ANTICANCER RESEARCH *38*: 3753-3756 (2018)
doi:10.21873/anticanres.12656

An Instrument for Estimating the 6-Month Survival Probability After Whole-brain Irradiation Alone for Cerebral Metastases from Gynecological Cancer

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Abstract. *Background/Aim: Patients with cerebral metastases from gynecological cancer who receive whole-brain irradiation (WBI) alone require personalized therapy. This study contributes to personalized care by creating an instrument to predict 6-month survival probability. Patients and Methods: In 49 patients, six pre-treatment variables, namely age, Eastern Cooperative Oncology Group performance score (ECOG-PS), primary tumor type, number of cerebral metastases, metastasis outside the brain, and interval between diagnosis of gynecological cancer and WBI, were analyzed for survival. Results: Of the six pre-treatment variables, ECOG-PS was significantly associated with survival (p=0.014) and metastasis outside the brain showed a trend for association (p=0.096). Six-month survival rates divided by 10 resulted in scores of 0, 2 or 7 points for ECOG-PS and of 2 or 7 points for metastasis outside the brain. Scores for individual patients were 2, 4, 7, 9 or 14 points. Three groups were created, those with 2-7, 9 and 14 points, with 6-month survival rates of 10%, 53% and 100%, respectively (p=0.004). Conclusion: An instrument was designed to predict the 6-month survival of patients receiving WBI for cerebral metastases from gynecological cancer and facilitate personalized care.*

Many patients with cerebral metastases from gynecological cancer are not candidates for local therapies such neurosurgical resection and stereotactic radiosurgery due to their having too many cerebral lesions, a poor performance status, or many comorbidities (1). Therefore, the majority of these patients receive whole-brain irradiation (WBI) alone.

Several dose-fractionation regimens are available for WBI, including short-course programs such as 5×4 Gy in 1 week or longer-course programs with doses of 2 to 3 Gy per fraction lasting 2 to 4 weeks.

It has been reported for patients with cerebral metastases from a variety of solid tumors that intracerebral control and survival were no worse in those with poor prognoses after 5×4 Gy than after longer-course WBI (2). Therefore, short-course WBI is recommended for patients with a short survival time in order to avoid spending many of their remaining days receiving radiotherapy. According to the results of a previous study, longer-course WBI with total doses greater than 30 Gy and doses of less than 3 Gy per fraction resulted in improved intracerebral control and survival in patients with a longer expected remaining lifespan (3). Moreover, it has been reported that using doses of less than 3 Gy per fraction led to less pronounced neurocognitive deficits (4, 5). Therefore, for patients with longer expected survival times, longer-course WBI programs appear more appropriate. The results of those previous studies demonstrate the importance of estimating a patient's remaining lifespan as precisely as possible in order to choose the appropriate WBI regimen, ideally with the help of prognostic instruments (survival scores). This study aimed to create a prognostic instrument that helps predict the 6-month survival probability particularly for patients receiving WBI alone for cerebral metastases from gynecological cancer.

Patients and Methods

Data of 49 patients treated with WBI alone for cerebral metastases from gynecological cancer between 1988 and 2017 were retrospectively evaluated. Dose-fractionation regimens included shorter-course WBI with 5×4 Gy in 1 week (n=16), longer-course WBI with 10×3 Gy in 2 weeks (n=18) and other longer-course WBI programs (n=15). The dose-fractionation regimen (5×4 Gy *vs.* longer-course programs) and six pre-treatment variables were

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Key Words: Whole-brain irradiation, brain metastases, gynecological cancer, 6-month survival probability, prognostic instrument.

analyzed for possible associations with survival. These variables included age (≤59 *vs.* ≥60 years, median age=59 years), Eastern Cooperative Oncology Group performance score (ECOG-PS) (0-1 *vs.* 2 *vs.* 3), type of primary tumor (ovarian *vs.* uterine *vs.* cervical *vs.* vaginal/vulvar cancer), number of cerebral metastases (1-3 *vs.* ≥4), metastasis outside the brain (no *vs.* yes) and the interval between first diagnosis of the gynecological cancer and WBI (≤24 *vs.* ≥25 months, median interval=24 months). The distribution of patients according to all seven variables is summarized in Table I.

Statistical methods included the Kaplan–Meier method and the log-rank test for univariate analyses (6). Variables with a *p*-value of less than 0.05 were regarded significant and additionally included in a multivariate analysis, which was performed with the Cox proportional hazards model. Those pre-treatment variables that were significant ($p<0.05$) or showed a trend ($p<0.10$) for association in the multivariate analysis were used to create the prognostic instrument.

