A New Predictive Tool for Optimization of the Treatment of Brain Metastases from Colorectal Cancer After Stereotactic Radiosurgery

DIRK RADES[1], MARKUS DAHLKE[1], NIKLAS GEBAUER[2], TOBIAS BARTSCHT[2], DAGMAR HORNUNG[3], NGO THUY TRANG[4], PHAM CAM PHUONG[4], MAI TRONG KHOA[4,5] and JAN GLIEMROTH[6]

Departments of [1]Radiation Oncology, [2]Medical Oncology and Hematology, and [6]Neurosurgery, University of Lübeck, Lübeck, Germany;
[3]Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany;
[4]Nuclear Medicine and Oncology Center, Bach Mai Hospital, Hanoi, Vietnam;
[5]Department of Nuclear Medicine, Hanoi Medical University, Hanoi, Vietnam

Abstract. *Aim: To develop a predictive tool for survival after stereotactic radiosurgery of brain metastases from colorectal cancer. Patients and Methods: Out of nine factors analyzed for survival, those showing significance ($p<0.05$) or a trend ($p\leq0.06$) were included. For each factor, 0 (worse survival) or 1 (better survival) point was assigned. Total scores represented the sum of the factor scores. Results: Performance status ($p=0.010$) and interval from diagnosis of colorectal cancer until radiosurgery ($p=0.026$) achieved significance, extracranial metastases showed a trend ($p=0.06$). These factors were included in the tool. Total scores were 0-3 points. Six-month survival rates were 17% for patients with 0, 25% for those with 1, 67% for those with 2 and 100% for those with 3 points; 12-month rates were 0%, 0%, 33% and 67%, respectively. Two groups were created: 0-1 and 2-3 points. Six- and 12-month survival rates were 20% vs. 78% and 0% vs. 44% ($p=0.002$), respectively. Conclusion: This tool helps optimize the treatment of patients after stereotactic radiosurgery for brain metastases from colorectal cancer.*

The liver is the most commonly affected organ in patients with metastatic colorectal disease (1-4). Brain metastases are less common and occur in 1%-23% of patients with colorectal cancer during the course of their malignant disease (5-7). The majority of these patients presents with multiple (more than three) cerebral lesions and receive whole-brain irradiation. The number of brain metastases was reported to be significantly associated with survival. In two studies of patients with brain metastases from a less radiosensitive tumor such as colorectal cancer, patients with up to three brain metastases had a significantly better survival than those patients with more than three lesions (8, 9). Thus, patients with 1-3 brain metastases may benefit from more intensive therapies including resection of the lesions or stereotactic radiosurgery (10-12). Many of these patients undergo stereotactic radiosurgery alone (without additional whole-brain irradiation) in order to minimize the risk of radiation-related decline in neurocognition, which can occur several months following irradiation (13). The treatment following stereotactic radiosurgery should take into account an individual patient's specific situation, his personal needs and his survival prognosis.Therefore, it is very important to determine a patient's survival prognosis. This can be considerably facilitated with prognostic tools that should ideally be available for each tumor entity, since different tumor entities have different biology and prognoses. The present study was performed to develop a tool that allows for estimation of the survival prognosis of patients treated with stereotactic radiosurgery alone for brain metastases from colorectal cancer.

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 4515003324, e-mail: rades.dirk@gmx.net

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Patients and Methods

Nineteen patients treated with stereotactic radiosurgery alone for up to three brain metastases from colorectal cancer at two German University Hospitals between 2000 and 2014 were included in this study. In these patients, nine factors were retrospectively analyzed for potential associations with survival. These nine factors were: tumor type (rectal cancer *vs.* colon cancer), age (<66 *vs.* ≥66 years,

median age=66 years), gender, Karnofsky performance score (70-80 *vs.* 90-100), number of brain metastases (1 *vs.* 2-3), maximum diameter of all brain metastases (≤15 mm *vs.* >15 mm), extracranial metastases (no *vs.* yes), interval from first diagnosis of colorectal cancer until radiosurgery (≤24 *vs.* >24 months), and radiosurgery dose (16-18 Gy *vs.* 20-22 Gy).

The survival analysis for each factor was performed with the Kaplan–Meier method and the log-rank test. The factors that achieved significance ($p<0.05$) or showed a strong trend ($p\leq0.06$) were included in the predictive tool for estimation of survival. For each of these factors, 0 points were assigned to the parameter associated with worse survival and 1 point to the parameter with better survival. The survival score for each patient represented the sum of the scores of the factors included in the predictive tool.

Results

The results of the survival analysis are summarized in Table I. In this analysis, the Karnofsky performance score ($p=0.01$) and the interval from the first diagnosis of colorectal cancer until radiosurgery ($p=0.026$) achieved significance, and extracranial metastases showed a strong trend ($p=0.06$) for being associated with survival. Therefore, these three factors were included in the predictive tool. The corresponding scoring points are given in Table II. The addition of the scoring points resulted in sums of 0 (n=6), 1 (n=4), 2 (n=6) and 3 (n=3) points. The 6-month survival rates were 17%, 25%, 67% and 100%, respectively, while the 12-month survival rates were 0%, 0%, 33% and 67%, respectively, and the median survival times were 2.0, 3.0, 10.5 and 18.0 months, respectively. According to the survival data associated with the total scores, two prognostic groups were created: those with 0 or 1 points (n=10), and those with 2 or 3 points (n=9). The survival rates were 20% *vs.* 78% at 6 months, and 0% *vs.* 44% at 12 months, respectively ($p=0.002$) while the median survival times were 2.0 and 11.0 months, respectively.

