Predicting the Risk of New Cerebral Lesions After Stereotactic Radiosurgery (SRS) for Brain Metastases from Breast Cancer

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Abstract. *Aim: To generate a tool that estimates the probability of developing new cerebral metastases after stereotactic radiosurgery (SRS) in breast cancer patients. Patients and Methods: SRS dose plus seven characteristics (age, performance score, number of cerebral metastases, maximum diameter of all metastases, location of metastases, extra-cerebral spread and time from breast cancer diagnosis until SRS) were analyzed regarding their ability to predict the probability of new cerebral metastases development following SRS. For those characteristics deemed significant, points of 0 (higher risk of new lesions) or 1 (lower risk) were given. Scores were generated by adding the points of significant characteristics. Results: Performance score (p=0.013) and maximum diameter of all metastases (p=0.022) were associated with development of subsequent brain metastases. Two groups were created, 0-1 and 2 points. Freedom from new cerebral metastases rates were 27% and 92%, respectively, at 15 months (p=0.003). Conclusion: This tool helps select breast cancer with few cerebral metastases receiving SRS who may benefit from additional whole-brain irradiation.*

Out of all patients with cerebral metastases, those with breast cancer account for 20-25% and, therefore, require for special attention (1, 2). A considerable number of these patients present with few brain lesions and are treated with stereotactic radiosurgery (SRS). Among physicians involved in the treatment of cerebral metastases, controversy exists whether some could benefit from adding whole-brain irradiation (WBI) to SRS.

Several studies have shown that the combined approach (SRS plus WBI) results in both improved local control of irradiated lesions and improved freedom from new cerebral metastases outside the irradiated areas of the brain compared to SRS-alone (3-6). This is a strong argument to add WBI to treatment schedule. On the other hand, addition of WBI does not translate into survival benefit. Furthermore, two randomized trials demonstrated that SRS plus WBI resulted in a significant increase in neuro-cognitive deficits (7, 8). However, those two trials investigated neuro-cognitive function at only 3 and 4 months, respectively, following radiotherapy. At one year, when intra-cerebral control was significantly better after SRS-plus-WBI than after SRS-alone, neuro-cognitive function was not assessed in either trial. Since several studies have shown that an intra-cerebral recurrence (and not WBI) is the most important reason for a decline in neuro-cognitive function, both randomized trials may be of limited value in judging the role of WBI in addition to SRS (9, 10) for patients living beyond 4 months. Therefore, it is still unclear whether SRS-plus-WBI or SRS-alone is the better option for few brain metastases in the long-term.

Patients who are at high risk of developing new cerebral metastases outside the irradiated areas after SRS alone are those most likely to benefit from the addition of WBI. In order to identify these patients prior to start of treatment, a predictive tool would be helpful. Such tools have already been developed in a cohort of patients treated with SRS alone for few cerebral metastases from several different primary tumor types and from malignant melanoma (11, 12). Since specific tumor types vary considerably with respect to prognosis and patterns of spread, it has been recognized that

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Key Words: Cerebral metastases, breast cancer, stereotactic radiosurgery, freedom from new cerebral metastases, prognostic tool.

Table I. *Characteristics evaluated with respect to new brain metastases following SRS.*

	Distribution of patients N (%)
SRS dose	
18-19 Gy	12 (35)
20 Gy	22 (65)
Age	
≤58 years	18 (53)
≥59 years	16 (47)
Karnofsky performance score	
70-80	16 (47)
90-100	18 (53)
Number of cerebral metastases	
N=1	27 (79)
N=2-3	7 (21)
Maximum diameter of all metastases	
≤15 mm	19 (56)
>15 mm	15 (44)
Location of the metastases	
Supra-tentorial alone	23 (68)
Infra-tentorial involvement	11 (32)
Extra-cerebral spread	
No	13 (38)
Yes	21 (62)
Time from diagnosis of breast cancer until SRS	
≤48 months	17 (50)
≥49 months	17 (50)

Table II. *Analysis with respect to freedom from new cerebral metastases.*

	Freedom from new cerebral metastases at 6 months (%)	Freedom from new cerebral metastases at 1 year (%)	*p*-Value
SRS dose			
18-19 Gy	58	58	
20 Gy	90	79	0.19
Age			
≤58 years	83	83	
≥59 years	73	56	0.38
Karnofsky performance score			
70-80	67	56	
90-100	89	83	0.013
Number of cerebral metastases			
N=1	81	70	
N=2-3	71	71	0.27
Maximum diameter of all metastases			
≤15 mm	89	83	
>15 mm	67	53	0.022
Location of the metastases			
Supra-tentorial alone	77	64	
Infra-tentorial involvement	82	82	0.37
Extra-cerebral spread			
No	85	68	
Yes	75	75	0.66
Time from diagnosis of breast cancer until SRS			
≤48 months	81	74	
≥49 months	76	68	0.49

specific tools for single tumor types such as breast cancer are required to deliver optimal individualized care. Therefore, the present study aimed to provide a tool specifically for breast cancer patients with few cerebral lesions that allows for prediction of probability of developing new cerebral metastases following SRS alone.

