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research article

Clinical and volumetric predictors of local control after robotic stereotactic radiosurgery for cerebral metastases: active systemic disease may affect local control in the brain

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Background. The aim of the study was to assess the association between physical and biological dose normalized to volume of the metastatic tumor as well as clinical factors with local control in patients with brain metastases who underwent robotic stereotactic radiosurgery.

Patients and methods. A cohort of 69 patients consecutively treated with robotic radiosurgery between 2011 and 2016 was analyzed. The patients were treated with either single fraction radiosurgery or hypofractionated regimens. Biologically effective dose (BED) was calculated assuming alpha/beta value = 10 and both physical dose and BED were normalized to the tumor volume to allow dose-volume effect evaluation. Moreover, clinical and treatment-related variables were evaluated to asses association with local control.

Results. A total of 133 tumors were irradiated and their volumes ranged between 0.001 and 46.99 cm3. Presence of extracranial progression was associated with worse local control whereas higher total dose, BED_{10} > 59 Gy and single metastasis predicted statistically significantly better local outcome. BED_{10}/cm^3 > 36 Gy, and BED_2 > 60 Gy negatively affected local control in univariate analysis. In multivariate analysis performed on all these variables, presence of a single metastasis, BED_{10} > 59 Gy and extracranial progression retained their significance. Excluding a priori the BED_2/cm^3 parameter resulted with a Cox model confirming significance of all remaining variables.

Conclusions. Hypofractionated treatment schemes have similar efficiency to single fraction treatment in terms of local control and the effect depends on BED irrespective of fractionation schedule. Effective control of extracranial sites of the disease is associated with higher probability of local control in the brain which in turn is consistently lower in patients with multiple lesions.

Key words: brain metastases; radiosurgery; radiobiology; local control

Introduction

Although the number of studies focusing on overall survival after radiosurgery for brain metastases is impressive, much less is known about factors affecting local control. Tumor volume/diameter, volume of edema, large (> 15) number of lesions, concurrent chemotherapy and other factors are listed by various authors but without consistency and the findings usually are not reproduced by others.[1-5] Of course, assuming that metastatic tumors contain a constant number of clonogenic cells per volume unit, there is indeed a risk that larger tumors may be treated less effectively. This is because lower doses are used to kill larger number of cancer stem cells per tumor. According to the RTOG 9005 protocol, brain metastases exceeding 3 cm in diameter were treated with a single dose of 15 Gy as opposed to 24

Gy for tumors smaller than 2 cm.[6] This results with almost five times more stem cells treated with less than two thirds of the dose delivered to a smaller tumor. Alternatively, fractionated schemes of still uncertain efficacy can be implemented. Their postulated equivalence to single fraction schedules in terms of biological dose is based on radiobiological calculations but the assumptions taken, need confirmation in clinical studies. The first studies aimed at detailed analysis of the effect of the dose normalized to volume of the lesion and probability of local control were made by Amsbaugh *et al*. but they analyzed single fraction regimens only.[7,8]

The aim of our study was to assess the association between physical and biological dose delivered per volume unit of a metastatic tumor as well as clinical factors with local control in patients with brain metastases after robotic stereotactic radiosurgery.

Patients and methods

All patients treated with the CyberKnife system for cerebral metastases between 2011 and 2016 were retrospectively evaluated to find those with follow-up imaging studies allowing for evaluation of local control. No selection was made in terms of pathology of the tumor, prior treatment or primary tumor status. This resulted with identification of 69 patients for further evaluation.

Patients were immobilized with thermoplastic masks for treatment. CT and MR images were made and the target volume and critical structures were defined on registered images. Usually, no additional margin was added to the GTV. Patients were qualified to a single fraction or hypofractionated treatment after individual assessment of the target volume and proximity of organs at risk. Single doses were prescribed following the RTOG 9005 study. If V_{12} exceeded 10 cm^3 or dose constraints for critical structures were violated, fractionated treatment was prescribed. The dose was specified to isodose encompassing the target, usually between 78 and 90%. All patients were treated with the CyberKnife VSI system.

