Technische Universität München

TUM School of Medicine and Health

Tumor shrinkage assessed by volumetric MRI in long-term follow-up after fractionated stereotactic radiotherapy of nonfunctioning pituitary adenoma and fractionated stereotactic radiotherapy in the treatment of pituitary adenomas

Nektarios Poullos

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Vorsitz: Prof. Dr. Ernst J. Rummeny

Prüfende der Dissertation:

1. Prof. Dr Michael Molls
2. Prof. Dr Stephanie E. Combs

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Contents

1. Generally

1.1. Pituitary adenoma

1.1.1. Introduction

Pituitary adenomas are histopathologically benign tumors that arise from the anterior lobe of the pituitary gland with an incidence of 10-15 % of all the intracranial tumors. 80% of the adenomas are hormonactive and 20 % are hormoninactive (50 % prolactinoma, 25 % STH-producing adenoma, 25% ACTH-producing adenoma). They tend to expand locally, therefore causing compression of adjacent structures such as optic chiasm and optic nerve. Visual impairment and pituitary insufficiency are often encountered clinical symptoms in non-functioning pituitary adenomas (NFPAs). Hormonal overproduction and its specific symptoms generally lead to diagnosis of functioning pituitary adenomas [26].

1.2. Therapy

1.2.1. Surgery

Surgical resection is the widely accepted initial treatment for both functioning and non-functioning pituitary adenomas, except prolactinomas, which generally respond to medical therapy. Still, complete tumor resection is not possible in every case, mainly when the tumor extends into the cavernous sinus or dural invasion is present.

1.2.2. Radiotherapy

Radiotherapy is generally used in patients with residual or recurrent disease following previous surgery. It is an effective treatment achieving excellent rates of tumor control up to 99% at 5 years and 91% at 10 years [3, 6, 26, 27, 28, 31]. Tumor regrowth has been observed in a significant proportion of pituitary adenomas after initial surgical treatment [8, 11, 18, 29, 30, 44, 45]. As NFPAs lack signs of hormonal overproduction they tend to be detected at larger sizes, therefore tumor regrowth after surgical resection occurs quite often in this subgroup of patients [8, 11, 30, 44, 45]. For incompletely resected or recurrent tumours, conventional radiotherapy has been used in the past [2, 3, 25, 35, 37, 46]. Despite excellent long term tumor control rates, ranging well above 90%, reports about complications after conventional radiotherapy make its use a matter of debate and give cause for some concern [1, 35].

1.1.2.3 Stereotactic radiotherapy

Despite advances in microsurgical techniques, recurrent disease or residual tumor in large lesions are still of concern. Excellent long term tumor control can be achieved by using stereotactic radiotherapy immediately after surgery for large or residual pituitary adenomas or in a delayed setting for recurrent disease [5, 6, 26, 27, 28, 31].

Stereotactic radiotherapy, allowing for higher dose conformity, at the same time spearing normal surrounding tissue, can be considered a low-risk treatment. It might help overcome the long-term toxicity concerns of conventional radiotherapy. Single fraction stereotactic radiotherapy, applied as gamma knife radiosurgery or with a modified linear accelerator, has been reported in the management of patients with NFPAs but also for hormone secreting tumors [14, 20, 23, 32, 34, 36]. Since single fraction stereotactic radiotherapy is usually offered to selected patients, fractionated stereotactic radiotherapy (FSRT) can be applied irrespective of tumor size or proximity to the optic apparatus.

2. Diagnostic

Generally, MRI is used to assess radiological response of the NFPAs to treatment. Still, there is lack of evidence-based guidance regarding type, frequency and duration of radiological assessment during follow-up.

Data for radiological response after radiotherapy of pituitary adenomas are reported as ranging from 86 % to 98% of all treated NFPAs [6, 26, 27, 28, 31]. This heterogeneity depends on variations in point in time of examination and definition of response.

Radiological regression is defined for cancer therapy according to the Response Evaluation Criteria in Solid Tumors (RECIST) [9]. Unfortunately, such guidelines are not available for benign tumors. In a radiologic follow-up study for pituitary adenomas after Gamma knife stereotactic radiosurgery by Tung et al the total volume was estimated from the three maximal tumor diameters of height, width, and anterior-to-posterior diameters from MRI scans [43]. The authors mention, that in their study, the volumes were estimated similar to the study of Lundin et al. [24]. In a recently published study about the outcome of FSRT in patients with pituitary adenomas resistant to conventional treatments, the authors report pituitary tumor volumes of 20 non-functioning and 10 functioning macroadenomas. In their study three orthogonal diameters were measured, if possible, from MRI scans, and tumor volume was calculated. In cases of irregular or multilobular tumors, the authors mention that the longest diameter in one dimension was recorded. Progressive disease was defined as tumour growth $\geq$ 25%, stable disease as < 25% change in tumor volume or longest diameter, partial response as tumor shrinkage $\geq$ 25% and complete response as no visible tumor [38].

3. Purpose

Since all the above criteria are not sufficient for irregularly formed tumors, one aim of this study is to quantitatively analyze tumor shrinkage after FSRT of pituitary adenomas by 3-D MRI. Exact evaluation of radiological tumor response to stereotactic radiotherapy seems to us of major importance in the subgroup of NFPAs, as compared to hormone secreting pituitary adenomas, where hormone levels are the main criteria to evaluate response to therapy, NFPAs lack these criteria for clinical evaluation of tumor control.

The other aim of this study is to evaluate the role of FSRT (fractionated stereotactic radiotherapy) in the management of non-functioning and functioning pituitary adenomas in the postoperative setting, with respect to tumor control and side effects of radiotherapy.

4. Methods and Materials

4.1. Patients

Between April 2000 and July 2008, 37 consecutive patients, 19 male, 18 female, with a median age of 56 years (range 14 – 75 years) with pituitary adenomas were treated at the Department of Radiation Oncology at the Technical University Munich. Stereotactic radiotherapy was delivered in all cases in a fractionated manner by an adapted linear accelerator.

From 37 patients, 29 had non-functioning pituitary adenomas (NFPAs) and 8 functioning pituitary adenomas. Three adenomas were classified as adrenocorticotropic-hormone-secreting (ACTH), 2 as growth-hormone-secreting (STH) and 3 were prolactinomas.

