3c: LOCAL PROGRESSION AND PSEUDO PROGRESSION AFTER SINGLE FRACTION OR FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR LARGE BRAIN METASTASES

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ABSTRACT

Purpose: The 1-year local control rates after single-fraction stereotactic radiotherapy (SRT) for brain metastases >3 cm diameter are less than 70%, but with fractionated SRT (FSRT) higher local control rates have been reported. The purpose of this study was to compare our treatment results with SRT and FSRT for large brain metastases.

Materials and methods: In two consecutive periods, 41 patients with 46 brain metastases received SRT with 1 fraction of 15 Gy, while 51 patients with 65 brain metastases received FSRT with 3 fractions of 8 Gy. We included patients with brain metastases with a planning target volume of >13 cm^3 or metastases in the brainstem.

Results: The minimum follow-up of patients still alive was 22 months. Comparing 1 fraction of 15 Gy with 3 fractions of 8 Gy, the 1-year rates of freedom from any local progression (54% and 61%, p=0.93) and pseudo progression (85% and 75%, p=0.25) were not significantly different. Overall survival rates were also not different.

Conclusion: The 1-year local progression and pseudo progression rates after 1 fraction of 15 Gy or 3 fractions of 8 Gy for large brain metastases and metastases in the brainstem are similar. For better local control rates, FSRT schemes with a higher biological equivalent dose may be necessary.

Stereotactic radiotherapy (SRT) is an established treatment modality for patients with brain metastases [1]. Local control of the metastases is the aim of treatment as progressive tumor growth may lead to new neurologic symptoms [2]. The dose that can be safely administered depends upon the size of the metastasis [3]. In Radiation Therapy Oncology Group (RTOG) study 90–05 the maximum tolerated single fraction dose for metastases with a diameter >3 cm was found to be 15Gy, as a higher dose of 18Gy was associated with an unacceptably high rate of grade 3–5 neurotoxicity. Progression after radiotherapy may be caused by proliferation of tumor cells but may also be a manifestation of radiation toxicity (pseudo progression). The distinction between these two types of progression is difficult to make on magnetic resonance imaging (MRI), but perfusion MRI may be helpful in this respect [4].
The 1-year local control of metastases >3 cm is reported to be 37–62% after 15 Gy [3, 5, 6]. With FSRT 1-year local control rates >70% were reported [7, 8]. However, a comparative study of SRT and FSRT for large brain metastases has not yet been published. Furthermore, only scarce data are available about the rates of pseudo progression after SRT or FSRT. We observed a disappointing 12-month local control rate of 37% after a single-fraction dose of 15 Gy in our patients with large brain metastases [6]. In an attempt to improve local control rates we embarked on an FSRT protocol in September 2007, treating this category of patients with 3 fractions of 8 Gy. The purpose of the present study is to compare the local control rates as well as the rates of pseudo progression between these two treatment protocols.

MATERIALS AND METHODS

PATIENTS

Two patient cohorts received SRT for brain metastases in two consecutive periods. In both cohorts we included patients with metastases with a planning target volume (PTV) of >13 cm^3 or metastases in or close to the brainstem. The prescribed dose was 15 Gy between June 2004 and January 2007 (group A) and 24 Gy in 3 fractions of 8 Gy (in 8 days) between September 2007 and September 2009 (group B).
To be able to study the effect of SRT dose on local control, we excluded the patients who had SRT as a boost after whole brain irradiation (WBI). Karnofsky performance scores (KPS) were determined prospectively and the RTOG recursive partitioning analysis (RPA) scores were determined retrospectively in all patients.