Table I. *Distributions of the investigated seven variables.*

Factor	Number of patients (%)
Dose-fractionation regimen of WBI	
5×4 Gy in 1 week	16 (33)
Longer-course programs	33 (67)
Age at the time of WBI	
≤59 Years	25 (51)
≥60 Years	24 (49)
ECOG performance score	
0-1	15 (31)
2	27 (55)
3	7 (14)
Primary tumor type	
Ovarian cancer	26 (53)
Uterine cancer	13 (27)
Cervix cancer	8 (16)
Vaginal/vulvar cancer	2 (4)
Number of cerebral metastases	
1-3	13 (27)
≥4	36 (73)
Metastases outside the brain	
No	11 (22)
Yes	38 (78)
Interval between first diagnosis of the gynecological cancer and WBI	
≤24 Months	25 (51)
≥25 Months	24 (49)

WBI: Whole-brain irradiation, ECOG: Eastern Cooperative Oncology Group.

Results

On univariate analyses, the dose-fractionation regimen of WBI ($p=0.041$), ECOG-PS ($p=0.001$) and metastasis outside the brain ($p=0.017$) were significantly associated with survival (Table II) and were, therefore, included in the analysis with the Cox proportional hazards model. In this multivariate analysis, the ECOG-PS (hazard ratio (HR)=1.97, 95% confidence interval (CI)=1.15-3.37, $p=0.014$) was significantly associated with survival. In addition, metastasis outside the brain showed a trend for association (HR=2.00, 95% CI=0.89-5.12, $p=0.096$). The dose-fractionation regimen of WBI was not significant in the multivariate analysis (HR=1.58, 95% CI=0.80-3.35, $p=0.195$). Therefore, ECOG-PS and metastasis outside the brain were used to create the prognostic instrument for estimating the 6-month survival probability.

The instrument was based on the incorporation of these two variables by dividing the 6-month percentage survival rates by 10 (Table III). The score from the ECOG-PS and the extra-cranial metastases were then summed into a single prognostic score for each patient. This procedure resulted in prognostic scores of 2, 4, 7, 9 or 14 points. The corresponding 6-month survival rates were 0%, 14%, 0%, 53% and 100%, respectively ($p<0.001$). Based on these scores, three prognostic groups were created, namely 2-7 points, 9 points and 14 points. The 6-month survival rates of these groups were significantly different at 10%, 53% and 100%, respectively ($p=0.004$), and median survival times were 4, 7 and 9 months, respectively.

Discussion

Despite considerable research efforts in the field of metastatic gynecological cancer, many of these patients have a poor prognosis, especially in those with multiple brain metastases requiring WBI. Better outcomes may be achieved with the implementation of novel anticancer drugs (7). However, personalized cancer care can contribute to this ambitious goal. Personalized approaches consider many aspects of a patient's specific situation and preferences. One important aspect is the patient's survival prognosis. If it is quite poor, the treatment should not be long or burdensome. If it is favorable, therapy should aim to achieve the best possible long-term disease control with acceptable late toxicities.

These considerations also apply to patients who are assigned to WBI alone for cerebral metastases from gynecological cancer. In the case of a short remaining lifespan, a short course of WBI is preferable. In a large retrospective study performed on 416 patients with cerebral metastases from various tumor types and poor survival prognoses, standard WBI with 10×3 Gy in 2 weeks was as effective as higher dose, longer regimens (15×3 Gy in 3 weeks/20×2 Gy in 4 weeks) with respect to intracerebral control and survival (8). The 6-month intracerebral control rates were 39% after 10×3 Gy and 41% after higher doses, respectively ($p=0.61$), and the 6-month survival rates 33% and 29%, respectively ($p=0.86$). It was possible to reduce overall treatment time by 50% from 4 to 2 weeks without

Table II. *Survival rates at 6 months following whole-brain irradiation (WBI) on univariate analyses.*

Factor	Survival at 6 months (%)	*p*-Value
Dose-fractionation regimen of WBI		
5×4 Gy in 1 week	44	
Longer-course programs	27	**0.041**
Age at the time of WBI		
≤59 Years	44	
≥60 Years	21	0.074
ECOG performance score		
0-1	67	
2	22	
3	0	**0.001**
Primary tumor type		
Ovarian cancer	35	
Uterine cancer	23	
Cervix cancer	50	
Vaginal/vulvar cancer	0	0.635
Number of cerebral metastases		
1-3	46	
≥4	28	0.565
Metastases outside the brain		
No	73	
Yes	21	**0.017**
Interval between first diagnosis of the gynecological cancer and WBI		
≤24 Months	32	
≥25 Months	33	0.999

ECOG: Eastern Cooperative Oncology Group. Bold: Significant *p*-values.

