

# Overall Survival After Whole-Brain Radiation Therapy for Intracerebral Metastases from Testicular Cancer

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**Abstract.** *Background/Aim:* To identify predictors and develop a score for overall survival of patients with intracerebral metastasis from testicular cancer. *Patients and Methods:* Whole-brain radiation therapy program, age, Karnofsky performance score (KPS), number of intracerebral metastases, number of other metastatic sites and time between testicular cancer diagnosis and radiation therapy were analyzed for their association with overall survival in eight patients. *Results:* KPS of 80-90% was significantly associated with better overall survival ( $p=0.006$ ), one or no other metastatic sites showed a trend for a better outcome ( $p=0.10$ ). The following scores were assigned: KPS 60-70%=0 points, KPS 80-90%=1 point,  $\geq 2$  other metastatic sites=0 points, 0-1 other metastatic sites=1 point. Two groups, with 0 and with 1-2 points, were formed. Overall survival rates were 33% vs. 100% at 6 months and 0% vs. 100% at 12 months ( $p=0.006$ ), respectively. *Conclusion:* A simple instrument enabling physicians to judge the overall survival of patients with intracerebral metastasis from testicular cancer is provided.

Radiation therapy is by far the most frequently used type of treatment for intracerebral metastases, mainly in the form of whole-brain radiation therapy (1). However, for radiation oncologists, intracerebral metastasis from testicular cancer is a very rare situation. These patients account for only about 0.5% of patients with cancer with intracerebral spread. Therefore, only very little is known about the results of and prognosis after radiation therapy in this patient group. When presenting to a

radiation oncologist for irradiation of other systemic metastases, patients with testicular cancer experience a much more favorable outcome than the majority of patients with other metastatic cancer (2). This may also apply to patients with testicular cancer who have developed intracerebral lesions. Assuming this is true, these patients may require treatment strategies different from those for other patients with intracerebral metastases (3-5). Therefore, the current study was carried out to determine the overall survival rate of patients treated with whole-brain radiation therapy for intracerebral metastasis from testicular cancer. An additional goal was to identify predictors of overall survival that can be used for a prognostic instrument enabling physicians to judge the overall survival times of such patients. This is important when physicians wish to optimally tailor their treatment regimen to the situation of a particular patient with intracerebral metastasis from testicular cancer.

## Patients and Methods

Eight patients who received whole-brain radiation therapy for intracerebral metastases were included in this study. The whole-brain radiation therapy was administered with one of the two most common schedules, namely 20 Gy in five fractions and 30 Gy in 10 fractions, or with a higher dose, *i.e.* 40 Gy in 20 fractions. The program of whole-brain radiation therapy as well as age ( $\leq 34$  vs.  $\geq 35$  years; median age was 34.5 years), Karnofsky performance score (KPS) (80-90% vs. 60-70%), the number of intracerebral metastases (limited: 1-3 vs. multiple:  $\geq 4$ ), number of other (*i.e.* extracerebral) metastatic sites (0-1 vs.  $\geq 2$ ) and the time between diagnosis of testicular cancer and whole-brain radiation therapy ( $\leq 8$  vs.  $\geq 9$  months; median time was 8.5 months) were evaluated for associations with overall survival. For the analyses regarding overall survival, the Kaplan-Meier method and the Wilcoxon test were applied. Significance was defined as  $p < 0.05$ , a trend as  $p \leq 0.10$ .

## Results

In the entire series, the 6-month and 12-month overall survival rates were 75% and 63%, respectively. On overall survival

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Table I. Results of the analysis of overall survival.