TREATMENT

Patients had a CT scan with 2-mm slice thickness while fixed in a relocatable stereotactic head frame (Brainlab AG Feldkirchen, Germany) [9, 10]. All patients also had an MRI planning scan (T1-weighted 3D MPRAGE after gadolinium administration; voxel size 1.1×1.1×1.3 mm^3). Co-registration of CT and MRI, contouring and treatment planning were done on Brainscan 5.31 or iPlan 4.0 (Brainlab AG Feldkirchen, Germany). The gross tumor volume (GTV) was defined as the volume of the contrast-enhancing tumor as visualized on the MRI scan. The PTV was created by 3D expansion of the GTV with 2 mm. All patients were treated on the Novalis, a dedicated linear accelerator (Brainlab AG Feldkirchen, Germany). Dynamic conformal arc was used as treatment technique for all metastases. Doses were prescribed to the 80% isodose. We allowed a maximum dose of 8 Gy (SRT) and 15 Gy (FSRT) to the optic system and a maximum dose of 15 Gy (SRT) and 24 Gy (FSRT) to the brainstem.

FOLLOW-UP

All patients were followed-up at 3-month intervals at the outpatient clinic as long as their condition allowed them to come. These follow-up visits were combined with MRI scans at 1.5 T (Siemens, Erlangen, Germany). The imaging protocol consisted of T1-weighted images

	Group A (1x15 Gy) n (%)	Group B (3x8 Gy) n (%)	Group A vs Group B
Patients (n)	41	51	
Sex Male Female	 15 (37%) 26 (63%)	 19 (37%) 32 (63%)	p=0.9
Age (year) <65 ≥65	 22 (54%) 19 (46%)	 29 (57%) 22 (43%)	p=0.8
KPS <90 ≥90	 21 (51%) 20 (49%)	 29 (57%) 22 (43%)	p=0.6
RPA class 1 2 3	 7 (17%) 30 (73%) 4 (10%)	 8 (16%) 43 (84%) 0	p=0.7
Primary tumor Lung Breast Melanoma Other	 19 (46%) 10 (24%) 2 (6%) 10 (24%)	 24 (47%) 8 (16%) 9 (18%) 10 (19%)	p=0.2
Number of brain metastases 1 >1	 20 (49%) 21 (51%)	 28 (55%) 23 (45%)	p=0.6
Treatment: No WBI SRT as salvage after WBI WBI as salvage after SRT	 29 (70%) 6 (15%) 6 (15%)	 32 (63%) 13 (25%) 6 (12%)	p=0.4

Table 1. Patient and treatment characteristics in both groups.
Group A received 1 fraction of 15 Gy.
Group B received 3 fractions of 8 GyKPS Karnofsky performance score, RPA recursive partitioning analysis, WBI whole brain irradiation, SRT stereotactic radiotherapy.

without and with gadolinium, T2 images and diffusion-weighted imaging. MR perfusion imaging, using a SE-EPI sequence, was performed when increase or recurrence of gadolinium enhancement was observed in lesions. Analysis of the MR perfusion data was performed by calculating the relative cerebral blood volume (r-CBV) maps and by comparing the r-CBV

maps with the post-gadolinium T1-weighted images. R-CBV maps were considered to be suggestive for viable tumor tissue when r-CBV in the enhancing part of the tumor was equal to or higher than cerebral gray matter (based on visual assessment by a neuroradiologist). Telephonic follow-up was done if patients were not able to visit the hospital anymore; however, information thus acquired was only used for survival analysis. Local control was calculated from the first day of (F)SRT. All MRI scans were reviewed and tumors were measured in three dimensions. Response to treatment was classified according to the Macdonald criteria [11]. The date of the first MRI showing any local progression was used as the date of progression. Pseudo progression was diagnosed when perfusion MRI showed no signs of viable tissue [4]. Tumor progression was defined as tumor proliferation not caused by pseudo progression, i.e., with MR perfusion imaging characteristics compatible with viable tissue. Tumor progression could be preceded by pseudoprogression. Endpoints were any local progression, tumor progression and pseudo progression.

