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A Score to Identify Patients with Brain Metastases from Colorectal Cancer Who May Benefit from Whole-brain Radiotherapy in Addition to Stereotactic Radiosurgery/Radiotherapy

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Abstract. *Aim: To design a tool to predict the probability of new cerebral lesions after stereotactic radiosurgery/radiotherapy for patients with 1-3 brain metastases from colorectal cancer. Patients and Methods: In 21 patients, nine factors were evaluated for freedom from new brain metastases, namely age, gender, Karnofsky performance score (KPS), tumor type, number, maximum total diameter of all lesions and sites of cerebral lesions, extra-cranial metastases, and time from cancer diagnosis to irradiation. Results: Freedom from new lesions was positively associated with KPS of 90-100 (p=0.013); maximum total diameter ≤15 mm showed a trend for positive association (p=0.09). Points were assigned as: KPS 70-80=1 point, KPS 90-100=2 points, maximum diameter ≤15 mm=2 points and maximum diameter >15 mm=1 point. Six-month rates of freedom from new lesions were 29%, 45% and 100% for those with total scores of 2, 3 and 4 points, respectively, with corresponding 12-month rates of 0%, 45% and 100% (p=0.027). Conclusion: This study identified three risk groups regarding new brain metastases after stereotactic irradiation. Patients with 2 points could benefit from additional whole-brain radiotherapy.*

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Patients with colorectal cancer represent about 5% of patients referred to a radiation oncologist for treatment of brain metastases from solid cancers (1, 2). More than 50% of these patients have only 1-3 lesions and are often assigned to receive a local therapy such as resection, stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) (1-3). A resection should only be performed in the case of a single brain metastasis which is well accessible and not involving critical structures such as the brain stem and speech center (2-4). For other patients, SRS and FSRT are better choices, either alone or combined with sequential whole-brain irradiation (WBI) (3). It is controversial which if any patients benefit from the addition of WBI to SRS or FSRT (5-7). The addition of WBI was associated with a more pronounced decline in neurocognitive function than SRS or FSRT alone (5, 6). However, WBI improved intracerebral control, mainly by preventing the development of new brain metastases outside the areas treated with SRS/FSRT, *i.e.* distant brain metastases. It was reported that the development of new cerebral lesions also results in a decline in neurocognitive function (7). Therefore, it would be important for treating radiation oncologists to be able to predict the probability of new distant brain metastases after SRS/FSRT alone before selecting the treatment regimen for an individual patient. To improve this decision-making process, the present study was performed to design a scoring tool to estimate the risk of new brain metastases after SRS or FSRT in patients with 1-3 brain metastases from colorectal cancer.

Patients and Methods

Twenty-one patients treated with SRS (15-20 Gy, median 18 Gy) or FSRT (3-5 fractions of 8-11 Gy) alone for 1-3 brain metastases from colorectal cancer between 1999 and 2015 were included in this retrospective study. Nine factors were evaluated for associations with freedom from new cerebral metastases outside the irradiated regions of the brain, namely age at the time of SRS/FSRT (≤65 *vs*. ≥66 years, median=66), gender, Karnofsky performance score (KPS) (70-80 *vs*. 90-100, median=90), primary tumor type (colon cancer *vs*. rectal cancer), number of cerebral metastases (1 *vs*. 2-3), maximum total diameter of all cerebral lesions (≤15 *vs*. >15 mm), site of cerebral metastases (supratentorial alone *vs*. infratentorial±supratentorial), extracranial metastases (no *vs*. yes) and time from cancer diagnosis to SRS/FSRT (≤12 *vs*. >12 months). The distribution of these factors is shown in Table I.

For the statistical analysis of the nine factors with respect to freedom from new brain metastases, the Kaplan–Meier method and the log-rank test were applied (8). *p*-Values of less than 0.05 were regarded as significant, and $p<0.10$ were interpreted as showing a trend for association. The factors that were significantly associated with freedom from new brain metastases and those factors showing a trend were used to develop the scoring tool.

Results

A KPS of 90-100 was associated with significantly better freedom from new brain metastases when compared to a KPS of 70-80 ($p=0.013$). In addition, a maximum total diameter of all cerebral lesions of ≤15 mm showed a trend for association with better freedom when compared to those with >15 mm ($p=0.09$). Therefore, these two factors were incorporated into the scoring tool. The rates of freedom from new brain metastases at 6 and 12 months for all nine investigated factors are summarized in Table II.

When considering KPS and maximum total diameter of all cerebral lesions, the following scores were assigned: KPS 70-80=1 point, KPS 90-100=2 points, maximum total diameter ≤15 mm=2 points and maximum total diameter >15 mm=1 point. Thus, the total scores for individual patients were 2, 3 or 4 points. The corresponding rates of freedom from new lesions were 29%, 45% and 100%, respectively, at 6 months following SRS/FSRT, and 0%, 45% and 100%, respectively at 12 months ($p=0.027$, Figure 1).

Discussion

A number of studies have been performed in recent years in order to improve the prognoses of patients with colorectal cancer with both primary and metastatic disease (9-19). The number of patients with colorectal cancer presenting with brain metastases is quite small but will likely increase in the future due to improvement in survival of such patients (1). Currently, more than half of all patients with brain metastasis from colorectal cancer have only a very limited number of cerebral lesions (2). In the case of those with 1-3 lesions, it is not clear whether local therapy such as SRS and FSRT alone would be the best treatment, or whether local therapy would be better combined with WBI. There are arguments for and against both treatment approaches. In two randomized trials, the addition of WBI to SRS/FSRT led to greater decline in neurocognitive function than administration of a local therapy alone (5, 6). In the first of these trials, the rate of relevant neurocognitive deficits at 4 months following irradiation was 96% following SRS combined with WBI *versus* 24% following SRS alone ($p<0.001$) (5). In the second randomized trial, decline in neurocognitive function at 3 months following irradiation was found in 92% and 64% of the patients, respectively ($p<0.001$) (6). However, in both trials, the 12-month rates of intracerebral control, *i.e.* no progression of the treated lesions and freedom from new cerebral lesions, were significantly greater after the combined approach than after SRS alone (5, 6). In contrast, in a subgroup analysis of another randomized trial, the rates of preservation of neurocognitive function at 1 and 2 years following irradiation were greater after SRS plus WBI than after SRS alone, most likely due to improved intracerebral control (7). It is possible that some patients benefit from the addition of WBI to SRS/FSRT, whereas others do not.