All patients have previously undergone surgery and present at our clinic with residual (18 patients) or recurrent disease (19 patients). Eighteen patients underwent prior to radiotherapy one surgical intervention, 8 patients underwent microsurgical resections and 9 patients have been operated 3 times before radiotherapy was considered. One patient has been operated 4 times before FSRT, 4 transsphenoidal interventions. Another patient underwent 4 transsphenoidal operations and one osteoplastic craniotomy, so altogether 5 surgical interventions prior to FSRT. The applied mean dose was 49,4 Gy (45 -52,2 Gy), 5 fractions per week with daily dose 1,8 Gy per fraction. The mean follow-up time was 49 months, median 57 (range 2 – 111 months). The clinical features of the patients are summarized in Table 1+2.

n=patients		37
gender		
	female	18
	male	19
mean age (14 - 75)		
		56
Histologic type		
	Nonfunctioning	29
	Functioning	8
ACTH-secreting		3
STH-secreting		2
Prolactinomas		3

Operation (OP) n=37

1 x OP n=18

2 x OP n=8

3 x OP n= 9

4 x OP n=1

5 x OP n=1

Radiotherapy used for:

recurrence or progression after surgery	19
Residual disease after subtotal resection	18

Table 1: Clinical features of the patients.

	median dose (Gy)	median follow up (months)	mean follow-up time (months)
FSRT n = 37	49.4 (45 – 52,2)	57 (2 – 111 months)	49

Table 2: Stereotactic fractionated radiotherapy (FRST) and follow-up time

Two patients (n=2) from the 37 patients that were treated with stereotactic fractionated radiotherapy (FRST) in our department they did not have further follow-up with us because they returned to their county after completed the radiotherapy (Jordan and Palestine). All the rest 35 patients were invited for a detailed follow up study using 3D-MRI in stereotactic -sequence (1,6mm thin slight) for the procedure for the volumetric evaluation as the same MR sequence used for the treatment planning. Only 16 patients (n=16) accepted the invitation for the volumetric study and came for the detailed 3D-MRI in stereotactic sequence. Four patients died cause other reason, 1 patient died cause a Glioblastoma. Three other patients developed disease progression of the radiated pituitary adenomas, and they were excluded from the volumetric study, one of them was operated and the rest 2 were radiated with Cyberknife. Two other patients returned to Cyprus after the FRST and continued the further follow up with MRI by sending us the imaging and the medical information from our colleagues in Cyprus. Four patients declined the study because they lived in other Federal Land and they were far away from Munich. Three patients were not contactable for the invitation and one patient had multiple sclerosis, so she also declined the study due to her neurological deficits.

All 16 patients who entered this follow up study had nonfunctioning pituitary adenoma. All of them had previously undergone surgery and presented at our clinic with residual (8 patients) or recurrent (8 patients) disease. Eight patients underwent prior to radiotherapy one surgical intervention (7 transsphenoidal approach, 1 osteoplastic craniotomy). Three patients underwent two transsphenoidal resections prior to our treatment. Another three patients have been operated three times before radiotherapy was considered, two of them underwent 2 times transsphenoidal operation and a third time osteoplastic craniotomy was used, one of them had been operated 3 times using osteoplastic craniotomy. Two patients have been operated 4 times before stereotactic radiotherapy was applied by us, one patient underwent 4 transsphenoidal operations, the other one 3 transsphenoidal interventions and one osteoplastic craniotomy. The applied median dose was 49,4 Gy (45-50,4 Gy), 13 patients received 50,4 Gy, 3 patients 45 Gy. The ratio of male to female

patients was 1.29:1 (9 male, 7 female). The mean age was 57 years (range 14 – 75 years).

The median follow-up time was 63 months (range 28-100 months). The clinical features of the patients are summarized in Table 3.

n	16
gender	
female	7
male	9
mean age	57
histologic type	
nonfunctioning	16
timepoint of radiotherapy	
recurrence or progression after surgery	8
immediately after subtotal resection	8

Table 3: Clinical features of the patients for the volumetric study.

4.2. Treatment planning

Most patients received a total dose of 50, 4 Gy in 1, 8 Gy per fraction, 5 times a week (28 cases). In 8 elderly patients, the fractionation schedule was changed due to morbidity, making shorter treatment time necessary (25 x 1, 8 Gy or 27 x 1, 8 Gy one patient). Another patient received a total dose of 52, 2 Gy in 1, 8 Gy per fraction.

For treatment planning and radiation delivery an individual thermoplastic head mask (BrainLab) was modelled for each patient, allowing a positioning accuracy of 0.5 to 1.0 mm. This mask was attached to a stereotactic localisation system on the base of the frame (BrainLab) to obtain contrast-enhanced CT scans at a thickness of 1.5 – 2 mm. In addition, gadolinium enhanced T1-weighted MRI with 1.5-2mm slices in the axial plane was acquired. The co-registration of the MRI scans to the planning CT was achieved using a mutual information algorithm. The target volume and organs at risk were defined on each slice of a three-dimensional data cube using the three-dimensional treatment planning system, Brainscan, from BrainLab. The organ at risk delineated for each case consisted of optical nerves, optic chiasm, eyes, lens, pituitary stalk, thalamus, hypothalamus, and brainstem. The PTV (planning tumor volume) was defined as the area of contrast enhancement on T1-weighted MRI plus a 1.5-2 mm safety margin. Treatment was mainly performed using 5 to 6 isocentric beams.

An adapted Siemens-LINAC with 6 MeV photons and a micro-multileaf collimator with a leaf width of 3 mm were for treatment delivery.

4.3. Follow-up

Before radiotherapy, every patient had endocrinologic and ophthalmologic examinations. Visual assessment included Humphrey optic fields and visual acuity examinations, each eye being assessed separately. Regular follow-up included radiologic (CT / MR imaging), endocrinologic and ophthalmologic examinations. All patients were seen 6 weeks after completed radiotherapy for a first follow-up visit and then every 6 months for the next 2-3 years. Thereafter, follow-up examinations took place yearly.

Diagnostic radiology reports, starting with initiation of radiotherapy and during follow-up were analyzed for all patients in the study. MRI was performed every 6 months for the first 2 years after radiotherapy and yearly thereafter. No standardized protocol was used, but T1-weighted images after application of Gadolinium (Gd) in at least two planes with slice thickness of 3 -5 mm were included. All diagnostic reports contained measurements of the tumors, mostly the longest diameter in one plane. Patients were reported as being in “partial remission”, if there was any tumor shrinkage, as “stable disease”, if there was no tumor shrinkage and “progression” if there was any tumor growth.