	Group A (1x15 Gy) n (%)	Group B (3x8 Gy) n (%)	Group A vs Group B
Metastases (n)	46	65	
Primary tumor			
Lung	22 (48%)	26 (40%)	
Breast	11 (24%)	13 (20%)	
Melanoma	2 (4%)	10 (15%)	p=0.3
Other	11 (24%)	16 (25%)	
PTV Volume			
<13cm^3	11 (24%)	18 (28%)	
13-20 cm^3	17 (37%)	16 (25%)	p=0.4
>20cm^3	18 (39%)	31 (47%)	
Treatment			
No WBI	33 (72%)	42 (65%)	
SRT as salvage after WBI	7 (15%)	15 (23%)	p=0.6
WBI as salvage after SRT	6 (13%)	8 (12%)	

Table 2. Tumor characteristics in both groups.
Group A received 1 fraction of 15 Gy.
Group B received 3 fractions of 8 GyPTV planning target volume,
WBI whole brain irradiation, SRT stereotactic radiotherapy.

ANALYSES

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The Pearson X^2 test was used to analyze whether the characteristics of both cohorts were equally divided. Overall survival and local progression-free survival (LPFS) curves were calculated using the Kaplan–Meier method. For the calculation of the actuarial freedom from any progression only the first progression of a metastasis was used as an event. The logrank test was used for the univariate analyses.

RESULTS

PATIENTS, METASTASES AND TREATMENT

Group A consisted of 41 patients with 46 brain metastases and group B consisted of 51 patients with 65 brain metastases. The median follow-up of all patients was 5.3 months and the minimum follow-up of patients still alive was 22 months. Patient and treatment characteristics were equally divided between both groups (. Tab. 1). The tumor characteristics of both cohorts are shown in Tab. 2.

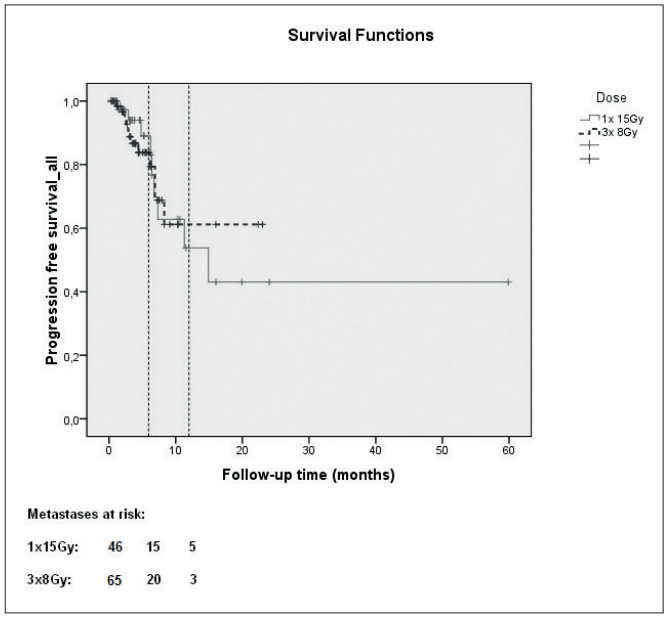

Figure 1. Theactuarial rate of freedom from all tumor progression in both groups of metastases. Tumor progression and peudo progression were considered as events. p=0.93

LOCAL PROGRESSION-FREE SURVIVAL (LPFS)

The actuarial rates of freedom from any local progression in group A and B are shown in Fig. 1. The 6- and 12-month local control rates were 89% and 54% with 1 fraction of 15 Gy and 84% and 61% with 3 fractions of 8 Gy. LPFS rates were not significantly different between the two groups (p=0.93). In two brain metastases tumor progression was preceded by pseudo progression. Only one resection of a progressive lesion was performed (in a patient from the SRT cohort). The histological diagnosis was radiation necrosis.

