RESEARCH ARTICLE

A New Tool to Predict Survival after Radiosurgery Alone for Newly Diagnosed Cerebral Metastases

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Abstract

Many patients with few cerebral metastases receive radiosurgery alone. The goal of this study was to create a tool to estimate the survival of such patients. To identify characteristics associated with survival, nine variables including radiosurgery dose, age, gender, Eastern cooperative oncology group performance score (ECOG-PS), primary tumor type, number/size of cerebral metastases, location of cerebral metastases, extra-cerebral metastases and time between cancer diagnosis and radiosurgery were analyzed in 214 patients. On multivariate analysis, age (p=0.03), ECOG-PS (p=0.02) and extra-cerebral metastases (p<0.01) had significant impacts on survival. Scoring points for each patient were obtained from 12-month survival rates (in %) related to the significant variables divided by 10. Addition of the scoring points of the three variables resulted in a patient's total predictive score. Two groups were designed, A (10-14 points) and B (16-17 points). Twelve-month survival rates were 33% and 77%, respectively (p<0.001). Median survival times were 8 and 20 months, respectively. Because most patients of group A died from extra-cerebral disease and/or new cerebral lesions, early systemic treatment and additional WBI should be considered. As cause of death in group B was mostly new cerebral metastases, additional WBI appears even more important for this group.

Keywords: Cerebral metastases - radiosurgery alone - survival - prognostic factors - predictive tool.

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Introduction

Many patients presenting with very few metastatic lesions within the brain receive radiosurgery, which is a non-invasive and effective treatment with only mild toxicity (Hyun et al., 2013; Duan et al., 2014). Furthermore, radiosurgery was reported to be more cost-effective than neurosurgical resection (Vuong et al., 2012; Vuong et al., 2013). Most patients with brain metastases have a very limited life span of only months (Dziggel et al., 2013; Rades et al., 2013; Akhavan et al., 2014). However, some patients, particularly those with a very limited number of lesions, may live considerably longer, sometime for years.

In order to treat patients with brain metastases appropriately, personalized treatment approaches are required. Such a personalized approach can only be regarded optimal, if the survival prognosis of the corresponding patients can be predicted as precisely as possible. This would be facilitated if predictive tools were applied. Of the three tools designed particularly for patients treated with radiosurgery so far, the score index for radiosurgery in brain metastases (SIR) was developed in 65 patients, of whom 89% had not received radiosurgery alone but whole-brain irradiation (WBI) during some phase of their treatment (Weltman et al., 2000). In 2004, the basic score for brain metastases (BS-BM) was presented (Lorenzoni et al., 2004). This tool was developed in 110 patients treated with Leksell Gamma Knife (cobalt 60) radiosurgery alone. The third tool, a subclassification of recursive partitioning analysis (RPA) class 2 patients was published on 2012 (Yamamoto et al., 2012). It was created from a large series of patients who had received Gamma Knife (cobalt 60) radiosurgery alone.

A predictive tool developed in a cohort of patients who received radiosurgery alone with photon beams from a linear accelerator has not yet been presented. In order to close this gap, the current study was initiated. A new predictive tool particularly designed for estimation of the survival prognosis after radiosurgery alone performed with a linear accelerator (LINAC-based radiosurgery or Cyberknife radiosurgery), was developed based on the present analysis, to contribute to further optimize personalized treatment for cerebral metastases.

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Materials and Methods

This retrospective study included 214 patients treated with radiosurgery alone for 1-3 newly diagnosed cerebral metastases. Of these patients, 186 received LINAC-based and 28 patients Cyberknife radiosurgery. A total of nine variables were investigated for associations with survival following radiosurgery. These variables included the radiosurgery dose (equivalent dose in 2 Gy fractions <20 Gy *vs* 20 Gy *vs* >20 Gy, which was prescribed to the 73-90% isodose level), age (≤60 years *vs* ≥61 years), gender, Eastern cooperative oncology group performance score (ECOG-PS 0-1 *vs* ECOG-PS 2), primary tumor type (breast cancer *vs* non-small lung cancer *vs* melanoma *vs* other tumors), number/size of cerebral metastases (1 lesion <15 mm *vs* 1 lesion ≥15 mm *vs* 2 or 3 lesions), location of cerebral metastases (supratentorial alone *vs* infratentorial ± supratentorial), extra-cerebral metastases (no *vs* yes), and time between cancer diagnosis and delivering of radiosurgery (≤15 months *vs* >15 months).