4.4. Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) was performed using a Philips 1.5 Tesla scanner Gryoscan ACS-NT for radiotherapy treatment planning as well as for follow-up studies. The MRI examination occurred in the Radiology Department in Klinikum Rechts der Isar. The acquisition was performed using a standard head coil. Axial, spin-echo T1-weighted sequences were acquired after application of contrast media gadolinium-diethylenetriaminepentacetic acid (Gd-DTPA, 0.1 mmol/kg body weight). 3D gradient echo T1-weighted sequences with 1.6 mm slice thickness without gap were acquired from foramen magnum to the vertex, perpendicular to the main magnetic field.

4.5. Image fusion

The co-registration of the gadolinium (Gd) enhanced T1-weighted MRI scans was achieved using a mutual information algorithm integrated into the planning software (BrainScan 5.21, BrainLAB), which is tested for its validity [4].

4.6. Tumor volume delineation

Delineation of the tumor volume was performed as gross tumor volume (GTV) without adding safety margins based on the Gd enhanced T1-weighted MRI. The tumor margins were delineated on each slice of the pre-radiotherapy and post-radiotherapy MRI-scans. Using the three-dimensional treatment planning system, Brainscan 5.21, BrainLab, 3-D volumes were calculated.

4.7. Analysis of diagnostic radiology reports

Diagnostic radiology reports, starting with initiation of radiotherapy and during follow-up were analyzed for all patients in the study. MRI was performed every 6 months for the first 2 years after radiotherapy and yearly thereafter. No standardized protocol was used, but T1-weighted images after application of Gd in at least two planes with slice thickness of 3-5 mm were included. All diagnostic reports contained measurements of the tumors, mostly the longest diameter in one plane. Patients were reported as being in „partial remission “, if there was any tumor shrinkage, as „stable disease“, if there was no tumor shrinkage and „progression“ if there was any tumor growth.

5. Results

5.1. Fractionated stereotactic radiotherapy (FSRT)

Fractionated stereotactic radiotherapy (FRST) was well tolerated by all patients and could be completed without interruption all cases. No acute toxicities were observed during FSRT, except for one single case of transient dizziness which was reported by one of the 37 treated patients during completion of radiotherapy. Some minor transient symptoms included headaches, reported by 8 patients and mild sleepiness reported by 5 patients. No late toxicity, such as brain necrosis, bleeding or radiation induced tumor was reported.

5.2. Tumor and disease control/Radiological response evaluation after FSRT.

Local tumor control was defined as lack of radiological progression on follow-up gadolinium enhanced, T1-weighted magnetic resonance images (MRI) and at the same time lack of signs of clinical progression. The tumor control rate was 91,9 % for the whole group (37 patients) at a median follow-up time of 57 months (range 2 – 111 months). At the most recent follow-up visit, tumor size was unchanged in 22 patients (59,5 %), based on diagnostic MRI interpretation. For 12 patients (32,4 %) comparison of last follow-up MRI with initial MRI revealed partial response.

Three patients (8,1 %) had radiological and /or clinical signs of tumor progression after fractionated stereotactic radiotherapy FSRT. One patient with NFPA who presented with visual field impairment one year postoperatively has been treated at our institution to a total dose of 50,4 Gy in 28 fractions, reporting marked recovery of visual fields within few weeks after completion of FSRT. Two years after FRST he had clinical signs of tumor progression needing surgical intervention with decompression of the optic chiasm, because of consecutive visual field impairment, consisting of bitemporal hemianopsia.

This patient additionally developed partial pituitary insufficiency due to tumor regrowth and consecutive pituitary stalk compression.

Two other patients with signs of radiological progression, one with intra and supra sellar tumor growth, the second one with involvement of the cavernous sinus, needed radiosurgical treatment of the area of recurrence. Both patients had ACTH-producing adenoma. One of them has been treated to a total dose of 50,4 Gy in 28 fractions and showed initially radiological partial remission until he had signs of tumor regrowth 4 years after FSRT. He was then treated by Cyberknife radiosurgery in another institution, another 2 years later he had again signs of radiological progression and received Cyberknife treatment for a second time at the same institution. Another patient who recurred after FRST had initially undergone 4 transphenoidal operations and one osteoplastic craniotomy. He has been treated by us to a total dose of 45 Gy in 1, 8 Gy per fraction. This patient always maintained clinical sighs of Cushing's disease. Additionally, he radiologically recurred 2 years after our treatment and received Cyberknife radiosurgery for this recurrence in another institution than ours, he died shortly thereafter.

One patient died 4 years after FSRT, at the age of 76 years, death cause being unrelated to her NFPA, another patient died 2 years after FSRT for NFPA, as a consequence of newly diagnosed glioblastoma at the age of 77 years. One patient with a macroprolactinoma died 6 and half years after FSRT of an unclear cause at the age of 53 years. During the follow-up (1.5 years after FSRT) he has been clinically stable with regard to both pituitary and visual function and showed signs of radiological tumor regression.

5.3. Pituitary function following FSRT

Before FSRT, 9/37 (24 %) patients had normal anterior pituitary function and 15 patients (15/37, 41 %) had evidence of decreased pituitary function, ranging from involvement of one single anterior pituitary hormonal axis to 3 involved axis, needing hormonal substitution. Mostly these patients had involvement of thyrotroph and corticotroph pituitary

axis. Thirteen patients (13/37, 35 %) had even complete hypopituitarism, requiring thyrotroph, corticotroph, gonadotroph and somatotroph replacement therapy before FSRT. Of these 13 patients 3 had additional involvement of posterior pituitary resulting in 2 of them in panhypopituitarism, and one of them with just partial involvement of posterior pituitary. After FSRT pituitary function remained normal in 8 patients (22%, 8/37), 16 patients (43 %, 16/37) had partial pituitary dysfunction of the anterior pituitary gland, 35 % (13/37) had a complete anterior hypopituitarism.

Before FSRT 3 patients with NFPA had elevated prolactin levels. After FSRT prolactin levels normalized in one of those patients, the two other patients maintained elevated prolactin levels. No new occurrence of hyperprolactinemia was registered after FSRT.