Patients and Methods

In this retrospective study, 34 patients receiving SRS alone for few (1 to 3) cerebral lesions from breast cancer were included. The SRS doses were 18-20 Gy prescribed to the margin of the metastatic lesions (75-85% isodose). The SRS dose (18-19 Gy *vs.* 20 Gy) plus seven other characteristics were evaluated for potential associations with freedom from new brain metastases following SRS. These seven characteristics were as follows: age (≤58 years *vs.* ≥59 years; median=58 years), Karnofsky performance score (70-80 *vs.* 90-100; median=90), number of cerebral metastases (n=1 *vs.* n=2-3), maximum diameter of all metastases (representing the sum of the maximum diameters of all lesions; ≤15mm *vs.* >15mm), location of metastases (supra-tentorial alone *vs.* infra-tentorial involvement), extra-cerebral spread (no *vs.* yes), and time from diagnosis of breast cancer until SRS (≤48 months *vs.* ≥49 months, median=48.5 months). Characteristics are summarized in Table I.

For analysis with respect to freedom from new cerebral metastases, a Kaplan-Meier analysis plus log-rank-test were used. The characteristics that showed a significant ($p<0.05$) association with subsequent cerebral metastases risk were included in the prognostic tool. For each of the significant characteristics, points of 0 (higher risk of developing new lesions) or 1 (lower risk of developing new lesions) were given. For each patient, the prognostic score was calculated by adding the points of each of these significant characteristics.

Results

Two of the investigated characteristics had a significant impact on freedom from new cerebral metastases, Karnofsky performance score ($p=0.013$) and the maximum diameter of all cerebral lesions ($p=0.022$). The findings from the analyses of freedom from new cerebral metastases for each characteristic are provided in Table II.

Considering the scoring of the two significant characteristics as shown in Table III, prognostic scores of 0, 1 or 2 points were obtained. The corresponding rates of freedom from new cerebral metastases were 64%, 63% and 100%, respectively, at 6 months, and 48%, 63% and 92%, respectively, at 1 year ($p=0.009$). Based on these data, two