Biologically effective dose (BED) was calculated assuming the alpha/beta value of 10. The total physical dose (TD) and BED were normalized to the tumor volume to allow better evaluation of the dose effect. Prescription dose was taken as reference for calculation. Threshold values of BED and BED/cm^3 were determined after a stepwise analysis and further included into statistical analysis as categorical variables. Age, gender, pathology, primary tumor status, WBRT use and other variables potentially associated with local control and survival were also analyzed. MR imaging after treatment was performed usually every 3-4 months during the first year and every 6-12 months thereafter. Local control (LC) was defined as lack of progression (complete or partial response or stable disease) of the irradiated lesion. Any increase in lesion size without evidence of radiation-induced necrosis was qualified as local progression. Local progression-free survival (LPFS) was defined as time between treatment and the first imaging showing progression of the irradiated lesion. Local progression (LP) was defined as growth of the irradiated lesion irrespective of the status of other lesions. Distant progression-free survival defined as time to development of new brain metastases (outside the irradiated lesions) was not evaluated.

TABLE 1. Basic characteristics of the study population

	Median (range)
Age	58 (32–84)
KPS	80 (70–100)
Number of lesions (1-9)	1 (1–9)
	Number of patients
1	40
2	12
3	9
4	4
5	1
6	2
9	1
Gender (M/F)	22/47
WBRT before SRS	
Yes	34
No	35
Location of the primary tumour	
Lung	23
Breast	20
Kidney	5
Skin (melanoma)	5
Colon	3
Unknown primary	3
Uterine corpus	2
Other*	8
Disease status	
Stable/NED	42
Progressive	27
Primary tumor controlled	
Yes	62
No	7
Extracranial metastases	
Present	39
No	30

* = One case of each: intestinal sarcoma, thyroid cancer, uterine cervix carcinoma, esophageal, gastric, oral cavity, ovarian, and bladder cancer; F = female; KPS = Karnofsky performance status; M = male; NED = no evidence of disease; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy

TABLE 2. Dosimetric and volumetric characteristics of the group

Variable	Median (range)	p
Total dose in SRS	18 Gy (5–24)	**p = 0.0036***
Total dose in HSRT	20 Gy (12–30)	
Dose per fraction in HSRT	7.25 Gy (6–13)	
BED_{10} in SRS	50.4 (7.5–81.6)	**p = 0.0237***
BED_{10} in HSRT	35.7 (19.2–60)	
Lesion volume	1.74 cm^3 (0.001–46.99)	
Single metastasis	4.68 cm^3 (0.05–39.2)	**p = 0.0002***
Multiple metastases	0.96 cm3 (0.001–46.99)	
Total tumor volume	4.9 cm^3 (0.05–63.95)	
Single metastasis volume	4.68 cm^3 (0.05–39.2)	**p = 0.0371***
Multiple metastases volume	4.90 cm^3 (0.48–63.95)	

*= comparison between groups, Mann-Whitney U test; BED_{10} = biologically effective dose for alpha/beta =10; HSRT = hypofractionated stereotactic radiotherapy; SRS – stereotactic radiosurgery

TABLE 3. Association of selected variables with local control

Variable	p	
	univariate	Multivariate
Single vs. multiple lesions	**0.00001**	**0.0161**
Gender	0.2508	
Total dose*	**0.0011**	0.0886
BED_{10}*	0.7026	
BED_{10} > 59 Gy	**0.0026**	**0.0105**
Fractionation (SRS vs. HSRT)	0.1265	
Tumor volume¶	0.1777	
Total tumor volume¶	0.8950	
Chemotherapy before SRS/HSRT	0.3785	
Chemotherapy after SRS/HSRT	0.2174	
Chemotherapy before and after SRS/HSRT	0.2606	
Time between diagnosis of primary and metastases*	0.6551	
BED_{10} per 1 ml tumor volume > median (24.3 Gy)	0.3709	
BED_{10} per 1 ml tumor volume > 36 Gy	**0.0281**	0.3032
Total dose/ml tumor volume > median (11 Gy)	0.3882	
Extracranial metastases	0.3130	
Control of primary tumor	0.8681	
Extracranial progression**	**0.0078**	**0.0011**
RPA class	0.8627	
WBRT use	0.3918	
BED_2/cm^3 > 60	**0.0392**	0.8638