The univariate analysis of survival was performed with the Kaplan-Meier method and the log-rank test. The variables that achieved significance (p<0.05) in the univariate analysis, were additionally evaluated in a multivariate manner (Cox proportional hazards model). Those variables that were significant in the multivariate analysis were incorporated in the predictive tool. The 12-month survival rates were divided by 10, which gives the scoring points for each incorporated variable. The total predictive score for each patient was derived from the sum of the scoring points of these variables.

Table 1. Survival Rates at 6 Months and 12 Months Following Radiosurgery.

	Survival at 6 months (%)	Survival at 12 months (%)	P-value
Radiosurgery dose			
<20 Gy (N=69)	58	32	
20 Gy (N=124)	61	45	
>20 Gy (N=21)	76	58	0.20
Age			
≤60 years (N=99)	69	55	
≥61 years (N=115)	56	32	0.002
Gender			
Female (N=112)	63	43	
Male (N=102)	60	43	0.49
Eastern Cooperative Oncology Group performance score			
0-1 (N=158)	66	45	
2 (N=56)	50	35	0.003
Primary tumor type			
Breast cancer	76	62	
Non-small cell lung cancer	65	47	
Malignant melanoma	58	38	
Other tumors	55	34	0.18
Number of cerebral metastases			
1 lesion <15 mm (N=77)	65	47	
1 lesion ≥15 mm (N=55)	60	36	
2 or 3 lesions (N=82)	60	42	0.23
Location of cerebral metastases			
Supratentorial alone (N=179)	62	41	
Infratentorial ± supratentorial (N=35)	60	49	0.52
Extra-cerebral metastases			
No (N=88)	81	58	
Yes (N=126)	48	32	0.001
Time from cancer diagnosis to radiosurgery			
≤15 months (N=95)	59	39	
>15 months (N=119)	64	45	0.13

Results

The results of the univariate analysis are presented in Table 1. Three variables, i.e. age (p<0.01), ECOG-PS (p<0.01) and extra-cerebral metastases (p<0.01), had a significant impact on survival. In the additional multivariate analysis, age (risk ratio [RR] 1.46; 95%-confidence interval (CI) 1.04-2.06; p=0.03), ECOG-PS (RR 1.57; 95%-CI 1.10-2.23; p=0.02), and extra-cerebral metastases (RR 1.63; 95%-CI 1.15-2.33; p<0.01) remained significant. Therefore, these three variables were incorporated in the predictive scoring tool. The corresponding scoring points of the three variables are summarized in Table 2. The addition of the scoring points resulted in total predictive scores of 10(n=23), 11(n=50), 13(n=26), 14(n=69), 16(n=7) or 17(n=39) points. The 12-month survival rates of these predictive scores were 24%, 32%, 37%, 36%, 71% and 78%, respectively (p<0.001). According to the total predictive scores, two survival groups were designated based on an obvious breakpoint in survival between those with scores of 10-14 points (group A) and those with scores of 16-17 points (group B). The 12-month survival rates of these two groups were 33% and 77%, respectively (p<0.001, Figure 1). The median survival times were 8 months and 20 months, respectively.

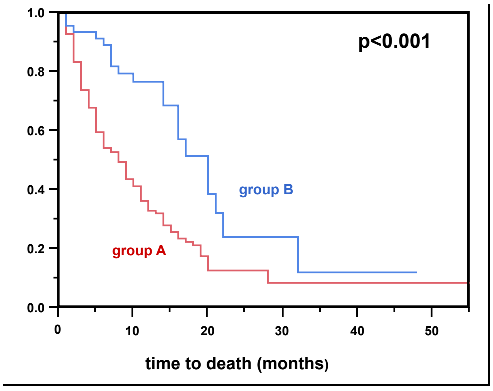

Figure 1. Kaplan-Meier curves of the two prognostic groups A (10-14 points) and B (16-17 points). The p-value was obtained from the log-rank test.

Table 2. Variables Integrated in the Predictive Tool: Twelve-Month Sutvival Rates and Corresponding Scoring Points.