The actuarial freedom from tumor progression in groups A and B are shown in Fig. 2. Pseudo progression was not considered an event in this figure. The 6- and 12-month rates of freedom from tumor progression were 89% and 67% with 1 fraction of 15 Gy and 92% and 75% with 3 fractions of 8 Gy. There was no significant difference between both groups (p=0.27).

The actuarial rates of freedom from pseudo progression in group A and B are shown in Fig 3. The 6- and 12-month rates of freedom from pseudo progression were 93% and 85% with 1 fraction of 15 Gy and 91% and 75% with 3 fractions of 8 Gy. There was no significant difference between the two groups (p=0.25).

In a univariate analysis dose (15 or 24 Gy), KPS, PTV, previous WBI only and all WBI (previous or later) were correlated with the occurrence of all tumor progressions, pseudo progres

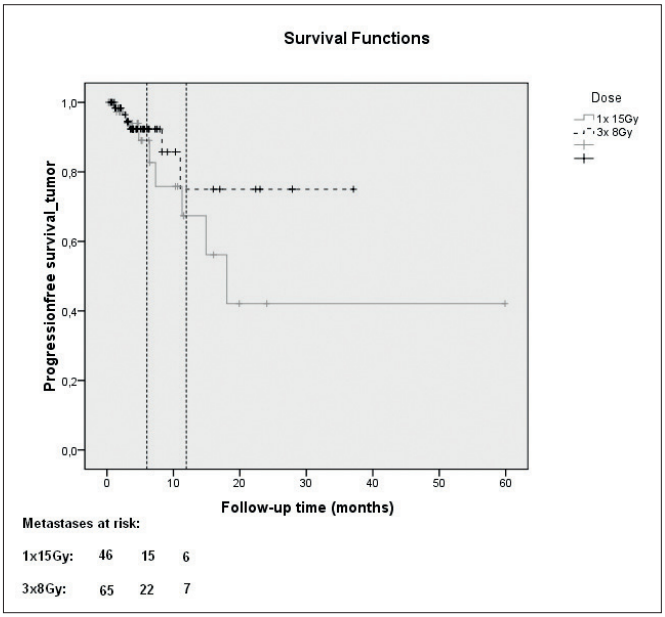

Figure 2. Theactuarial rate of freedom from tumor progression in both groups of metastases. Only tumor progressions, but not pseudo progressions were considered as events. p=0.27

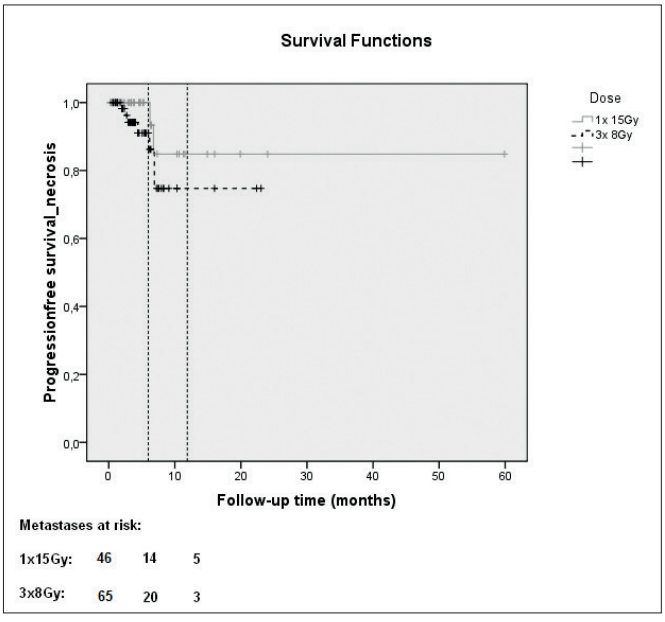

Figure 3. Theactuarial rate of freedom from pseudo progression in both groups of metastases. p=0.25

sion and tumor progression (Tab. 3). We found no relation between any type of progression and dose, KPS or tumor volume. However, after previous WBI a significantly higher rate of pseudo progression was found (p=0.02). Moreover, a higher rate of tumor progression was found with previous or later WBI. As this was the only significant relation, a multivariate analysis was not performed.