* = above vs. below or equal median; ** = progression of primary tumor or any of extracranial metastases; SRS = stereotactic radiosurgery; HSRT = hypofractionated stereotactic radiotherapy; BED_{10}, BED_2 = biologically effective dose for alpha/beta =10 and 2, respectively; WBRT = whole brain radiotherapy; RPA = recursive partitioning analysis

Kaplan-Meier method and log-rank test were used for calculations and intergroup comparisons. Kaplan-Meier estimations were calculated per lesion (progression of the index lesion was an event). If a new lesion occurred, the patient was censored for the purpose of the analysis (only the irradiated lesions were the subject of analysis and it was assumed that dose delivered to an existing lesion will not affect the probability of progression elsewhere in the brain). Patients dying without evidence of progression of the irradiated lesion were censored at the time of death. Cox regression was used for multivariate analysis which was performed on the set of variables significant in the univariate analysis. Mann-Whitney U test was used for intergroup comparisons. The p value < 0.05 was considered significant.

The study follows the principles of the Declaration of Helsinki.

Results

A total of 133 tumors in 69 patients were irradiated and their volumes ranged between 0.001 and 46.99 cm^3 (median 1.86). Basic patient characteristics is shown in Table 1.

Median total intracranial tumor volume was 4.1 cm^3. The doses used resulted with BED_{10} values of 11.9 – 81.6 Gy (median 46.2 Gy). Physical doses and BED per 1 cm^3 of tumor volume ranged between 0.3 - 1322 Gy (median 11), and 4.6-119733.5 Gy (median 24.3), respectively. Detailed dosimetric characteristics is shown in Table 2.

Median LPFS was 10.7 months. Actuarial 1-year local progression-free survival was 46%. No association between the volume of the tumor and local control could be found. Total dose, BED_{10} above 59 Gy (Figure 1), presence of a single metastasis (Figure 2), and extracranial progression (Figure 3) were significantly associated with LC variables. Presence of extracranial progression was associated with worse local control whereas higher TD, BED_{10} > 59 Gy and single metastasis predicted better local outcome. Moreover, negative association with BED_{10}/cm^3 (Figure 4), and BED_2/cm^3 and LC was identified (Table 3).

In multivariate analysis only presence of a single metastasis, BED_{10} > 59 Gy and extracranial progression retained their significance. Excluding a priori the BED_2/cm^3 parameter, which can be considered redundant in construction of the Cox model resulted with confirmation of significance of all of the remaining.

The results of analysis prompted to check also the difference in local control between patients with 1-3 and more metastases which was also highly significant (p = 0.0000), with median LPFS of 7.1 and 17.1 months, respectively. All patients with

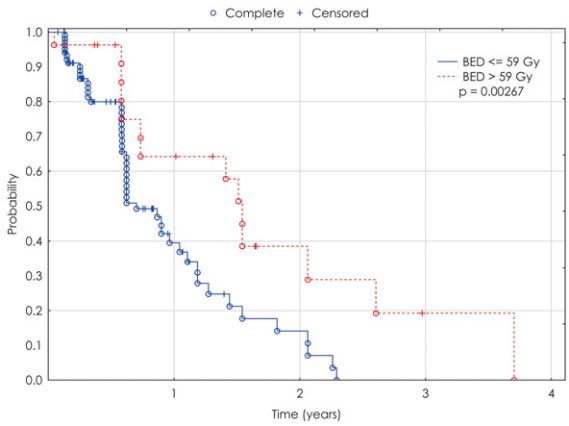

FIGURE 1. Local progression-free survival according to biologically effective dose $(BED)_{10}$. Doses above 59 Gy_{10} (red, dashed line) were associated with significantly longer local progression-free survival (LPFS) (median 7.5 *vs.* 18.4 months).

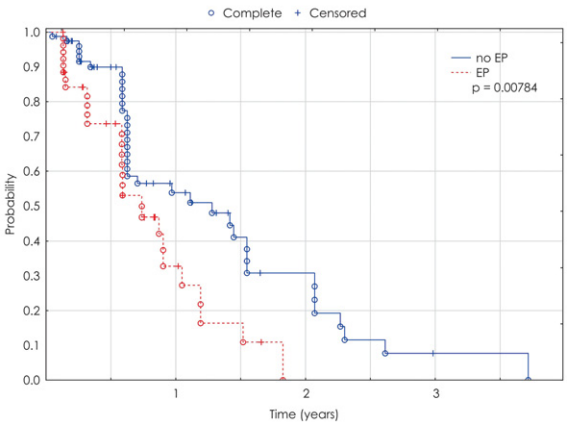

FIGURE 3. Local progression-free survival according to systemic disease status. Extracranial progression (red, dashed line) was an adverse prognostic factor.

