ANTICANCER RESEARCH *39*: 4273-4277 (2019)
doi:10.21873/anticanres.13591

Prognostic Role of Pre-Treatment Symptoms for Survival of Patients Irradiated for Brain Metastases

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Abstract. *Background/Aim: For treatment of brain metastases, a patient's survival prognosis should be considered. Existing survival scores appear complex and require complete tumor staging. For many patients, a faster and simpler tool would be helpful. Patients and Methods: This retrospective study investigated the prognostic value of the number of pre-treatment symptoms plus eight other factors on survival of patients irradiated for brain metastases. Other factors included whole-brain radiotherapy (WBRT) regimen, age, gender, performance score, primary tumor type, number of brain metastases, extracranial metastases, and interval between cancer diagnosis and WBRT. Results: The number of symptoms (p=0.002) and all other factors were significantly associated with survival on univariate analyses. On multivariate analysis, all factors but the number of symptoms (p=0.47) and primary tumor type (p=0.48) were significant. Conclusion: Since the number of symptoms was not an independent predictor of survival, it cannot replace existing scoring tools and may only serve for orientation.*

Whole-brain radiotherapy (WBRT), either alone or in combination with local therapies, is the most common treatment for brain metastases worldwide (1). For patients with multiple cerebral lesions and those with a limited performance status or severe comorbidities, WBRT alone is frequently used. Common WBRT regimens include 5×4 Gy over 1 week, 10×3 Gy over 2 weeks and 20×2 Gy over 4 weeks (1). A shorter program is preferred for patients with poor survival prognoses in order to give them as much time as possible with their family and friends, and enable them to get important things done before they die. Administration of a short course of WBRT for these patients is supported by the fact that 5×4 Gy was shown not to be inferior to 10×3 Gy regarding survival and intracerebral control in patients with multiple brain metastases (2). In contrast, patients with more favorable survival prognoses benefit from longer-course WBRT including total doses beyond 30 Gy and doses per faction of less than 3 Gy in terms of improved outcomes (survival and intracerebral control) with less neurocognitive decline (3, 4). Thus, prediction of a patient's remaining lifetime appears crucial for selecting the optimal treatment. This aspect is already well-recognized and scoring instruments facilitating the prediction of individual survival prognoses have been developed. Major instruments for patients receiving WBRT include recursive partitioning analysis (RPA) classification, graded prognostic assessment (GPA) classification, Rades Score and WBRT-30 score (5-8). All of these tools were based on four prognostic factors, including the presence or not of extracranial metastases. To use these instruments properly, *i.e.* to be able to state whether extracranial metastases are present, complete tumor staging is required, but often not possible. Complete staging can be time consuming and would delay the start of treatment. Moreover, it may be burdensome, particularly for patients with poor performance status and significant comorbidities. Thus, particularly for this latter group, a very simple scoring tool would be desirable for estimating their survival prognoses quickly and without significant effort. Such a tool could be based on the symptoms caused by the brain metastases, since patient history and physical examination are mandatory and available for all cases. The present study investigated the potential prognostic value of the number of pre-treatment symptoms for survival in a large cohort of patients irradiated for brain metastases. It was assumed that fewer symptoms were associated with a more favorable survival prognosis.

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Key Words: Brain metastases, pre-treatment symptoms, whole-brain radiotherapy, survival prognosis.

Patients and Methods

In a retrospective cohort study of patients who were treated with WBRT alone for brain metastases between 1994 and 2017, the number of pre-treatment symptoms (prior to WBRT and administration of corticosteroids) was evaluated for a potential association with survival. Data of patients obtained from an existing anonymized database were supplemented by data from patients treated at two German institutions between 2010 and 2017. To be eligible for this study, patients must have received WBRT alone and clinical symptoms must have been recorded in the patient files.