5.4. Visual outcome after FSRT

Visual acuity was stable in 76 % of patients (28/37), 19 % (7/37) showed an improved visual acuity, in 5 % (2/37) visual acuity showed some deterioration during the last follow-up visit. Visual field impairment was already present in 17 patients (46%, 17/37) before starting FSRT. During the last follow-up visit worsening of visual fields was found in one of those patients (2, 7 %), whereas one patient showed improved visual fields (2, 7 %).

All together visual fields remained therefore stable in 35 patients (94, 6%) were improved in one patient (2, 7 %) and worsened in one patient (2, 7 %) after FSRT.

5.5. Tumor volumes and overall size reduction

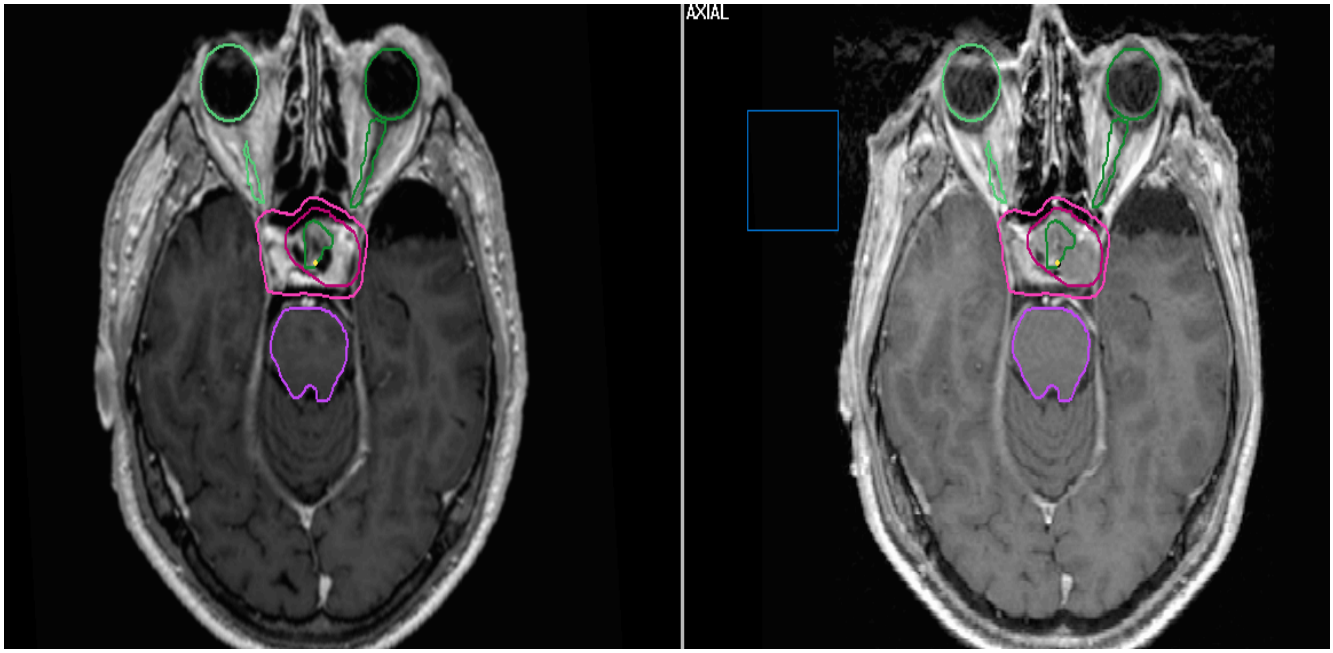
Of the 16 patients in our follow-up study none had progression of the pituitary adenoma. All patients underwent FSRT with a median dose of 49.4 Gy (45 – 50.4 Gy) in 25 respectively 28 fractions.

Mean tumor size of all 16 treated NFPAs was 7.4 ml (3.3 – 18.9 ml) before FSRT. All pituitary adenomas showed a size reduction of at least 0.9 ml. Within a median follow-up of 63 months (28 – 100 months) a mean absolute volume reduction of 3.8 ml (0.9 – 12.4 ml) was seen. The mean relative size reduction compared to the volume before radiotherapy was 51% (22 – 95%). The data are summarized in table 4. The difference between the volumes before and after radiotherapy was statistically significant ($p<0.001$, Wilcoxon Signed Ranks).

	median dose (Gy)	median follow up (months)	reduction of tumor volume (median)	
			ml	%
FSRT	49.4	63	3.8	51
n = 16	(45 – 50.4)	(28 - 100)	(0.9 - 12.4)	(22 - 95)

Table 4: Volumetric evaluation of tumorreduction of pituitary adenomas after FSRT.

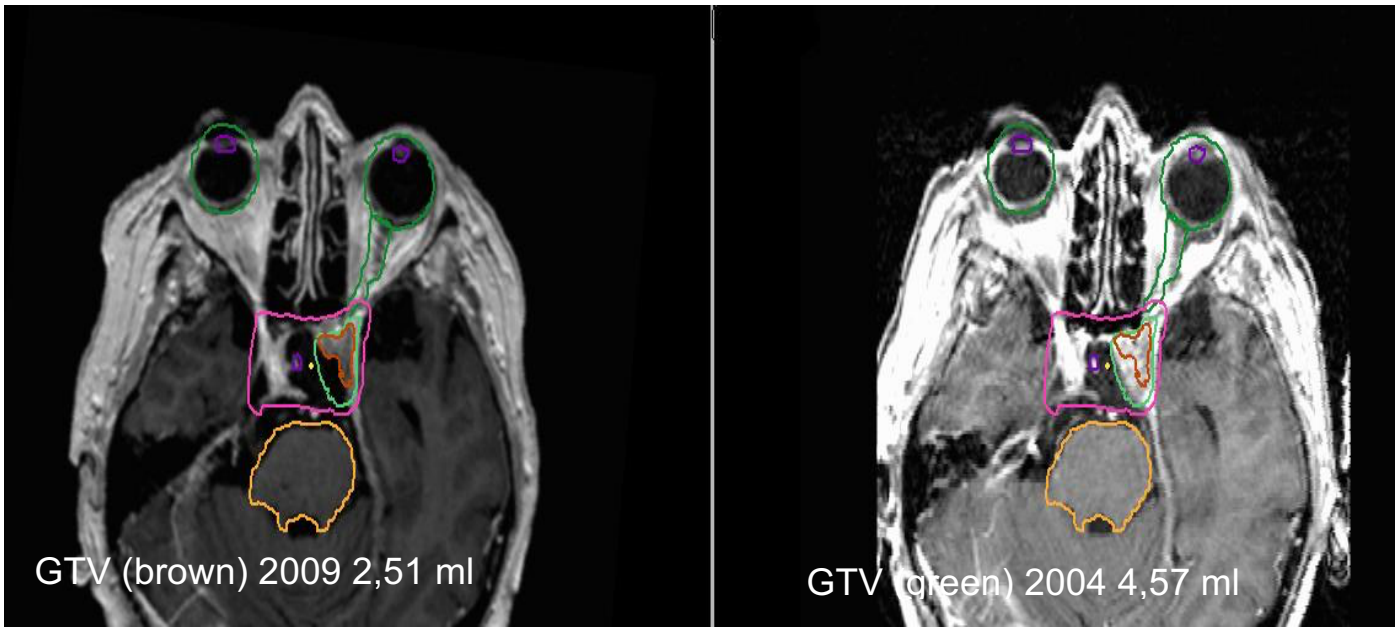
Figure 1 shows an example of significant tumor size reduction of pituitary adenoma 8 years after FSRT.