SURVIVAL

The median survival of all patients was 5.3 months. The 6- and 12-month overall survival rates were 41% and 23%, respectively. In the univariate analysis the only prognostic factor for survival was KPS (p=0.02). We found no difference in survival rates between group A and B (p=0.58).

DISCUSSION

This is a retrospective comparison of SRT (1 fraction of 15 Gy) and FSRT (3 fractions of 8 Gy) used in two consecutive cohorts of patients with large-sized brain metastases. Actuarial survival rates and rates of freedom from progression or pseudo progression were found not to differ significantly between 1 fraction of 15 Gy and 3 fractions of 8 Gy. Therefore, FSRT with 3 fractions of 8 Gy does not seem to be an improvement over 1 fraction of 15 Gy for large brain metastases and metastases in the brainstem.

Surgery may be the treatment of choice for large brain metastases, if feasible. SRT however is also an attractive option for patients with large metastases, although symptomatic improvement and local control are not optimal after single fraction treatment [6, 12, 13, 14]. There is no agreement on the optimal SRT dose for these tumors. Recently we performed a systematic literature search to summarize the evidence about the relation between SRT dose and local control [13]. We found that 12-month local control after SRT was highly dependent upon dose and was high after >21 Gy, but low after <15 Gy [13]. However, it is known from RTOG 90–05 that unacceptably high neurotoxicity rates are found after treating larger recurrent brain metastases (diameter >3 cm) with single doses >15 Gy [3]. Higher local control rates were reported after FSRT in larger metastases with acceptable rates of radiation toxicity (Tab. 4, [8, 15, 16, 17, 18]). Therefore, to improve the results of SRT of large brain metastases, FSRT is a logical step, enabling a higher tumor dose with a lower risk of neurotoxicity.

We decided to treat these patients with 3 fractions of 8 Gy, after we had observed the disappointing efficacy of 1 fraction 15 Gy. The rationale for this new scheme was the better biologically effective dose (BED) "profile" of the fractionated scheme [6]. The BED model describes the responses to ionizing radiation well at doses up to about 18 Gy [19, 20, 21]. The BED_2 values (for normal tissue, α/β = 2 Gy) for 1 fraction of 15 Gy and 3 fractions of 8 Gy are 127.5 Gy and 120 Gy respectively and the BED_{12} values (for tumor, α/β = 12 Gy) 33.8 Gy and 40 Gy respectively. Based on the BED model we initially expected an improved local control with less late toxicity. In hindsight these expected differences are probably too small to detect in the relatively small numbers studied here. To improve local control for brain metastases with a PTV >13 cm^3 it would be logical to use FSRT with a higher BED_{12}, keeping in mind that the rate of adverse treatment effects may also increase. In our department we decided to change the protocol for these large metastases to 3 fractions of 8.5 Gy, following the conclusions from our literature search [13].

As this is not a randomized comparison, conclusions from this study have to be viewed with caution. Local control was found to be independent upon PTV and all other factors that may influence local control are well balanced between the two cohorts. Therefore we think that it is justified to conclude that local control rates are similar with both dose schemes, with all well-known restrictions of a retrospective study.

		All local progressions	Tumor progression	Pseudo progression
Dose	1x15 vs 3x8 Gy	P=0.93	P=0.27	P=0.25
KPS	<90 vs ≥90	P=0.50	P=0.17	P=0.50
PTV Volume	<13cm^3 vs 13-20cm^3 vs >20cm^3	P=0.72	P=0.60	P=0.36
Previous and later WBI	Yes vs no	P=0.07	P=0.04[a]	P=0.02[b]
Only previous WBI	Yes vs no	P=0.02	P=0.63	P=0.02[c]