When considering the ongoing discussion, it becomes obvious that it would indeed be helpful to identify those patients who may benefit from additional WBI prior to

Table I. *Distributions of investigated potential prognostic factors.*

Factor	Number of patients (%)
Age at the time of SRS/FSRT	
≤65 Years	10 (48)
≥66 Years	11 (52)
Gender	
Female	6 (29)
Male	15 (71)
Karnofsky Performance Score	
70-80	10 (48)
90-100	11 (52)
Primary tumor type	
Colon cancer	14 (67)
Rectal cancer	7 (33)
Number of brain metastases	
1	13 (62)
2-3	8 (38)
Maximum total diameter of all lesions	
≤15 mm	9 (43)
>15 mm	12 (57)
Site of cerebral metastases	
Supratentorial alone	17 (81)
Infratentorial±supratentorial	4 (19)
Extra-cranial metastases	
No	6 (29)
Yes	15 (71)
Time from cancer diagnosis to SRS/FSRT	
≤12 Months	8 (28)
>12 Months	13 (62)

SRS: Stereotactic radiosurgery; FSRT: fractionated stereotactic radiotherapy.

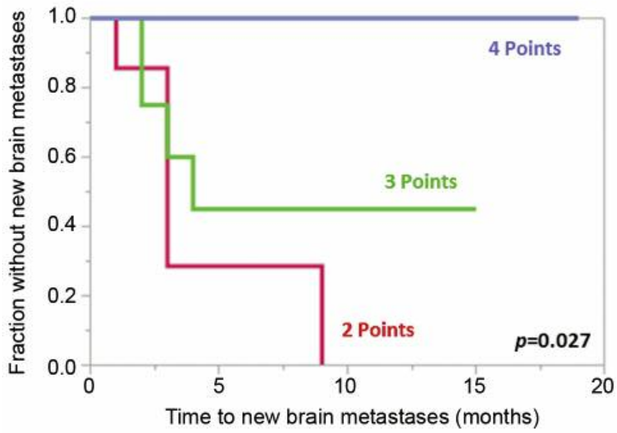

Figure 1. *Kaplan–Meier curves of the three prognostic groups with 2, 3 and 4 points. The p-value was determined with the log-rank test.*

treatment. Therefore, this study was initiated to create a scoring tool that identifies those patients who receive SRS/FSRT alone but have a high risk of developing new brain metastases outside the irradiated areas. These patients may benefit by the addition of WBI to SRS/FSRT. In order to optimally evaluate the individual characteristics various tumors, separate tools should be available for the different primary tumor types causing brain metastases (20-22). Therefore, the present study focused on a single tumor entity, colorectal cancer. The prognostic tool created in this study was based on two factors, KPS and maximum total diameter of all brain metastases. Three groups of patients were identified with significantly different rates of freedom from new brain metastases. In the group with 2 points, the corresponding rates were 29% at 6 months and 0% at 12 months following SRS or FSRT alone. In other words, 71% and 100% of the patients experienced new distant brain metastases after 6 and 12 months, respectively. Therefore, patients of this group likely would benefit from the addition of WBI in order to improve intracerebral control of metastatic disease. In contrast, 45% and 100% of the patients of the groups with 3 and 4 points, respectively, had not developed new distant brain metastases within 12 months following SRS or FSRT alone. Therefore, in patients with 4 points, WBI may be omitted in order to preserve neurocognitive function. In patients of the 3-point group, individual treatment decisions are required, particularly considering the patient preferences, regarding improved intracerebral control and less neurocognitive decline. The retrospective design of this study should be considered when interpreting these findings.

In conclusion, this study identified three groups with significantly different probabilities of new distant brain metastasis following SRS/FSRT alone. Patients of the group with 2 points could benefit from additional WBI, whereas WBI could be omitted in that with 4 points. In the group with intermediate risk (3 points), highly individual treatment decisions are required.

Table II. *Freedom from new brain metastases.*

Factor	Freedom from new brain metastases (%) At 6 months	At 12 months	*p*-Value
Age at the time of SRS/FSRT			
≤65 years	57	38	0.99
≥66 years	59	59	
Gender			
Female	60	30	0.46
Male	56	56	
Karnofsky Performance Score			
70-80	32	0	**0.013**
90-100	79	79	
Primary tumor type			
Colon cancer	60	48	0.88
Rectal cancer	56	56	
Number of brain metastases			
1	66	55	0.63
2-3	42	42	
Maximum total diameter of all lesions			
≤15 mm	75	75	0.09
>15 mm	41	21	
Site of cerebral metastases			
Supratentorial alone	61	49	0.87
Infratentorial±supratentorial	50	50	
Extra-cranial metastases			
No	67	67	0.29
Yes	56	37	
Time from cancer diagnosis to SRS/FSRT			
≤12 Months	67	67	0.92
>12 Months	53	37	
Entire cohort	59	50	

SRS: Stereotactic radiosurgery; FSRT: fractionated stereotactic radiotherapy. Significant *p*-values are shown in bold.

Conflicts of Interest

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

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