Table III. *Scoring points obtained by dividing the 6-month survival rates (in %) by 10.*

	Survival at 6 months (%)	Scoring points
ECOG performance score		
0-1	67	7
2	22	2
3	0	0
Metastasis outside the brain		
No	73	7
Yes	21	2

ECOG: Eastern Cooperative Oncology Group.

loss of efficacy. In another large retrospective study in a similar patient population (n=442), short-course WBI with 5×4 Gy in 1 week was not inferior to 10×3 Gy in 2 weeks (2). Six-month intracerebral control rates were 50% after 5×4 Gy and 37% after 10×3 Gy, respectively (p=0.07), and 6-month survival rates were 24% and 27%, respectively (p=0.29). Thus, the overall treatment time was further reduced to only 1 week. In contrast, patients with a more favorable survival prognosis can benefit from longer-course WBI in terms of improved intracerebral control and survival (3). Moreover, doses per fraction of less than 3 Gy were reported to be associated with less neurocognitive decline than doses of 3 Gy and more per fraction (4, 5).

Since a patient's survival time is an important factor to be considered when selecting the appropriate WBI regimen, it would be helpful if the treating radiation oncologists were able to estimate a specific patient's prognosis, ideally with a simple instrument. Several such instruments are already available for patients with cerebral metastases from specific tumor types such as breast cancer, lung cancer and others (9-13). In the present study, an additional prognostic instrument was developed particularly for patients treated with WBI alone for cerebral metastases from gynecological cancer. Since only patients treated with WBI alone were included, this score is more specific and carries less risk of hidden selection bias due to different treatment approaches than a previous instrument that also included patients receiving local modalities for cerebral metastases from gynecological cancer (14). In the present study, three prognostic groups were designated based on two variables, namely ECOG-PS and metastasis outside the brain: 2-7 points, 9 points and 14 points. The 6-month survival rate in the 2-7 points group was only 10%. Therefore, these patients appear to be good candidates for short-course WBI, for example with 5×4 Gy in 1 week. For the other two groups (9 points and 14 points), the 6-month survival rates were much more favorable, at 53% and 100%, respectively. Patients of both groups appear appropriate for treatment with longer-course WBI. Patients of the group with 9 points may receive 10×3 Gy in 2 weeks, and patients of that with 14 points may receive longer-course WBI with total doses >30 Gy and doses per fraction <3 Gy.

However, when considering these suggestions, the retrospective nature of the study and the risk of hidden selection biases must be considered. In order to further reduce the risk of WBI-related neurocognitive decline, WBI may be performed with hippocampal-sparing for selected patients with a limited number of cerebral lesions that are not close to the hippocampi (15).

In conclusion, a new instrument was designed to predict the 6-month survival probability of patients receiving WBI for cerebral metastases from gynecological cancer. Three predictive groups were created with significantly different survival prognoses, facilitating more personalized treatment in this specific patient group.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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.

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.

3 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*: 3853-3859, 2012.

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

5 Shaw MG and Ball DL: Treatment of brain metastases in lung cancer: strategies to avoid/reduce late complications of whole brain radiation therapy. Curr Treat Options Oncol *14*: 553-567, 2013.

6 Kaplan EL and Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.

7 Gadducci A and Guerrieri ME: Immune checkpoint inhibitors in gynecological cancers: Update of literature and perspectives of clinical tesearch. Anticancer Res *37*: 5955-5965, 2017.

8 Rades D, Haatanen T, Schild SE and Dunst J: Dose escalation beyond 30 Grays in 10 fractions for patients with multiple brain metastases. Cancer *110*: 1345-1350, 2007.

9 Sehmisch L, Schild SE and Rades D: Development of a survival score for patients with cerebral metastases from melanoma. Anticancer Res *37*: 249-252, 2017.

10 Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A and Schild SE: The first survival score for patients with brain metastases from small cell lung cancer (SCLC). Clin Neurol Neurosurg *115*: 2029-2032, 2013.

11 Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE, Trang NT and Khoa MT: A new survival score for patients with brain metastases from non-small cell lung cancer. Strahlenther Onkol *189*: 777-781, 2013.

12 Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE, Trang NT and Khoa MT: A simple survival score for patients with brain metastases from breast cancer. Strahlenther Onkol *189*: 664-667, 2013.

13 Rades D, Dziggel L, Veninga T, Bajrovic A and Schild SE: Overall survival after whole-brain radiation therapy for intracerebral metastases from testicular cancer. Anticancer Res *36*: 4817-4819, 2016.

14 Rades D, Janssen S, Bajrovic A, Veninga T, Fischer D and Schild SE: A new scoring tool to assess overall survival in patients with intracerebral metastases from gynecological cancers. Int J Gynecol Cancer *27*: 597-602, 2017.

15 Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L and Mehta MP: Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol *32*: 3810-3816, 2014.

Received April 18, 2018
Revised May 11, 2018
Accepted May 15, 2018