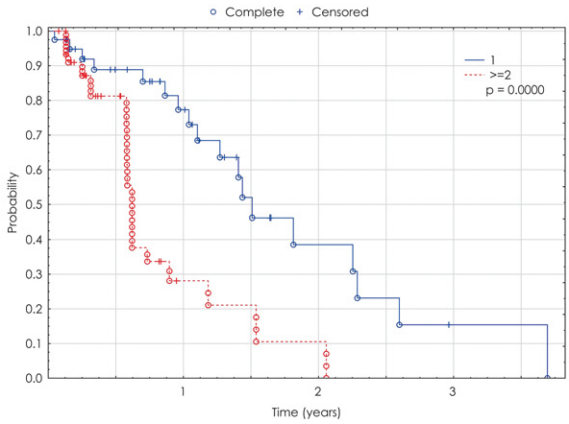

FIGURE 2. Local progression-free survival according to number of metastases. Presence of a single metastasis (blue, solid line) was a favorable prognostic factor.

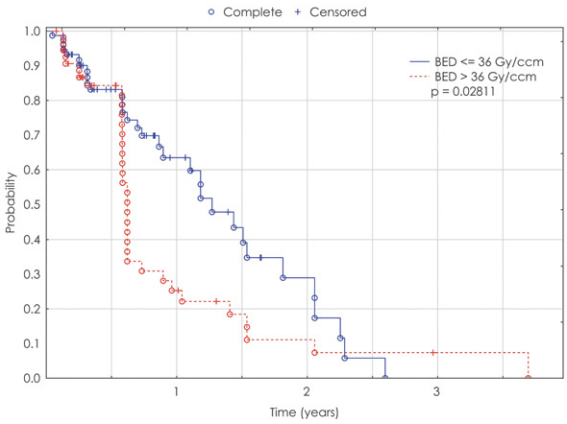

FIGURE 4. Local progression-free survival according to biologically effective dose $(BED)_{10}$ normalized to tumor volume. Exceeding the threshold value of 36 Gy_{10}/cm^3 (red, dashed line) was associated with reduced chances of maintaining local control.

more than 3 metastases failed locally before one year whereas actuarial 1-year LPFS in the group with 1-3 metastases was 68%.

Discussion

To the best knowledge of the authors this is the first study in which dose normalized to tumor volume is analyzed as a prognostic factor for local control for both single-fraction and hypofractionated regimens. Amsbaugh *et al*. used the dose per lesion diameter and dose per volume parameters to construct dose-volume response relationships.[7,8] They found strong correlation between doses and volumes of the tumor which was quite obvious because all patients in their series were treated with single fraction, so the larger the volume, the smaller total dose was used. This resulted with worse results in patients with larger metastases who were treated with lower doses. Similar patients in ours were treated with fractionated regimens which theoretically should result with similar effectiveness like after a large, single fraction. And indeed, no clear association between tumor volume and outcome could be identified here as opposed to increasing rates of local control corresponding to maximum dose per mm of tumor diameter (80%, 85%, and 90% for 1.67 Gy/mm, 2.86 Gy/mm, and 4.4 Gy/mm, respectively) reported in the Amsbaugh's paper.[7] They identified also a relationship between mean dose per volume and local control. Finally, they observed that patients with fewer number of metastases had worse local control (OR: 0.815,

95% CI: 0.72-0.93).[8] Similar observation was made by Yamamoto *et al*. in their study on stereotactic radiosurgery for multiple brain metastases.[9] They observed significant difference in local recurrence ratio and need for repeat treatment between group with 2-9 metastases (more recurrences) and group with 10 and more lesions. At the same time they admitted that the reason for that finding remains obscure. Contrary to their findings, in our series patients with larger number of metastases had worse local control than patients treated for single lesion. This is not an obvious finding whatsoever, especially knowing that the median volume of the tumor was significantly larger in patients with single lesion (median 4.68 cm^3) than in patients with multiple metastases (median 0.96 cm^3). Nevertheless, the effect was stunning which was confirmed by secondary analysis showing that all patients with more than 3 metastases fail locally before one year.