1a MRI 100 months after FSRT by the volumetric evaluation 1b MRI- Planning

Figure 1: GTV (gross tumor volume) contoured as dark pink of a pituitary adenoma before (right) and 100 months after (left) GTV contoured as green , fractionated stereotactic radiotherapy, (FSRT), corresponding to a volume reduction of 95%.

Figure 2 shows an example of partial size reduction of pituitary adenoma almost 5 years after FSRT.



2a MRI 52 months after FSRT by the volumetric evaluation 2b MRI- Planning

Figure 2: : GTV (gross tumor volume) contoured as green of a pituitary adenoma before (right) and 52 months after (left) GTV contoured as brown , fractionated stereotactic radiotherapy, (FSRT), corresponding to a volume reduction of 45%.

5.6. Time-dependency of tumor shrinkage

We tested if tumor shrinkage was time-dependent in the complete patient cohort. There was an inverse correlation between time after radiotherapy and extent of relative size reduction, which reached statistical significance, p=0.039 (figure 3). The earliest time point at which a size reduction in the volumetric assessment could be observed was 28 months after therapy. All patients showed a relative size reduction of at least 22% (figure 3).

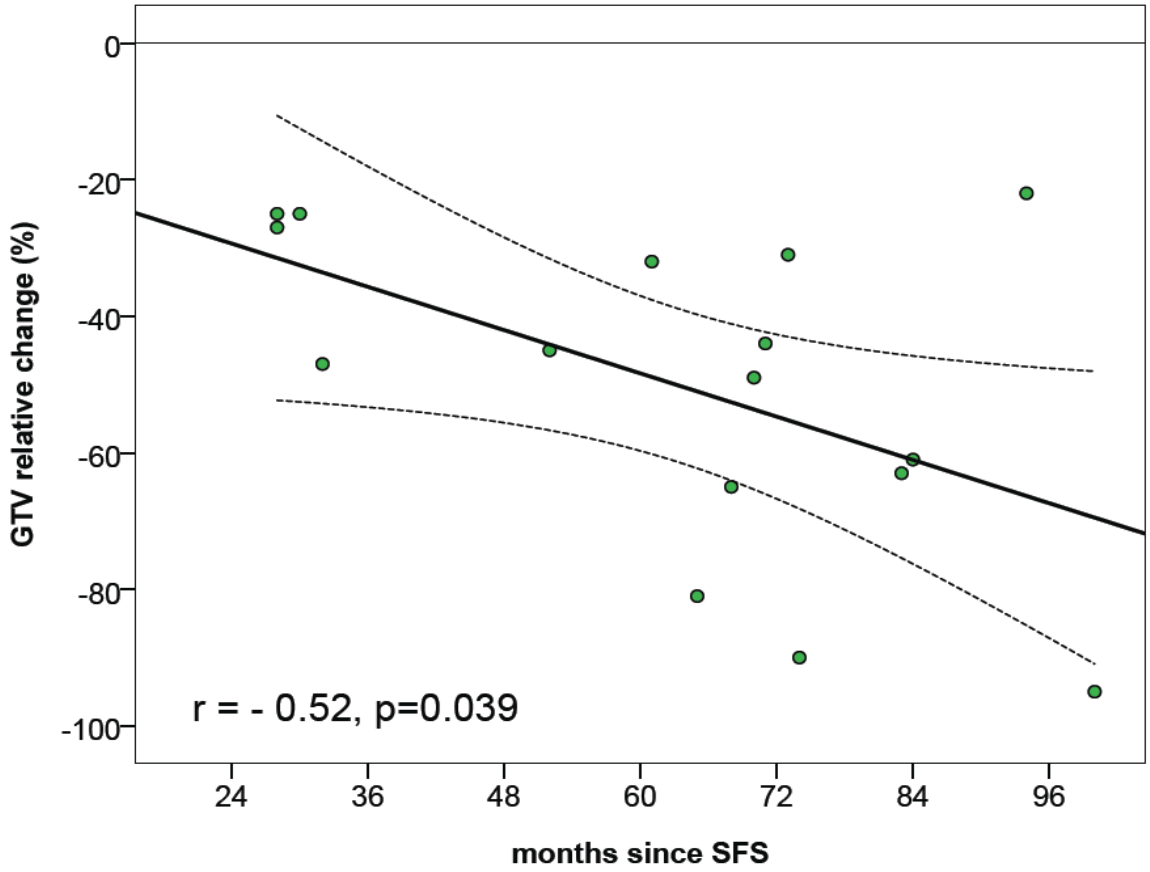


Figure 3: Scatter plot showing an inverse correlation between time after radiotherapy and relative tumor reduction. Dashed lines represent 95% confidence interval for the mean relative change of GTV in dependence on months since SFRT.

The mean relative tumor shrinkage was 26%, 47% and 62% for the patients treated with FSRT at ≤ 36, 36 – 72 and > 72 months after radiotherapy. This tendency towards increased tumor shrinkage with longer time intervals after radiotherapy is shown in figure 4 (non-parametric test for trend: p=0.106).