Variable	At 6 months	At 12 months	p-Value
Whole-brain radiation therapy			
20 Gy/5 fractions or 30 Gy/10 fractions (n=3)	67	67	
40 Gy/20 fractions (n=5)	80	60	0.88
Age			
≤34 years (n=4)	75	75	
≥35 years (n=4)	75	50	0.56
Karnofsky performance score			
80-90% (n=5)	100	100	
60-70% (n=3)	33	0	<b>0.006</b>
Number of intracerebral metastases			
Limited (1-3 lesions) (n=4)	100	100	
Multiple (≥4 lesions) (n=4)	50	25	0.13
Number of other metastatic sites			
0-1 (n=3)	100	100	
≥2 (n=5)	60	40	0.10
Time between diagnosis of testicular cancer and whole-brain radiation therapy			
≤8 months (n=4)	75	25	
≥9 months (n=4)	75	75	0.56

Significant p-values are shown in bold.

analysis (Table I), a KPS of 80-90% was significantly associated with a better outcome ( $p=0.006$ ). In addition, presence of only one or no other metastatic sites showed a trend for a better outcome ( $p=0.10$ ). These two parameters were subsequently used for the development of an instrument for rating the overall survival of patients with intracerebral metastases from testicular cancer. The following scores were assigned: KPS of 60-70%=0 points, KPS of 80-90%=1 point, ≥2 other metastatic sites=0 points; and 0-1 other metastatic sites=1 point. Thus, total scores were either 0, 1 or 2 points. The overall survival rates at 6 months were 33%, 100% and 100%, respectively, and the overall survival rates at 12 months 0%, 100% and 100%, respectively. Considering these rates, two groups were formed, with 0 points and with 1-2 points, resulting in overall survival rates at 6 and 12 months of 33% vs. 100% and 0% vs. 100%, respectively ( $p=0.006$ ). Figure 1 shows the Kaplan–Meier survival curves of these two groups.

### Discussion

In comparison to other cancer types, patients with testicular cancer have a much better prognosis (2). In order to deliver the best available therapy to an individual patient, considerable research has been carried out for patients with testicular cancer, including studies that aimed to define preclinical and clinical factors serving as markers for treatment outcomes (6-10). If patients with testicular cancer develop intracerebral metastases, whole-brain radiation therapy may be indicated (1). For this specific situation, to our knowledge no study has been reported that was

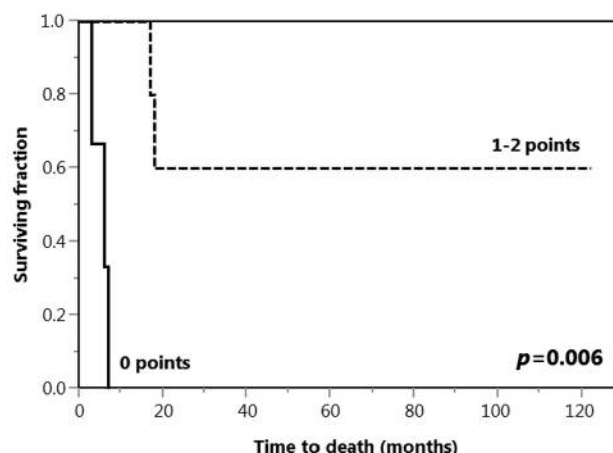


Figure 1. Overall survival curves of the two groups scoring 0 points and 1-2 points.

performed to define prognostic markers for overall survival in such cases. The present study aimed to fill this gap. Knowing a patient's overall survival time as precisely as possible would be momentous if one wishes to administer the optimal radiation treatment to a particular patient.

It has been well recognized that for patients with a poor overall survival prognosis, a 1-week course of whole-brain radiation therapy with 20 Gy in five fractions is the best option (1). A previous study of more than 400 patients with intracerebral metastases from many different cancer types

showed that 20 Gy in five fractions resulted in similar 6-month overall survival rate as the worldwide most frequently used 2-week whole-brain radiation therapy program of 30 Gy in 10 fractions (24% vs. 27%,  $p=0.29$ ) (11). In another study including patients with intracerebral metastases from various cancer types with mean overall survival time of at least 12 months, whole-brain radiation therapy with 40 Gy in 20 fractions (4 weeks) was significantly superior to 30 Gy in 10 fractions regarding the overall survival rate at 12 months (61% vs. 50%,  $p=0.008$ ) (3). Thus, in general, patients with a poor expected overall survival should receive 20 Gy in five fractions, those with an intermediate prognosis 30 Gy in 10 fractions, and those with a good prognosis 40 Gy in 20 fractions. In selected patients with a very limited number of intracerebral metastases and an intermediate or a good overall survival prognosis, whole-brain radiation therapy may be supplemented or replaced by local radiation therapy in form of stereotactic radiosurgery (a single fraction with a high dose, for example of 20-24 Gy) or fractionated stereotactic radiation therapy (for example three fractions of 10-12 Gy) (4, 5).