BED above 59 Gy_{10} was associated with improved chances of local control. This parameter retained significance in multivariate analysis indicating that appropriate biologically effective dose increases the probability of local control irrespective of the fractionation method. What is more intriguing, biological doses normalized to tumor volume above 36 Gy_{10}/cm^3 (the threshold value calculated for the nervous tissue - BED_2 was 60 Gy_2/cm^3 and was also significant) resulted with significantly worse local control. This phenomenon did not retain significance in multivariate analysis including all variables significant in the univariate analysis. However, in an additionally constructed model without incorporating BED_2/cm^3 it did. Amsbaugh *et al*. did not identify a threshold dose per cm^3 of tumor volume associated with plateau of local effect or local control decrease. The exact meaning of this finding is uncertain and it may be just a statistical artifact. One could also speculate that it may indicate existence of some kind of threshold dose and after reaching the optimal dose level its further escalation might facilitate concurrent negative processes. In situ recurrence of the radiosurgically ablated tumor due to damage of the surrounding tissues resulting with easier penetration of the circulating tumor cells may be one of possible explanations. Local progression was significantly associated also with extracranial progression which may further support this theory of re-seeding of the site of previously ablated tumor by circulating cells originating from extracranial foci. The concept of radiation-induced metastases, and more generally – treatment-induced metastases (TIM), although described in the 50—ties of the XX-th century, was mostly forgotten but regained attention in recent years.[10–12] In this specific case it would be rather treatment-induced/facilitated local recurrence associated with exceeding a safe dose for local microenvironment. Of course we cannot provide a proof of sterilization of the irradiated tumor or distinct characteristics of the progressing lesion but we believe our observation is worth further studies. Radiation resistance associated with general resistance to the treatment also can be an explanation and presumably should be given first, as a more probable one. In this case, in spite of delivering high doses to low-volume lesions, we would face local failure without prior elimination of the lesion. Currently, it can be only concluded that patients with systemic progression are more likely to progress also in the brain.

Better outcome after larger single dose in terms of probability of local control was confirmed for example by Mohammadi *et al*. They found that tumors smaller than 2 cm of diameter are better controlled with 24 Gy than lower doses.[13] This finding supports the assumption that there is a dose-response relationship but, on the other hand, it shows the drawbacks of using a single fraction in case of tumors which cannot be treated with sufficiently large doses. In our series, the dose-response relationship was also identified but was best seen when the dose exceeded 59 Gy_{10}, irrespective of the fractionation method and tumor volume. Interestingly, some authors did not find any correlation between local control and dosimetric or clinical factors.[5] The only factor significantly associated with local control in the study by Loo *et al*. for example, was the total volume of edema, not volume of the tumors or dose delivered.[2]

Our study has drawbacks typical for retrospective evaluations. We cannot exclude patient selection bias and we did not have follow-up imaging available for every patient treated in our center which limited the study sample. We realize also that metastases in a single patients share a lot of common properties important for the prognosis and their independent analysis may be somewhat misleading. On the other hand, it should facilitate demonstration of the dose and volume effect because lesions of various sizes in one patient were often irradiated with different doses.

Our results suggest that local control in the brain can depend on several factors including those not directly related to the local treatment and may be associated also with systemic progression. In turn, this may influence overall survival in much more complex way than we assume. The results suggest

also that escalating the dose above certain limits may not be beneficial. The threshold dose for this effect calculated for the nervous tissue is similar to the dose of 60 Gy used in conventional radiotherapy for primary brain tumors. Further escalation did not prove beneficial but was associated with increased risk of adverse effects.[14]

Conclusions

Hypofractionated treatment schemes have similar efficiency to single fraction treatment in terms of local control and the effect depends on BED, irrespective of fractionation schedule. Effective control of extracranial sites of the disease is associated with probability of local control in the brain which is consistently lower in patients with multiple lesions.

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