Defining the Optimal Dose of Stereotactic Radiosurgery for Treating Cerebral Metastases in Elderly Patients

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Abstract. *Background/Aim: In oncology, elderly people are a separate group of patients requiring special consideration. This applies to the treatment of cerebral metastases as well. The present study focused on elderly patients receiving stereotactic radiosurgery (SRS) for few cerebral lesions. Patients and Methods: In 95 patients aged ≥65 years, two SRS doses, 16-18 Gy (n=44) and 20 Gy (n=51), were compared regarding outcomes of SRS. Results: The overall intracerebral control rates at 12 months were 30% after 16-18 Gy and 45% after 20 Gy (p=0.53). Twelve-month rates of freedom from new intracerebral lesions were 41% and 52%, respectively (p=0.63). Twelve-month local control rates of the irradiated lesions were 55% and 81%, respectively (p=0.069). Overall survival rates at 12 months were 29% and 31%, respectively (p=0.67). Conclusion: SRS with 16-18 Gy was not significantly inferior to SRS with 20 Gy in elderly patients with few cerebral metastases.*

Elderly patients have gained importance in anticancer treatment since the proportion of this group is constantly growing in many countries due to demographic changes and since they often require for specific precautions due to a higher comorbidity index (1-5). This applies to elderly patients presenting with metastatic disease, such as cerebral metastases. Patients aged 65 years or older with cerebral metastasis were reported to have a significantly worse survival prognosis than younger patients (6, 7). Thus, patients aged ≥65 years should be considered a separate group of patients.

Most patients with metastases to the brain receive radiotherapy, either as whole-brain irradiation, stereotactic radiosurgery (SRS), or as a combination of both modalities. Most patients with multiple cerebral lesions have a very poor overall survival prognosis and are, therefore, treated with whole-brain irradiation alone (7, 8). In contrast, patients with very few cerebral lesions have a significantly better prognosis (8). A considerable number of the patients of the latter group receive SRS, either alone or in combination with whole-brain irradiation. A small randomized study suggested the neurocognitive decline was significantly more pronounced after the combined approach than after SRS alone (9). Therefore, many radiation oncologists prefer to omit additional whole-brain irradiation (9-11). This applies particularly to elderly patients, in whom neurocognitive functions may already be impaired. Therefore, many elderly patients treated for a few cerebral lesions receive SRS alone. The optimal SRS dose for these patients is undefined. This study compared two dose levels of SRS alone in elderly patients presenting with 1-3 cerebral metastases.

Patients and Methods

Ninety-five elderly patients (age: ≥65 years) who received SRS alone with photon beams from a linear accelerator (Varian Medical Systems, Palo Alto, CA, USA or Siemens Medical Systems, Concord, CA, USA) for newly-diagnosed cerebral metastases between January 1999 and April 2014 were retrospectively analyzed. In these patients, the doses prescribed to the outer margin of the metastatic lesions ranged from 16 Gy to 20 Gy. Two groups were formed: 16-18 Gy (n=44) and 20 Gy (n=51). The two groups were compared with respect to overall intracerebral control, local control of the irradiated lesions, freedom from new intracerebral

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lesions and overall survival. The corresponding analyses were performed using the Kaplan–Meier method and the log-rank test. The median follow-up period was 6 months (range=1-38 months) in the entire cohort and 9.5 months (range=6-38 months) in those patients alive at the last follow-up.

Results

The two compared dose groups, 16-18 Gy and 20 Gy, were balanced with respect to nine investigated patient characteristics. These characteristics included age (≤70 years *vs.* ≥71 years, median age=70 years), gender, type of primary tumor (lung cancer *vs.* melanoma *vs.* other tumors), Eastern Cooperative Oncology Group (ECOG) performance score (0-1 *vs.* 2), interval between first diagnosis of the malignant disease and SRS (≤24 months *vs.* >24 months, median interval=24 months), number of cerebral lesions (1 *vs.* 2-3), site of cerebral lesions (supra-tentorial *vs.* infra-tentorial plus/minus supra-tentorial), maximum diameter of all cerebral lesions (≤15 mm *vs.* >15 mm, median diameter=15 mm) and presence of extracranial metastases (no *vs.* yes).