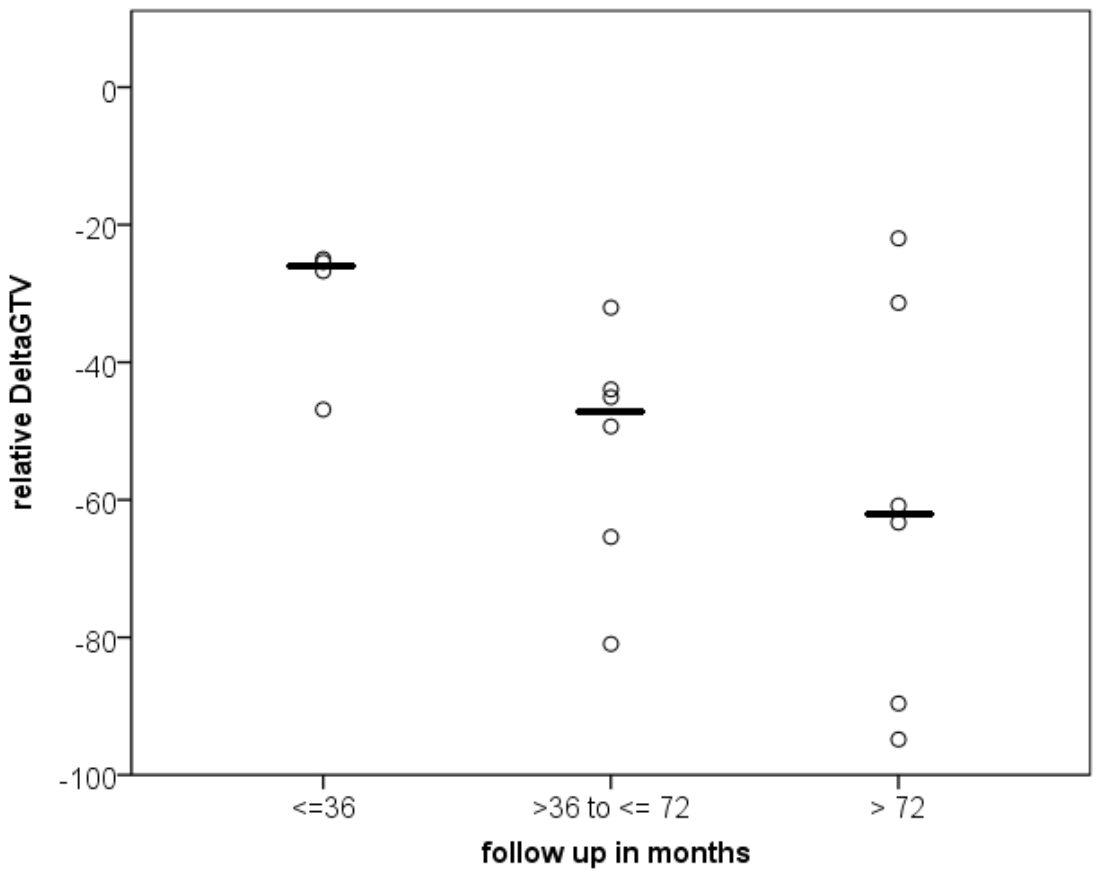


Figure 4: Shrinkage of tumors in the time intervals ≤ 36, 36 – 72 and > 72 months after radiotherapy for all patients.

5.7. Prognostic factors for tumor shrinkage

We tested if tumor shrinkage depends on the absolute tumor volume before radiotherapy and if there is a correlation between tumor shrinkage and patient age, gender or previous surgery. Absolute tumor volume reduction of pituitary adenomas after FSRT did show a strong negative correlation with initial GTV, p=0.001 (figure 5).

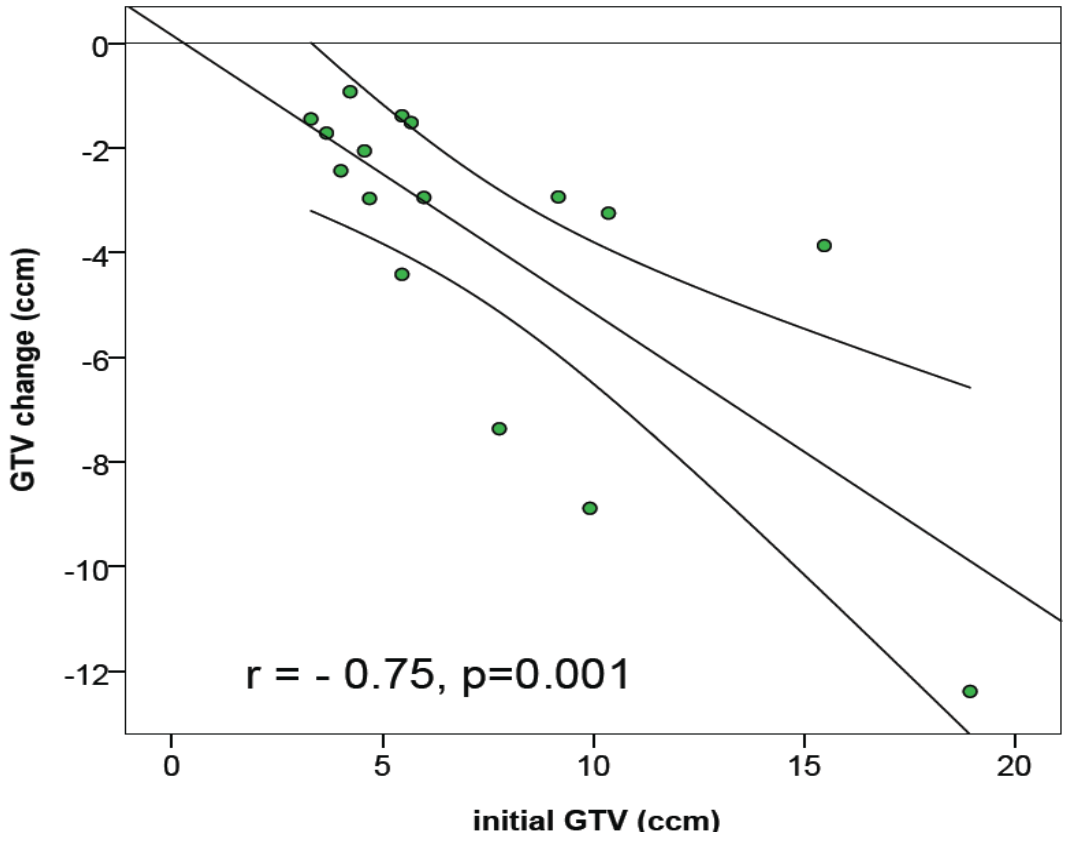


Figure 5: Scatter plot showing a strong negative correlation between the tumor volume before radiotherapy (initial GTV) and the absolute tumor size reduction after radiotherapy (GTV change).