Symptoms included seizures, dysarthria, motor deficits, sensory deficits, neurocognitive deficits, headache, nausea/vomiting, vertigo, vision disturbance, and hearing problems. The number of symptoms was grouped as 0, 1, 2, or 3 or more symptoms. In addition to the number of symptoms, eight other factors were analyzed for survival including dose-fractionation of WBRT (5×4 Gy *vs.* 10×3 Gy *vs.* 20×2 Gy), age (≤62 *vs.* ≥63 years, median=63 years), gender, Eastern Cooperative Oncology Group performance score (ECOG-PS) (0-1 *vs.* 2 *vs.* 3-4), primary tumor type [breast cancer *vs.* non-small cell lung cancer *vs.* small cell lung cancer *vs.* renal cell carcinoma *vs.* malignant melanoma *vs.* cancer of unknown primary (CUP) *vs.* gastrointestinal cancers *vs.* other tumors], number of brain metastases (1 *vs.* 2-3 *vs.* ≥4), extracranial metastases (no *vs.* yes) and interval between cancer diagnosis and WBRT (≤6 *vs.* ≥7 months, median=7 months). Distributions of these factors are shown in Table I.

It was planned to follow-up patients until death or for at least 6 months. They were censored at the time of death or last follow-up visit. The study was approved by the Ethics Committee of the University of Lübeck (reference: 19-103A). Univariate analyses were performed with the Kaplan–Meier method supplemented by the log-rank test. The Bonferroni correction for multiple comparisons was used to adjust the *p*-values derived from the univariate analysis. Since nine factors were investigated, p-values of less than 0.0056 were considered significant representing an alpha-level of less than 0.05. Significant factors were analyzed for independence and to minimize the influence of confounding variables in a multivariate analysis (Cox proportional hazards model).

Table I. *Distribution of number of pre-treatment symptoms and other investigated factors.*

Factor	Patients, n (%)
Number of pre-treatment symptoms	
0	168 (9)
1	802 (42)
2	632 (33)
≥3	305 (16)
Dose-fractionation of WBRT	
5×4 Gy	399 (21)
10×3 Gy	958 (50)
20×2 Gy	550 (29)
Age	
≤62 Years	953 (50)
≥63 Years	954 (50)
Gender	
Female	918 (48)
Male	989 (52)
ECOG PS	
0-1	717 (38)
2	773 (41)
3-4	417 (22)
Primary tumor type	
Breast cancer	321 (17)
Non-small-cell lung cancer	794 (42)
Small-cell lung cancer	270 (14)
Renal cell carcinoma	54 (3)
Malignant melanoma	77 (4)
Cancer of unknown primary	117 (6)
Gastrointestinal cancer	115 (6)
Other	159 (8)
Number of brain metastases	
1	313 (16)
2-3	334 (18)
≥4	1260 (66)
Extracranial metastases	
No	516 (27)
Yes	1335 (70)
Unknown	56 (3)
Interval between cancer diagnosis and WBRT	
≤6 Months	950 (50)
≥7 Months	957 (50)

ECOG PS: Eastern Cooperative Oncology Group performance score; WBRT: whole-brain radiotherapy.

Results

A total of 1,907 patients, 1,354 from an existing anonymized database and 553 additional patients, met the eligibility criteria. On univariate analysis (Table II), improved survival was significantly associated with a lower number of pre-treatment symptoms (p=0.002). Since survival rates of patients with 0, 1 and 2 symptoms were similar, they were subsequently combined into one group. Survival rates of patients with 0-2 symptoms at 3, 6, 9 and 12 months were 50%, 32%, 24% and 18%, respectively, and significantly better than in patients with 3 or more symptoms (p<0.001).

On multivariate analysis, the number of pre-treatment symptoms (p=0.82) was not a significant factor (Table III). In an additional multivariate analysis, the different grouping of pre-treatment symptoms (0-2 *vs.* ≥3) did also not achieve significance (hazard ratio=1.02, 95% confidence interval=0.95-1.10, p=0.54).

