
Yes	39	4
Number of intracerebral metastases		
1–3	36	4
≥4	24	2
Metastasis outside the brain		
No	49	5
Yes	19	2

PPVs of the worst prognostic groups of the previous scores. These were 88% for the Rades-NSCLC (scores of 5–9 points) and 86% for the updated DS-GPA classification (scores of 0.0–1.0) [8, 9]. The PPV of group D of the present study (most favorable prognostic group) to identify patients who lived for at least 6 months following WBRT was 100%, which was also higher than that for the most favorable groups of the previous scores. These were 74% for the Rades-NSCLC (15 points) and 78% for the updated DS-GPA classification (scores of 3.5–4.0) [8, 9].

Regarding the WBRT-30-NSCLC, the 6-month survival differences between group A and group B ($p<0.001$), between group B and group C ($p<0.001$), and between group C and group D ($p=0.040$) were all significant. For the updated DS-GPA classification, the differences between 0.0 and 1.0 and 1.5 and 2.0 points ($p<0.001$) and between 1.5 and 2.0 and 2.5 and 3.0 points ($p<0.001$) achieved significance but the difference between 2.5 and 3.0 and 3.5 and 4.0 points ($p=0.83$) was not significant [8]. In the Rades-NSCLC score, both the difference between the poor (5–9 points) and the intermediate (11–12 points) prognostic group ($p<0.001$) and between the intermediate (11–12 points) and the favorable (15 points) prognostic group ($p=0.019$) were significant [9].

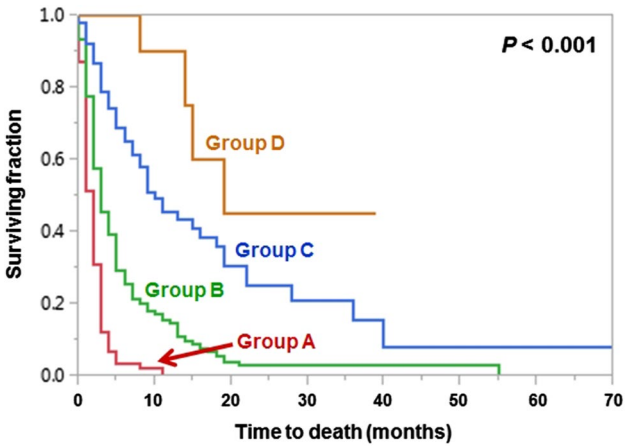

Fig. 2 Kaplan–Meier curves of prognostic groups A (9–12 points), B (13–17 points), C (18–20 points), and D (22 points). The *p* value was received from the comparison of the curves with the log-rank test

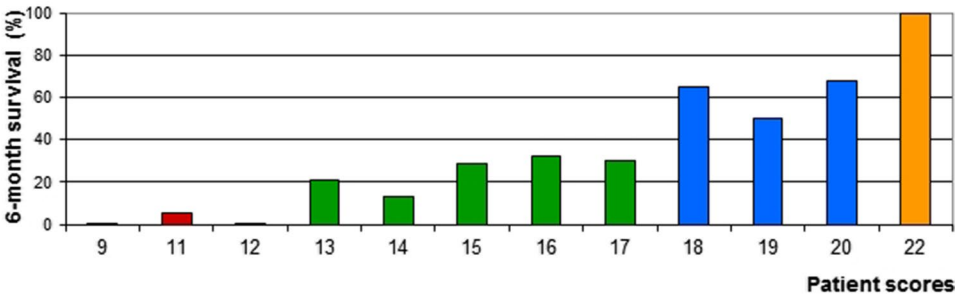

Fig. 1 The 6-month survival rates of different scoring points ranging from 9 to 22 points

Discussion

Most patients with intracerebral metastases from NSCLC have poor survival prognoses. In addition to modern radiation techniques and novel targeted therapies, the patients' situations may be improved with the use of individualized treatment regimens. This includes the choice of the appropriate dose-fractionation schedule if patients are assigned to receive WBRT accounting for a patient's survival prognosis [2]. Overtreatment and undertreatment are best avoided.

For patients with relatively unfavorable survival prognoses, a short course of WBRT, e.g., 5×4 Gy over 1 week appears reasonable, particularly for patients with multiple intracerebral lesions. In a previous study of 442 patients treated with WBRT alone for more than three lesions, 5×4 Gy over 1 week ($n=232$) was non-inferior to 10×3 Gy over 2 weeks ($n=210$). [5] The 3-month and 6-month survival rates were 47% and 24%, respectively, after 5×4 Gy and 52% and 27%, respectively, after 10×3 Gy. Thus, overall treatment time can be reduced from 2 weeks to 1 week in patients with more than three lesions and a limited survival prognosis. For patients with intracerebral metastases from NSCLC and a very short remaining lifespan, WBRT may be omitted and supportive care (OSC) including dexamethasone alone can be given. In a randomized trial of 538 patients, the quality-adjusted life-years were 46.4 days in the OSC + short-course WBRT (5×4 Gy) group compared to 41.7 days in the OSC alone group [12].