Discussion

Many patients with metastatic colorectal cancer have a poor survival prognosis. This applies particularly to patients with brain metastases. Therefore, much experimental, translational and clinical research has been and is being still performed for metastatic colorectal cancer (14-17). New combinations of anticancer drugs have been introduced (2-4). However, most systemic agents are not able to pass the blood–brain barrier. Therefore, radiotherapy is still the most frequently used treatment modality for brain metastases. In order to optimize the radiotherapy of cerebral metastases from colorectal cancer, personalized treatment strategies tailoring the therapy to individual situations are important. Such strategies need to take into account the patient's survival prognosis. For example, long-term intracerebral control and radiation-related late toxicities are less important in patients with a very limited survival prognosis (18). In general, patients with up to three cerebral metastases live longer than patients with more than three lesions and, therefore, often receive stereotactic radiosurgery with whole-brain irradiation rather than whole-brain irradiation alone (10-12). However, a certain proportion of patients with 1-3 brain metastases have a poor survival prognosis, mostly due to the presence of visceral metastases (8, 9, 18). Since stereotactic radiosurgery may be associated with discomfort for patients, it may be questioned whether patients with a poor survival prognosis are really appropriate candidates for stereotactic radiosurgery. These patients may be better treated with short-course whole-brain irradiation alone or even best supportive care alone (18).

In order to choose the best treatment for an individual patient, a predictive tool for estimation of the remaining survival time would be of great benefit. In the current study, we created such a predictive tool for patients with no more than three brain metastases from colorectal cancer. In order to avoid selection bias caused by different types of treatment, only patients treated with stereotactic radiosurgery were included. According to the results of the study, the Karnofsky performance score and the interval from first diagnosis of colorectal cancer until radiosurgery were significantly positively associated with survival. In addition, the presence of extracranial metastases showed a strong trend for an association with poorer survival. These results mostly agree with the findings of previous studies including patients with brain metastases from colorectal cancer. In the study of Heisterkamp *et al.* in patients receiving whole-brain irradiation alone, survival was significantly associated with the Karnofsky performance score and extracranial metastases (8). In the studies of Meyners *et al.* (9) and Dziggel *et al.* (18) of patients receiving whole-brain irradiation for brain metastases from less radiosensitive tumors including colorectal cancer, the Karnofsky performance score and extracranial metastases had a significant impact on survival. The prognostic significance of the interval between the first diagnosis of colorectal cancer and radiotherapy has not yet been described for patients with brain metastases from colorectal cancer but for patients with cerebral metastases from other primary tumors (19, 20).

Based on the three factors Karnofsky performance score, interval from first diagnosis of colorectal cancer until radiosurgery, and presence of extracranial metastases, a predictive tool was designed to estimate the survival time of patients treated with stereotactic radiosurgery for brain metastases from colorectal cancer. Two prognostic groups were identified, one for patients with 0 or 1 point and another for those with 2 or 3 points. Only 20% of the patients with 0 or 1 point survived six months, and no patient of this group was alive at one year following stereotactic radiosurgery. Therefore, such patients may be candidates for a short course

Table I. *Potential prognostic factors related to survival rates at 6 and 12 months.*

	At 6 months (%)	At 12 months (%)	*p*-Value*
Tumor type			
Rectal cancer (n=5)	20	20	
Colon cancer (n=14)	57	21	0.22
Age			
<66 Years (n=9)	56	22	
≥66 Years (n=10)	40	20	0.75
Gender			
Female (n=6)	33	17	
Male (n=13)	54	23	0.86
Karnofsky performance score			
70-80 (n=10)	30	0	
90-100 (n=9)	67	44	**0.010**
Number of brain metastases			
1 (n=11)	55	27	
2-3 (n=8)	38	13	0.31
Maximum diameter of all brain metastases			
≤15 mm (n=9)	67	33	
>15 mm (n=10)	30	10	0.18
Extracranial metastases			
No (n=5)	100	40	
Yes (n=14)	29	14	**0.06**
Interval from first diagnosis of colorectal cancer until radiosurgery			
≤24 months (n=8)	25	0	
>24 months (n=11)	64	36	**0.026**
Radiosurgery dose			
16-18 Gy (n=12)	50	8	
20-22 Gy (n=7)	43	43	0.30

*Significant factors and those showing a strong trend for association with survival are shown in bold.

Table II. *Significant prognostic factors and survival according to score.*

	Score	Survival at 6 months (%)	Survival at 12 months (%)
Karnofsky performance score			
70-80 (n=10)	0	30	0
90-100 (n=9)	1	67	44
Extracranial metastases			
No (n=5)	1	100	40
Yes (n=14)	0	29	14
Interval from the first diagnosis of colorectal cancer until radiosurgery			
≤24 months (n=8)	0	25	0
>24 months (n=11)	1	64	36

of whole-brain irradiation or for best supportive care (18). Out of the patients who achieved scores of 2 or 3 points, 78% survived at least six months and almost half of the patients were alive at one year following stereotactic radiosurgery. Since 78% of the patients with 2 or 3 points died from extracranial metastatic disease and not from an intracerebral recurrence, intensification of systemic treatment is important for this group, whereas whole-brain irradiation in addition to stereotactic radiosurgery appears dispensable.

In conclusion, the present study provides a new predictive tool that allows for estimation of the survival prognosis of patients with up to three brain metastases from colorectal cancer treated with stereotactic radiosurgery. Patients with 0 or 1 point have a very poor survival and appear better-treated with short-course whole-brain irradiation or best supportive care following stereotactic radiosurgery. Patients with 2 or 3 points have significantly more favorable prognoses and should receive stereotactic radiosurgery plus intensive systemic treatment.

Conflicts of Interest

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

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