Discussion

Despite recent developments favoring the treatment with neurosurgery or radiosurgery alone, a considerable number of patients with brain metastases are still candidates for WBRT (1). When aiming to provide an individual treatment including the WBRT regimen appropriately addressing the patient's personal situation and needs, the patient's remaining lifetime should be regarded.

For most patients with a short survival time, short-course WBRT with 5×4 Gy is the preferred regimen. In a previous

Table II. *Results of the univariate analyses of survival at 3, 6, 9 and 12 months.*

Factor	3 Months (%)	6 Months (%)	9 Months (%)	12 Months (%)	*p*-Value
Number of pre-treatment symptoms					
0	49	32	25	21	
1	51	33	26	19	
2	50	31	22	16	
≥3	41	21	15	8	**0.002**
Dose-fractionation of WBRT					
5×4 Gy	56	34	25	18	
10×3 Gy	46	28	21	16	
20×2 Gy	47	32	25	17	0.020
Age					
≤62 Years	58	38	30	22	
≥63 Years	39	22	16	11	**<0.001**
Gender					
Female	52	34	27	2	
Male	46	26	19	12	**<0.001**
ECOG PS					
0-1	66	49	40	30	
2	49	27	18	12	
3-4	17	4	2	1	**<0.001**
Primary tumor type					
Breast cancer	58	41	35	28	
Non-small cell lung cancer	44	30	22	16	
Small cell lung cancer	48	26	18	11	
Renal cell carcinoma	61	31	27	21	
Malignant melanoma	45	27	16	6	
Cancer of unknown primary	46	27	19	14	
Gastrointestinal cancers	40	20	16	9	
Other tumors	55	29	18	14	**<0.001**
Number of brain metastases					
1	56	42	32	27	
2-3	58	40	33	25	
≥4	44	25	18	12	**<0.001**
Extracranial metastases					
No	68	51	41	32	
Yes	42	23	17	11	**<0.001**
Interval between cancer diagnosis and WBRT					
≤6 months	45	29	21	15	
≥7 months	52	32	25	18	0.004

ECOG PS: Eastern Cooperative Oncology Group performance score; WBRT: whole-brain radiotherapy. According to the Bonferroni adjustment, *p*-values <0.0056 were considered significant and are shown in bold.

study of 442 patients treated with WBRT alone for more than three brain metastases, 5×4 Gy was not inferior to 10×3 Gy with respect to survival and intracerebral control (2). Grade 3 radiation-related acute toxicity rates were 9% and 6%, respectively (p=0.35). For selected patients with very limited survival prognoses, best supportive care (BSC) including corticosteroids without WBRT may be considered. In a randomized trial of patients with brain metastases from non-small cell lung cancer and very poor prognoses, BSC including dexamethasone was not inferior to BSC combined with 5×4 Gy of WBRT (9). In the WBRT group, more episodes of drowsiness, hair loss, nausea, and dry or itchy scalp were recorded. However, serious adverse events were not more common. The difference between mean quality-adjusted life-years was only 4.7 days, *i.e.* 41.7 days in the BSC alone group and 46.4 days in the BSC plus WBRT group. Thus, WBRT did not provide a significant benefit for this group of patients.

In patients with more favorable survival prognoses, intracerebral control and survival are also important endpoints. These patients are not uncommon, and a considerable number receive WBRT without local treatment. For example, in the study performed to create the RPA classification, all patients received WBRT without local

Table III. *Results of the multivariate Cox proportional hazards model.*

Factor	Hazard ratio	95% Confidence interval	*p*-Value
Number of pre-treatment symptoms	1.01	0.94-1.08	0.82
Age	1.30	1.17-1.44	**<0.001**
Gender	1.20	1.08-1.33	**<0.001**
ECOG PS	1.75	1.62-1.89	**<0.001**
Primary tumor type	1.00	0.98-1.02	0.70
Number of brain metastases	1.06	1.02-1.11	**0.007**
Extracranial metastases	1.70	1.51-1.92	**<0.001**
Interval between cancer diagnosis and WBRT	1.20	1.08-1.32	**<0.001**