In contrast to patients with poor or very poor survival prognoses, those patients with a longer expected survival time are not optimally treated with short-course WBRT and/or OSC. They should receive longer-course WBRT and may even benefit from total doses higher than 30 Gy. In a previous study of 186 patients with very favorable prognoses, 20×2 Gy of WBRT over 4 weeks resulted in significantly higher intracerebral control and survival rates than 10×3 Gy over 2 weeks [7]. At one year, survival rates were 61% after 20×2 Gy and 50% after 10×3 Gy, respectively ($p=0.008$ on multivariate analysis), and intracerebral control rates were 44% and 28%, respectively ($p=0.047$ on multivariate analysis). In addition, the risk of developing WBRT-related neurocognitive deficits can be reduced with the use of lower doses per fraction [6]. Another potential option to lower the risk of neurocognitive dysfunction is WBRT sparing of the hippocampi. A phase 2 trial had investigated neurocognitive deficits 4 months after 10×3 Gy of WBRT and found significant neurocognitive dysfunction in 7% of the patients, which was significantly less than the 30% observed in a historical control group ($p<0.001$) [13]. According to a placebo-controlled phase 3 trial, the addition of memantine to WBRT can also decrease the rate of patients experiencing neurocognitive deficits [14]. At 24 weeks following WBRT, significant neurocognitive dysfunction was observed in 54% of the patients receiving WBRT plus memantine and in 65% of those patients receiving WBRT alone.

Thus, patients with different survival prognoses require different dose-fractionations of WBRT. Therefore, scoring systems were created to enable the treating physicians to estimate an individual patient's remaining lifespan. To account for different tumors associated with intracerebral metastases, separate systems were designed for single entities including NSCLC. In 2012, the updated version of separate DS-GPA classifications for several entities including NSCLC was published [8]. This classification included four prognostic groups (Table 2) with different median survival times of 3.0 (0.0–1.0 points), 5.5 (1.5–2.0 points), 9.4 (2.5–3.0 points), and 14.8 (3.5–4.0 points) months, respectively ($p<0.001$). However, the DS-GPA classifications were developed in a cohort of patients who all received WBRT but quite heterogeneous treatments including different WBRT regimens, the addition of different systemic treatments, and the addition of radiosurgery [8]. This heterogeneity of treatments may have led to inclusion of hidden selection biases. Therefore, another scoring system, the Rades-NSCLC, was created and presented in 2013 that included three prognostic groups with 6-month survival rates of 9% (5–9 points), 54% (11–12 points), and 79% (15 points), respectively, in the test group ($p<0.001$) and 14, 56, and 78%, respectively, in the validation group ($p<0.001$) (Table 3) [9]. For the Rades-NSCLC, only patients were included, who received WBRT alone without systemic treatment or radiosurgery. However, different WBRT regimens were allowed and a certain risk of a hidden bias, although likely lower than for the development of the DS-GPA, remained.

Therefore, a new tool, the WBRT-30-NSCLC was developed in the present study that included only patients treated with 10×3 Gy of WBRT alone and represents the survival score developed in the most homogeneously treated cohort of patients with intracerebral metastases from NSCLC presented so far. This scoring system consists of four prognostic groups with 6-month survival rates of 3, 26, 65, and 100%, respectively. The PPVs of the new WBRT-30-NSCLC to correctly identify patients who died within 6 months following WBRT and those patients who survived for at least 6 months were very high (97% and 100%) and higher than obtained when applying the DS-GPA (86% and 78%) and the Rades-NSCLC (88% and 74%) [8, 9].

Thus, the WBRT-30-NSCLC appeared more accurate than the other two scoring systems when aiming to predict whether patients will likely die within 6 months or will survive for 6 months following WBRT. However, when following the subsequent recommendations, the retrospective nature of the data used to create the WBRT-30-NSCLC should be kept in mind despite the homogeneous treatment the patients received. Retrospective studies always bear a

risk of hidden selection biases. Moreover, systemic treatment of NSCLC improved during the period of 20 years when the patients used to build the WBRT-30-NSCLC were treated, which likely had an impact on their survival [13, 14].

Due to their very poor survival, patients of group A appear appropriately with 5×4 Gy of WBRT plus OSC or even with OSC alone as suggested in the QUARTZ trial [12]. Since patients of group B also have a limited survival prognosis with only 26% living 6 months or longer following WBRT, they can be considered candidate for short-course WBRT with 5×4 Gy. The survival prognosis of group C patients can be regarded as intermediate with almost two-thirds of the patients living for at least 6 months after WBRT, and these patients may be considered for 10×3 Gy of WBRT. Group D patients achieving had a very favorable survival prognosis with a 6-month survival rate of 100% and should therefore receive longer-course WBRT with total doses higher than 30 Gy and doses per fraction of less than 3.0 Gy, i.e., 20×2 Gy or 14–15×25 Gy. For patients of groups C and D, the novel approaches of hippocampal sparing and the addition of memantine should be considered and discussed with the patients to decrease the risk of neurocognitive decline [15, 16].

In conclusion, the new WBRT-30-NSCLC appeared precise and more accurate than previous tools in identifying patients with intracerebral metastases from NSCLC who will likely die within 6 months and patients who likely survive 6 months or longer. This new tool can be very helpful for physicians when they develop a personalized treatment approach and can be used from proper stratification of patients included in future clinical trials.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval All procedures performed were in accordance with ethical standards and the Helsinki declaration from 1964 and its later amendments. The study was approved by the ethic committee of the University of Lübeck (reference number: 19-003A). Due to its retrospective design, informed consent specifically for this study was not required.

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