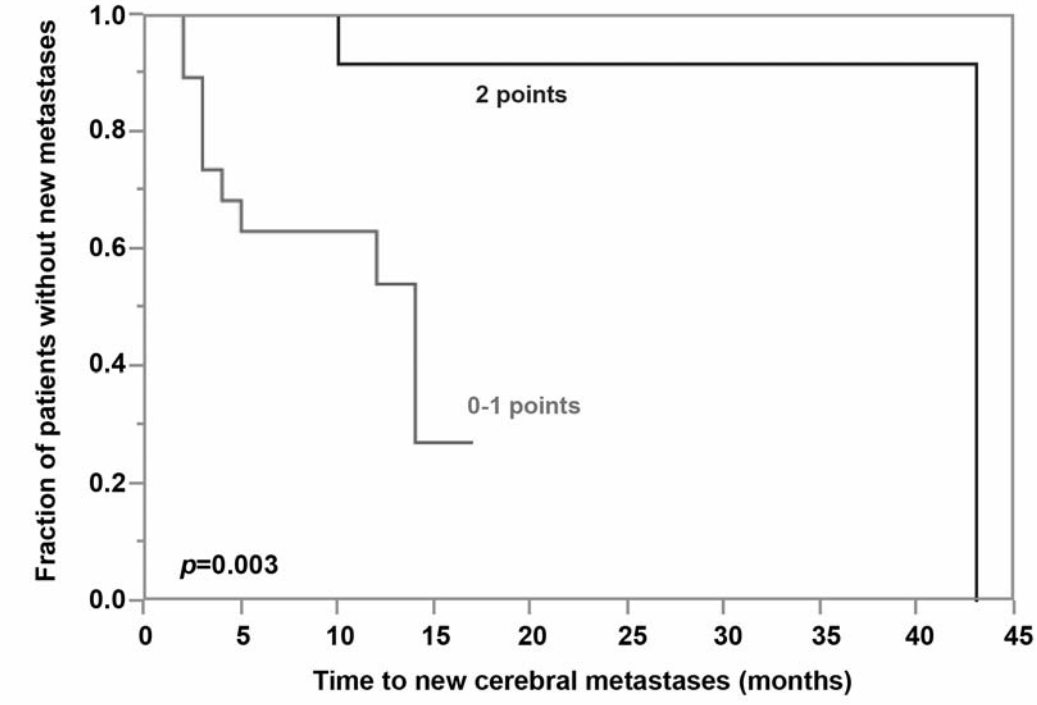

Figure 1. *Kaplan-Meier-curves of the prognostic groups 0-1 points and 2 points.*

groups were created, 0-1 points and 2 points. The rates of freedom from new cerebral metastases of these groups were 63% and 100%, respectively, at 6 months, 54% and 92%, respectively, at 1 year, and 27% and 92%, respectively, at 15 months (p=0.003). The Kaplan-Meier-curves of both groups are presented in Figure 1.

Discussion

Treatment of breast cancer has further improved during the last decade, and more breast cancer patients live longer (13-19). Since the risk of developing metastases to the brain increases with life time, the number of breast cancer patients presenting with brain metastases has increased and will likely further increase in the future. The majority of these patients have several lesions when diagnosed with cerebral metastases and receive WBI alone (2, 20-22). However, a considerable proportion of patients presenting with metastases to the brain have only few lesions. Many of these patients are suitable for local therapies such as surgical resection and SRS (23-25). In patients with 1 to 3 cerebral metastases, SRS has been shown to be superior to resection with respect to local control of treated lesions (23-25). Therefore, many patients with a limited number of cerebral metastases receive SRS, either alone or combined with WBI.

Table III. *Characteristics associated with freedom from new cerebral metastases and corresponding points.*

	Points
Karnofsky performance score	
70-80	0
90-100	1
Maximum diameter of all cerebral lesions	
≤15 mm	1
>15 mm	0

The role of WBI when added to SRS is very controversial with most physicians currently leaning against its use. This is primarily based on the findings from 2 widely publicized randomized trials. In one of these two trials, the decline in neuro-cognitive function was significantly greater at four months after combined treatment than after SRS alone (96% *vs*. 52%) (7). However, the 1-year intra-cerebral control rates were 73% and 27%, respectively (p=0.0003). Unfortunately, the authors did not assess the neuro-cognitive functions at 1 year when the majority of patients who did not receive WBI had subsequent brain metastases elsewhere. Previous studies have shown that intra-cerebral recurrence is the major cause of neuro-cognitive decline (9, 10). Thus, the results of this

trial may be less conclusive with respect to the value of adding WBI to SRS. A second randomized trial of patients with few cerebral metastases recently presented in abstract form has similar limitations (8). Neuro-cognitive function was assessed only at 3 months following treatment (SRS-plus-WBI *vs*. SRS-alone), and not at 6 months or 12 months when intra-cerebral control was significantly better after SRS plus WBI than after SRS alone (88% *vs*. 66% at 6 months, and 85% *vs*. 51% at 12 months, $p<0.001$).

Therefore, the role of additional WBI should be further studied and clarified especially for patients living more than 3 or 4 months. A prognostic tool that can estimate the probability of developing new cerebral metastases would be valuable. Patients at a higher risk of developing new lesions may benefit from the addition of WBI, whereas in patients at lower risk, WBI could be safely ommitted. In the present study such a tool was created. The ideal condition would for availability of separate tools for patients with cerebral metastases to exist for each particular type of primary tumor, taking into account the diverging biology of each tumor type. Therefore, this study focused on a single primary tumor type, breast cancer. Two characteristics, performance status and maximum diameter of all cerebral metastases, were identified as having a significant impact on the risk of new cerebral metastases following SRS alone. These two characteristics form the basis of this prognostic tool, that includes two prognostic groups (0-1 *vs*. 2 points). Out of patients with 2 points, only 8% had new cerebral lesions at 15 months following SRS alone and would, therefore, not potentially benefit from the addition of WBI. Out of patients with 0-1 points, 73% had new metastases at 15 months. Therefore, patients with 0-1 points could benefit from additional WBI.

In conclusion, the present study provides a new prognostic tool for the estimation of the probability of breast cancer patients with few cerebral metastases to develop new lesions within the brain after SRS alone. Therefore, this tool will be helpful when physicians consider whether WBI should be added to SRS.

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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Received August 12, 2015
Revised September 10, 2015
Accepted September 14, 2015