ECOG PS: Eastern Cooperative Oncology Group performance score; WBRT: whole-brain radiotherapy. Bold values indicate significant *p*-values.

treatment. The 236 patients of RPA class 1 (representing 20% of the entire cohort) had a median survival time of 7.1 months (5). In the study creating the GPA classification, 9% (N=102) of patients had a median survival of 11.0 months, and an additional 16% (N=168) of patients had a median survival of 6.9 months (6). Patients with longer expected survival were reported to achieve better intracerebral control and survival with longer-course WBRT including total doses >30 Gy. A retrospective study of 184 patients with favorable prognoses compared 10×3 Gy and 20×2 Gy (4). Survival rates at 1 and 2 years were 50% and 14%, respectively, after 10×3 Gy, and 61% and 30%, respectively, after 20×2 Gy. Intracerebral control rates at 1 and 2 years were 28% and 11%, respectively, after 10×3 Gy, and 44% and 20%, respectively, after 20×2 Gy.

It becomes obvious that precise estimation of a patient's prognosis is important to optimally tailor the treatment. Several major scoring tools addressing this aspect exist (5-8). However, they are relatively complex and require complete tumor staging prior to the start of treatment which may result in a considerable treatment delay. Such delay is generally not acceptable for patients with brain metastases requiring relief of their debilitating symptoms. Thus, a very simple and fast tool would be preferable, particularly for patients with a poor performance status and severe brain symptoms. This study aimed to provide such a tool, simply based on the number of significant pre-treatment symptoms. In a large cohort of 1,907 patients treated with WBRT alone, 10 major pre-treatment symptoms were recorded. The majority of patients presented with one (42%) or two (33%) symptoms. Fewer than 10% were symptom-free, and 16% of patients had three or more symptoms. On univariate analysis, the number of symptoms was significantly inversely associated with survival. However, on multivariate analysis, significance was not achieved. Thus, the number of symptoms was not an independent predictor of survival and appeared not useful for the creation of a survival score. As the survival rates of patients with 0-2 symptoms were almost identical at 3 and 6 months and still similar at 9 and 12 months, we performed an additional analysis to investigate the potential prognostic value of the number of symptoms and compared 0-2 to ≥3 symptoms. However, again the results were significant on univariate but not on multivariate analysis. When interpreting these results, one should take into account the limitations of this study, mainly its retrospective design. Retrospective studies always bear the risk of hidden selection biases. Another limitation of the study is that it has not yet been externally validated. Since all patients included in this study received WBRT alone, the results cannot be generalized to other treatments for brain metastases including neurosurgical resection alone, radiosurgery alone and such local therapies combined with WBRT.

Since the number of symptoms was not significant on multivariate analyses, we feel that it cannot replace existing scoring tools designed to predict the survival prognoses of patients irradiated for brain metastases. It may only serve for orientation. One may consider re-evaluation of the existing scoring tools after the exclusion of visceral metastases as a predictive factor to avoid the need for complete tumor staging, which often results in a delay of treatment. This may also be considered for diagnosis-specific scoring tools (10-15).

In conclusion, the number of symptoms was not an independent predictor of survival in patients irradiated for brain metastases and, therefore, cannot replace existing tools. It may only serve for orientation. Since existing tools are based on presence/absence of visceral metastases, they require complete tumor staging. Such staging may result in treatment delay, which is often not acceptable, particularly for patients requiring urgent relief of symptoms. Existing tools may be re-evaluated after exclusion of visceral metastases as an essential component in order to hopefully provide a fast-to-use survival score based on independent prognostic factors.

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., H.C.H., S.J. and S.E.S. participated in the design of the study. D.R., H.C.H., L.D. and S.J. provided data. D.R. and S.E.S. performed the analyses and the interpretation of the data. D.R. and S.E.S. drafted the article, which was reviewed and approved in its final form by all Authors.