Neither age nor gender of the patients showed any correlation with absolute tumor size reduction (figure 6, figure 7).

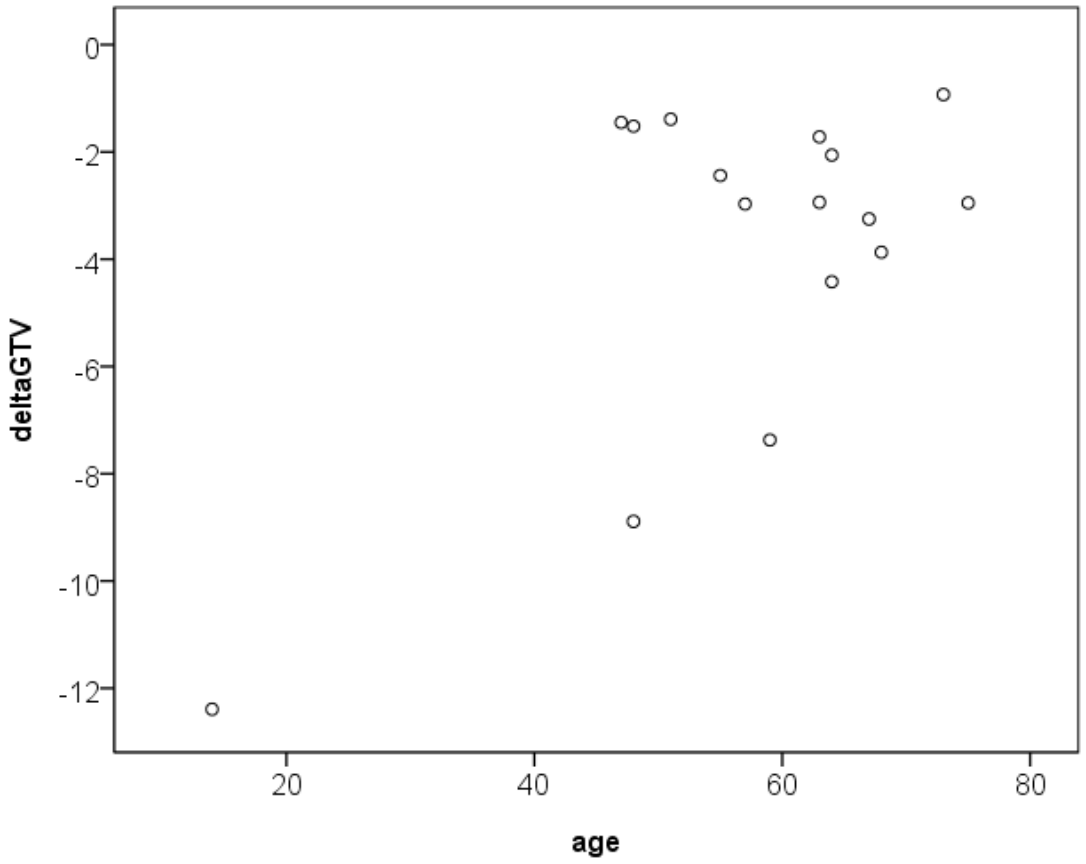


Figure 6: The graph shows no correlation between patient age and relative size reduction of tumor volume.

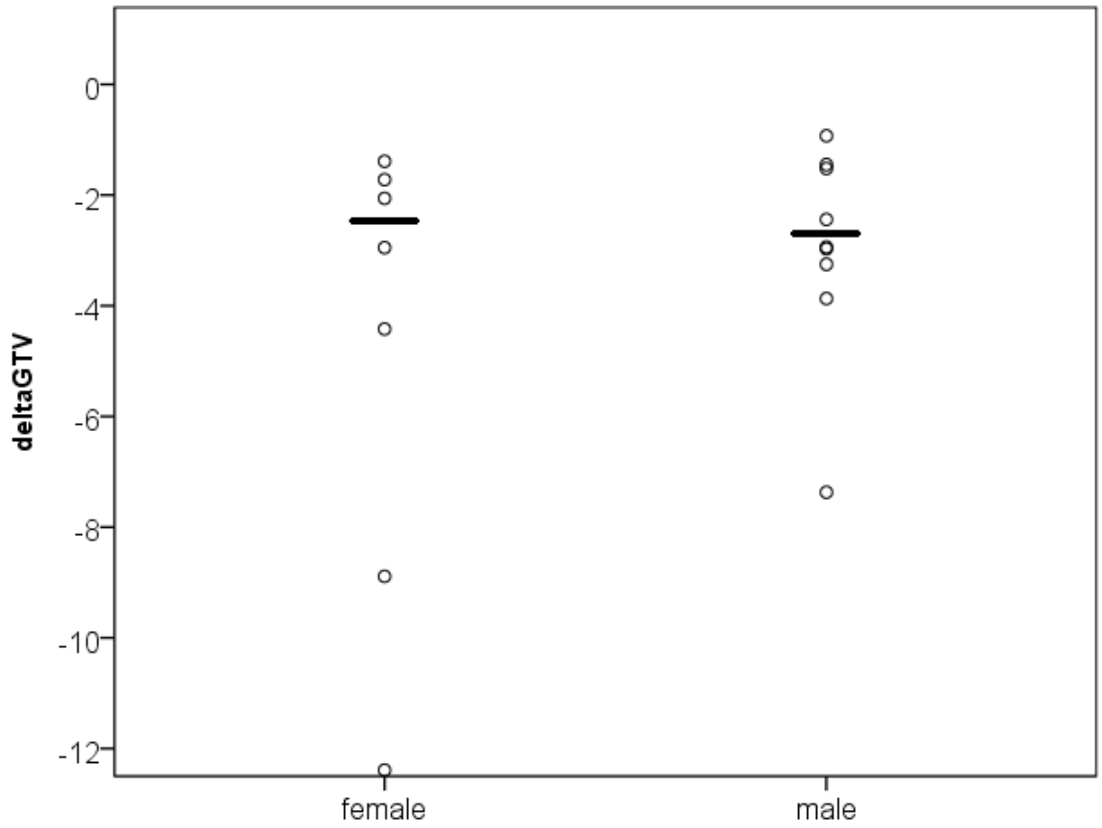


Figure 7: The graph shows no statistically significant difference between gender and relative size reduction of tumor volume.