Table 3. Univariate analysis of prognostic factors for local progression.
Log rank: p value
[a] 6 out of 75 metastases without WBI developed tumor progression,
8 out of 36 metastases with WBI developed tumor progression.
[b] 3 out of 75 metastases without WBI developed pseudo progression,
6 out of 36 metastases with WBI developed pseudo progression.
[c] 6 out of 22 metastases with previous WBI developed pseudo progression,
3 out of 89 metastases without previous WBI developed pseudo progression.
No metastasis with WBI after SRT developed pseudo progression

Author	Diameter/volume	Dose (Gy)	BED_{12} (Gy)	12-month local control (%)	Radiation toxicity (%)
Vogelbaum [16]	3 - 4.5cm	1 x 15Gy	33.8	45	na
Ernst- Stecken [18]	1 - 5cm	5-6 x 7Gy	45-55.4	76	14% (V_{4Gy} <23cc)[c] 70% (V_{4Gy} >23cc)
Narayana [17]	2 - 5cm	5 x 6Gy	45	70	na
Higuchi [8]	3 - 4.5cm	3 x 10Gy	55	76	0[b]
Marchetti [15]	0.3 - 48.2cm^3	3 x 8Gy	40	59	2[b]
This series	76% > 3cm 76% > 3cm	1 x 15Gy 3 x 8Gy	33.8 40	54 61	15[a] 25[a]

Table 4. Results from the literature on SRT for large brain metastases
[a] pseudoprogression
[b] late radiation necrosis
[c] new or increasing necrotic lesions
na: not available
V4Gy: volume of tissue receiving at least 4Gy per fraction

An enlargement of the treated volume after radiotherapy may be caused by an increased proliferation rate of tumor cells but may also be a manifestation of radiation toxicity (pseudo progression). We prefer to use the term pseudo progression instead of radiation necrosis like it is used in gliomas, where real progression can also be preceded by pseudo progression [22]. The histology of this radiation effect usually is a chronic inflammatory reaction of brain tissue combined with necrosis of normal brain tissue and tumor tissue [23]. The distinction between real tumor progression and pseudo progression is difficult to make using standard morphologic MR imaging, but modern MR imaging techniques, especially perfusion MRI, may be helpful to differentiate viable tumor tissue from tissue with radiation effects [4, 24]. In our patients a substantial proportion of all progressions were diagnosed as pseudo progression. As the rate of pseudo progression was not significantly different between group A and B (15% versus 25% at 1 year), whereas the metastases in group B were slightly larger than those in group A, 3 fractions of 8 Gy is certainly feasible for the larger metastases.

Not much is known about ways to reduce the rate of pseudo progression. A relation has been reported between the rate of radiation necrosis and the V12 (volume of tissue that received a single dose of ≥12 Gy) [25, 26]. A lower BED to normal brain tissue and at the same time a higher BED to tumor tissue would be needed to reduce the rate of pseudo progression without compromising local control. To this end FSRT may be used, but more research is needed to find the optimal scheme.

An interesting finding in our study is the higher rate of pseudo progression in patients with prior WBI. This would imply that it would be safe to give higher biological doses than advised based on RTOG 90–05 if no prior WBI has been given. Until now, only a few and somewhat conflicting data are available on this issue. Chao *et al.* [5] retreated 111 patients with SRT for recurrence after WBI and found only two cases of radiation necrosis. Yang *et al.* [14] treated 70 patients with metastases >3 cm diameter with SRT, 33 of whom had previous WBI. After 2 months patients with previous WBI had slightly worse edema response and symptom relief than those without. Fourteen of 29 patients with imaging assessment >6 months after SRT had adverse radiation effects (48%), but the authors did not mention a relation with previous WBI.

We conclude that local control rates with 1 fraction of 15 Gy or 3 fractions of 8 Gy for large brain metastases are similar. Large brain metastases can be safely treated with a hypofractionated scheme, but the optimal dose remains to be determined.

Conflict of interest: No statement made.

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