	Survival at 12 months (%)	Scoring points
Age		
≤60 years (N=99)	55	6
≥61 years (N=115)	32	3
Eastern Cooperative Oncology Group performance score		
0-1 (N=158)	45	5
2 (N=56)	35	4
Extra-cerebral metastases		
No (N=88)	58	6
Yes (N=126)	32	3

Discussion

A considerable proportion of adult cancer patients may develop cerebral metastases during the course of their disease (Chindaprasirt et al., 2012; Demircioglu et al., 2013; Mutlu et al, 2013; Sun et al., 2014). Different treatment modalities including conventional radiotherapy, radiosurgery, neurosurgical resection, and systemic therapy are used (Liu et al., 2012; Zeng et al., 2012; Zhang et al., 2012; Erten et al., 2013; Inamoto et al., 2014). Many patients with metastases to the brain receive radiosurgery alone. During recent years, personalized treatment approaches have become more important in oncology, particular in palliative settings such as patients with cerebral metastases. However, to optimize personalized approaches to each patient's specific needs, it is helpful to estimate as precisely as possible an individual patient's remaining life time. This goal can be achieved with predictive tools. In the present study a new predictive survival tool was developed particularly for patients who had received radiosurgery alone with photon beams from a linear accelerator. This tool incorporated three variables that had a significant impact on patient survival in both the univariate and the multivariate analyses. The three variables were age, ECOG performance score, and the presence/absence of extra-cerebral metastases. These variables had also been included in the SIR, which was developed in 65 patients treated with radiosurgery plus/minus WBI during some phase of treatment (Weltman et al., 2000). Performance status and extra-cerebral metastases were incorporated in the BS-BM, which was created from the data of 110 patients treated with Gamma Knife radiosurgery, and in the subclassification of RPA class 2 patients treated radiosurgically (Lorenzoni et al., 2004; Yamamoto et al., 2012). However, the new tool presented here is the first one based on the data of patients receiving radiosurgery alone performed with a linear accelerator and, therefore, unique and supplementary to the existing tools for patients treated with radiosurgery for cerebral metastases.

In the current study, the 12-month survival rates of the three significant variables were translated into two distinct survival groups with 12-month survival rates of 33% in group A and 77% in group B, respectively. As a considerable number of patients in group A died due to progression of extra-cerebral disease, treatment with systemic agents should be strongly considered and administered as soon as early as possible. Of the group A patients who died from intra-cerebral progression, new cerebral metastases was the major cause of death. These patients may also benefit from WBI in addition to radiosurgery.

In group B patients, the majority of deaths occurred from progressive new metastases within the brain at locations outside the irradiated lesions without extra-cerebral metastases. Therefore, these patients appear reasonable candidates for additional WBI to supplement radiosurgery. Systemic therapy may be withheld until extra-cerebral metastatic disease occurs. Because more than three fourth of group B patients live for one year or longer following radiosurgery, additional WBI should be administered with doses per fraction of 2.5 Gy or less in order to reduce the risk of decline in neurocognitive function (De Angelis et al., 1989). For further reduction of neurocognitive dysfunction, sparing of the hippocampus should be considered if technically possible and available. Memantine administration also appears to decrease the cognitive decline associated with whole brain radiotherapy (Brown et al., 2013). In order to provide better intra-cerebral control, 20x2 Gy has been suggested to be more effective than 10x3 Gy (Rades et al., 2012). However, some degree of caution is indicated when considering these recommendations. One should be aware that this new predictive tool was created from a retrospective cohort of patients. Furthermore, this tool should be validated in a separate series of patients being treated with radiosurgery alone for a very limited number of cerebral metastases.

In conclusion, this new tool developed to estimate the survival of patients receiving radiosurgery alone with a linear accelerator for 1-3 cerebral metastases included three variables and two prognostic groups. Only one third of group A patients survived for at least 12-months; most patients of this group died from extra-cerebral disease and/or new cerebral lesions distant from the irradiated ones. Early administration of systemic treatment and WBI in addition to radiosurgery should be considered. More than three fourths of group B patients did survive 12 months or longer. The reason for death was mainly new cerebral metastases. Therefore, additional WBI appears even more important for this group of patients, preferentially with doses per fraction of 2.5 Gy or less.

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