The overall intracerebral control rates at 6 months and at 12 months were 43% and 30%, respectively, in the 16-18-Gy group compared to 59% and 45%, respectively, in the 20-Gy group (p=0.53; Figure 1). The rates of freedom from new intracerebral lesions at 6 months and 12 months were 50% and 41%, respectively, in the 16-18 Gy group *vs.* 61% and 52%, respectively, in the 20 Gy group (p=0.63; Figure 1). The local control rates at 6 months and 12 months were 72% and 55%, respectively, after 16-18 Gy in comparison to 91% and 81%, respectively after 20 Gy (p=0.069; Figure 1). Overall survival rates at 6 months and 12 months were 57% and 29%, respectively, after 16-18 Gy *vs.* 53% and 31%, respectively after 20 Gy (p=0.67; Figure 1).

Table I. *Patient characteristics of the dose groups 16-18 Gy and 20 Gy.*

Characteristic	16-18 Gy N patients (%)	20 Gy N patients (%)	p-Value
Age			
≤70 years (n=48)	21 (48)	27 (53)	
≥71 years (n=47)	23 (52)	24 (47)	0.73
Gender			
Female (n=43)	22 (50)	21 (41)	
Male (n=52)	22 (50)	30 (59)	0.56
ECOG performance score			
0-1 (n=61)	29 (66)	32 (63)	
2 (n=34)	15 (34)	19 (37)	0.86
Type of primary tumor			
Lung cancer (n=23)	11 (25)	12 (24)	
Melanoma (n=35)	14 (32)	21 (41)	
Other tumors (n=37)	19 (43)	18 (35)	0.80
Interval from the first diagnosis of the malignant disease until SRS			
≤24 months (n=48)	24 (55)	24 (47)	
>24 months (n=47)	20 (45)	27 (53)	0.60
Number of cerebral lesions			
1 (n=62)	27 (61)	35 (69)	
2-3 (n=33)	17 (39)	16 (31)	0.67
Site of cerebral lesions			
Supra-tentorial (n=69)	31 (70)	38 (75)	
Infra-tentorial with/without Supra-tentorial (n=26)	13 (30)	13 (25)	0.81
Maximum diameter of all cerebral lesions			
≤15 mm (n=48)	21 (48)	27 (53)	
>15 mm (n=47)	23 (52)	24 (47)	0.73
Extracranial metastases			
No (n=35)	18 (41)	17 (33)	
Yes (n=60)	26 (59)	34 (67)	0.64

ECOG: Eastern Cooperative Oncology Group.

Discussion

The proportion of elderly patients in oncology is growing. Therefore, greater research efforts in the elderly are focused on altering chemotherapy regimens, increasing supportive care and accounting for comorbidities (1-6, 12-15). In patients presenting with cerebral metastases, age is an important prognostic factor. Elderly patients aged 65 years or older have poorer survival than younger patients (6, 7). Therefore, elderly patients require for particular attention. The treatment of cerebral metastases in elderly patients should ideally be effective but not very toxic or burdensome for patients. Neurocognitive function is an especially challenging issue to many of these patients. Therefore, SRS alone appears preferable to SRS plus whole-brain irradiation, since the combined approach can result in significantly worse neuro-cognition than SRS alone (10). The optimal dose for elderly patients receiving SRS alone needs to be defined. In order to spare as much brain tissue, the radiation dose to the brain should be as low as is reasonable providing the overall intracerebral control and surivival is not compromised. Furthermore, a lower SRS dose means a shorter treatment session and less time on the treatment couch within a tight head mask, which may be particularly uncomfortable for elderly patients. Therefore, the present study compared a SRS dose of 20 Gy which has been previously recommended for patient cohorts of any age with brain metastases from primary tumors such as breast and lung cancer rather than lower SRS doses (16-18).