These considerations highlight how important it is to know a patient's remaining overall survival time when the best treatment option is to be decided. This also applies to patients with testicular cancer who are planned to be irradiated for intracerebral metastases. In this study, one significant marker for overall survival was identified, the performance status given as KPS. In addition, a trend was found for the number of other metastatic sites outside of the brain. Based on these two clinical markers, a simple scoring instrument was designed, which included two groups (with 0 points and 1-2 points) with a great difference regarding the overall survival rates at both 6 and 12 months. In the 0-points group, the 6-month overall survival rate was only 33%, and no patient survived longer than 7 months. Therefore, these patients appear to be good candidates for 20 Gy in five fractions (11). In the group of patients with 1-2 points, all patients survived for 12 months or longer and, therefore, should receive 40 Gy in 20 fractions to achieve best possible outcomes (3). In the latter group, local radiation therapy may be considered for selected patients with 1-3 intracerebral lesions in addition to or instead of whole-brain radiation therapy (1, 4, 5). Whether stereotactic radiosurgery or fractionated stereotactic radiation therapy can be given without whole-brain radiation therapy depends on the risk of developing new intracerebral metastases outside of the treated lesions. This risk can be estimated with another scoring instrument specifically designed to answer this question (12).

In summary, a simple instrument is provided that enables physicians to judge the overall survival times of patients with intracerebral metastases from testicular cancer. With this new instrument, the decision regarding the treatment protocol for a particular patient belonging to this rare group can be made easier.

## 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 Haugnes HS, Solhaug O, Stenberg J, Hjelle LV and Bremnes RM: Seminoma patients treated at a minor oncological department during 1986-2010: treatment and outcome. *Anticancer Res* 34: 4253-4560, 2014.
- 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 Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP and Curran WJ Jr.: Whole-brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 363: 1665-1672, 2004.
- 5 Rades D, Pluemer A, Veninga T, Hanssens P, Dunst J and Schild SE: Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases. *Cancer* 110: 2285-2292, 2007.
- 6 Hjelle LV, Gundersen PO, Oldenburg J, Brydøy M, Tandstad T, Wilsgaard T, Fosså SD, Bremnes RM and Haugnes HS: Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study. *Anticancer Res* 35: 1619-1625, 2015.
- 7 Burczynska BB, Kobrouly L, Butler SA, Naase M and Iles RK: Novel insights into the expression of CGB1 and 2 genes by epithelial cancer cell lines secreting ectopic free hCG $\beta$ . *Anticancer Res* 34: 2239-2248, 2014.
- 8 Heidegger I, Borena W and Pichler R: The role of human papilloma virus in urological malignancies. *Anticancer Res* 35: 2513-2519, 2015.
- 9 Bezan A, Geger A and Pichler M: MicroRNAs in testicular cancer: implications for pathogenesis, diagnosis, prognosis and therapy. *Anticancer Res* 34: 2709-2713, 2014.
- 10 Spiekermann M, Dieckmann KP, Balks T, Bullerdiek J and Belge G: Is relative quantification dispensable for the measurement of microRNAs as serum biomarkers in germ cell tumors? *Anticancer Res* 35: 117-121, 2015.
- 11 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.
- 12 Huttenlocher S, Dziggel L, Hornung D, Blanck O, Schild SE and Rades D: A new prognostic instrument to predict the probability of developing new cerebral metastases after radiosurgery alone. *Radiat Oncol* 9: 215, 2014.

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