References

1 Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn CA and Chang EL: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol *2*: 210-225, 2012. PMID: 25925626. DOI: 10.1016/j.prro.2011.12.004

2 Rades D, Kieckebusch S, Lohynska R, Veninga T, Stalpers LJ, Dunst J and Schild SE: Reduction of overall treatment time in patients irradiated for more than three brain metastases. Int J Radiat Oncol Biol Phys *69*: 1509-1513, 2007. PMID: 17689033.

3 DeAngelis LM, Delattre JY and Posner JB: Radiation-induced dementia in patients cured of brain metastases. Neurology 39: 789-796, 1989. PMID: 2725874.

4 Rades D, Panzner A, Dziggel L, Haatanen T, Lohynska R and Schild SE: Dose-escalation of whole-brain radiotherapy for brain metastasis in patients with a favorable survival prognosis. Cancer *118*: 3852-3859, 2012. PMID: 22170514. DOI: 10.1002/cncr.26680

5 Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG and Byhardt R: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys *37*: 745-751, 1997. PMID: 9128946.

6 Rades D, Dunst J and Schild SE: A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol *184*: 251-255, 2008. PMID: 18427755. DOI: 10.1007/s00066-008-1831-5

7 Sperduto PW, Berkey B, Gaspar LE, Mehta M and Curran W: A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys *70*: 510-514, 2008. PMID: 17931798. DOI: 10.1016/j.ijrobp.2007.06.074

8 Rades D, Dziggel L, Nagy V, Segedin B, Lohynska R, Veninga T, Khoa MT, Trang NT and Schild SE: A new survival score for patients with brain metastases who received whole-brain radiotherapy (WBRT) alone. Radiother Oncol *108*: 123-127, 2013. PMID: 23830191. DOI: 10.1016/j.radonc.2013.06.009

9 Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, Moore B, Brisbane I, Ardron D, Holt T, Morgan S, Lee C, Waite K, Bayman N, Pugh C, Sydes B, Stephens R, Parmar MK and Langley RE: Dexamethasone and supportive care with or without whole-brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet *388*: 2004-2014, 2016. PMID: 27604504. DOI: 10.1016/S0140-6736(16)30825-X

10 Dziggel L, Gebauer N, Bartscht T, Schild SE and Rades D: Performance status and number of metastatic extra-cerebral sites predict survival after radiotherapy of brain metastases from thyroid cancer. Anticancer Res *38*: 2391-2394, 2018. PMID: 29599366. DOI: 10.21873/anticanres.12488

11 Janssen S, Hansen HC, Schild SE and Rades D: An instrument for estimating the 6-month survival probability after whole-brain irradiation alone for cerebral metastases from gynecological cancer. Anticancer Res *38*: 3753-3756, 2018. PMID: 29848738. DOI: 10.21873/anticanres.12656

12 Rades D, Dziggel and Schild SE: A specific survival score for patients receiving local therapy for single brain metastasis from a gynecological malignancy. In Vivo *32*: 825-828, 2018. PMID: 29936465. DOI: 10.21873/invivo.11314

13 Rades D, Dziggel L, Manig L, Janssen S, Khoa MT, Duong VN, Khiem VH and Schild SE: Predicting survival after whole-brain irradiation for cerebral metastases in patients with cancer of the bladder. In Vivo *32*: 633-636, 2018. PMID: 29695570. DOI: 10.21873/invivo.11285

14 Dziggel L, Schild SE, Veninga T, Bajrovic A and Rades D: Clinical factors asssociated with treatment outcomes following whole-brain irradiation in patients with prostate cancer. In Vivo *31*: 35-38, 2017. PMID: 28064217. DOI: 10.21873/invivo.11021

15 Staackmann C, Janssen S, Schild SE and Rades D: A tool to predict the probability of intracerebral recurrence or new cerebral metastases after whole-brain irradiation in patients with head-and-neck cancer. Anticancer Res *38*: 4199-4202, 2018. PMID: 2997055. DOI: 10.21873/anticanres.12714

Received May 28, 2019
Revised July 4, 2019
Accepted July 5, 2019