According to the results of the present study, 16-18 Gy was not significantly inferior to 20 Gy with respect to overall cerebral control, freedom from new cerebral lesions and overall survival. With respect to the local control of the irradiated lesions, a trend was observed towards better local control after 20 Gy than 16-18 Gy (p=0.069). However, this difference did not translate into better intracerebral control

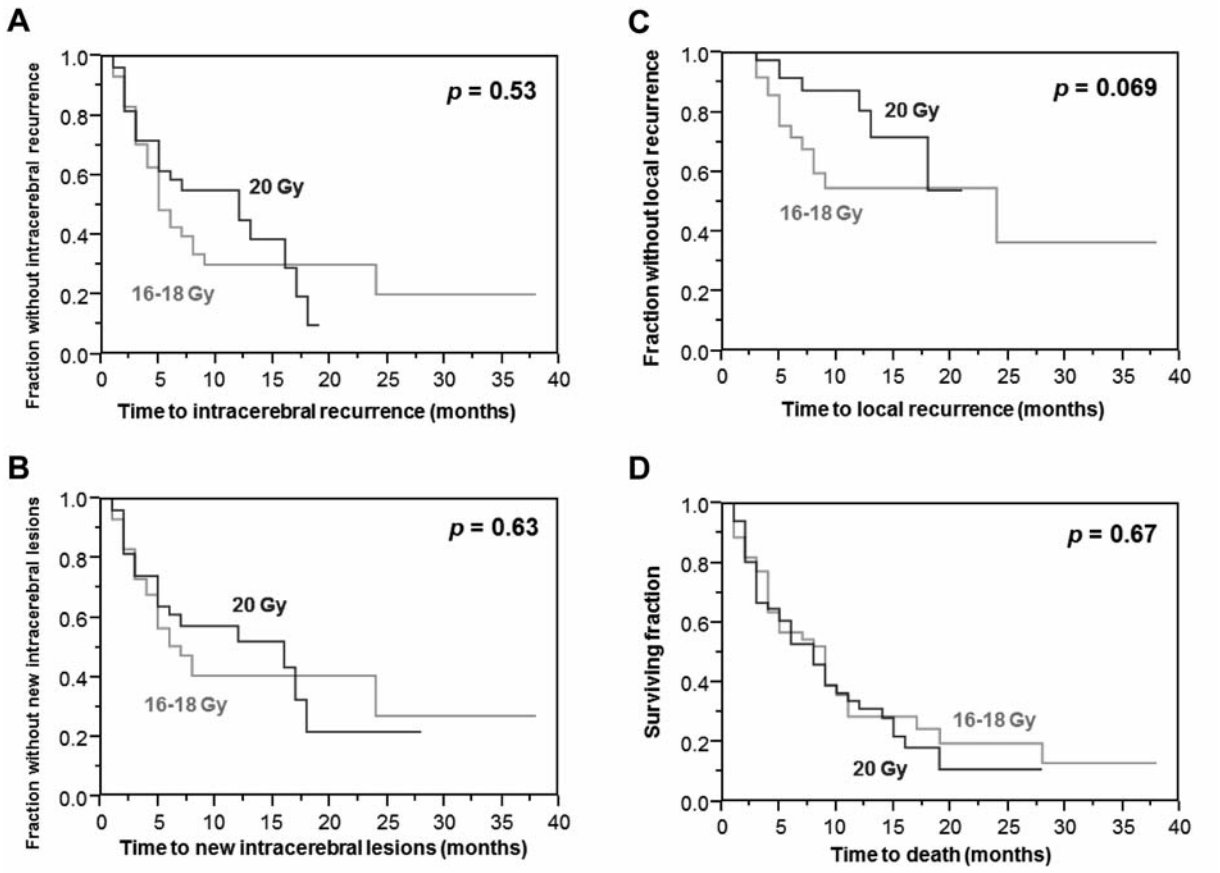

Figure 1. *Comparison of the dose groups of 16-18 Gy and 20 Gy with respect to overall intracerebral control (A), freedom from new intracerebral lesions (B), local control of the irradiated intracerebral lesions (C) and overall survival (D).*

or overall survival. Therefore, doses of 16-18 Gy appear to be sufficient for the treatment of 1-3 cerebral metastases in elderly patients. Since a certain dose effect can be expected, 18 Gy would be recommended at this stage (17).

In summary, since SRS with 16-18 Gy was not significantly inferior to that with 20 Gy in elderly patients irradiated for few cerebral metastases, SRS doses of 16-18 Gy (preferably 18 Gy) appear sufficient for this group of patients.

Conflicts of Interest

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

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