Furthermore, the number of surgical interventions undertaken prior to FSRT was not predictive for the magnitude of tumor shrinkage (figure 8).

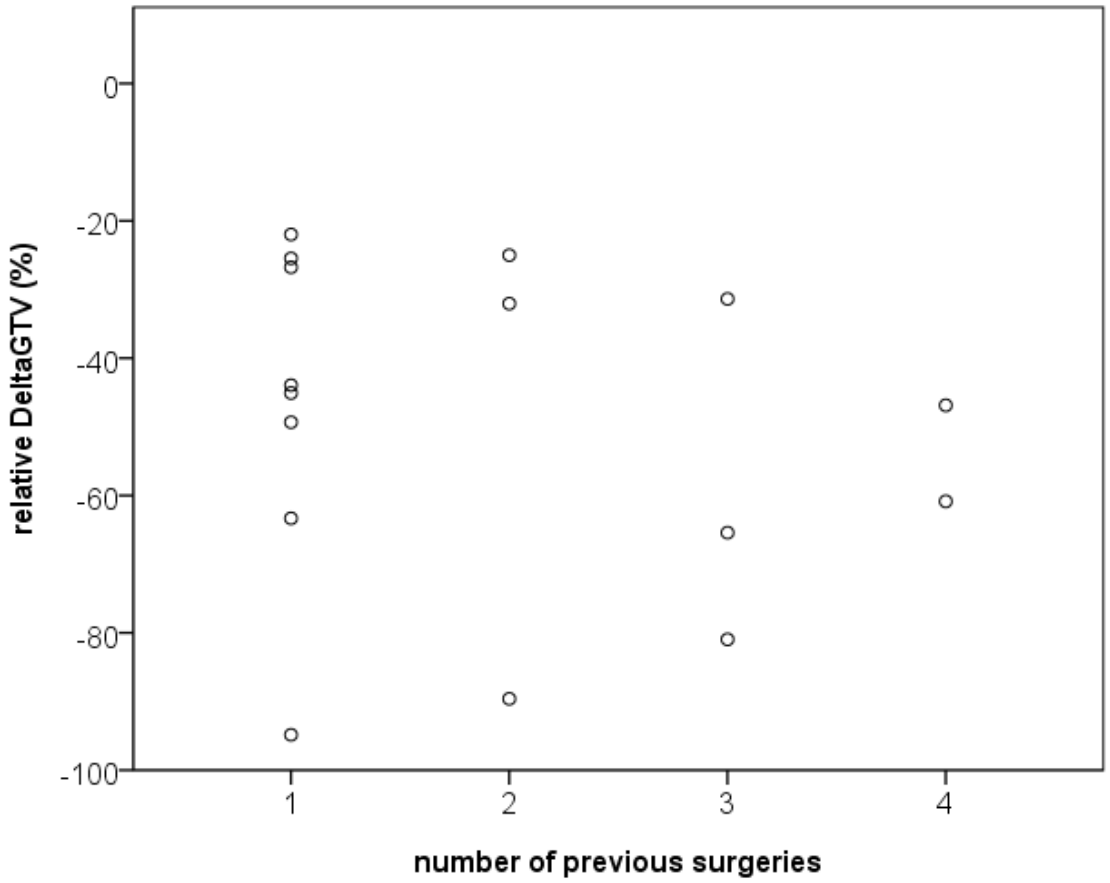


Figure 8: Scatter plot showing no correlation between number of previous surgeries and relative size reduction of pituitary adenomas after radiotherapy.

5.8. Comparison with radiological reports

All patients in the study underwent continuous follow-up by regular diagnostic MRI after radiotherapy. We compared the diagnostic radiology reports with our volumetric assessment. In only 5 patients (31%) the tumor measured by three dimensions revealed a size reduction and was therefore considered as partial remission according to the diagnostic MRI report. In contrast to our volumetric assessment, in 11 patients (69%) the NFPAs were considered to be unchanged in size.

6. Discussion

In the treatment of pituitary adenoma surgical resection is the recommended initial treatment modality, except for prolactinomas. For inoperable patients, radiotherapy has been indicated as a sole treatment modality [12, 36]. Radiotherapy is also a widely accepted treatment of pituitary adenomas following surgery with residual disease but also for recurrence after surgery, either local tumor progression or hormonal overproduction [4]. The goal of treatment for hormone-producing pituitary adenomas is endocrine normalization. For non-functioning pituitary adenomas, the goal is control of tumor growth.

As pituitary adenomas account for approximately 14 % of all intracranial tumors, among them, non-functioning pituitary adenomas (NFPAs) represent approximately 30 % and therefore represent the most common type of pituitary neoplasm. As they lack signs of hormonal overproduction, NFPAs generally become evident with signs of compression of adjacent structures, such as pituitary stalk, optic nerves, and chiasm. Therefore, being generally asymptomatic at smaller sizes they often become clinically evident after considerable growth leading to hypopituitarism and /or visual field impairment. At the same time complete resection of pituitary tumors of such size is challenging and not possible in all cases. In the present series we report about 29 patients with NFPAs and 8 patients with functioning pituitary adenomas treated with stereotactic radiotherapy for residual or recurrent disease.

The goal of treatment in the management of pituitary tumors is disease control in the long-term follow-up. In order to reach this goal a number of cases, especially the larger, often non-functioning pituitary adenomas require a multimodal approach, consisting of surgical resection followed at some point by radiotherapy. When it comes to radiotherapy, different

options of application have been used in the past, ranging from conventional fractionated radiotherapy to highly precise stereotactic techniques. Single fraction stereotactic radiotherapy has been applied rather as Gamma Knife, Cyberknife or Linear Accelerator radiosurgery, efficacy being not significantly different between these methods. Still, the use of a single fraction has been reported to be associated with neurologic toxicity to the optic apparatus and normal brain tissue [10, 21, 22, 42]. To avoid/minimize the risk of these toxicities the application of radiosurgery is generally restricted in the current practice to small pituitary adenomas, located not in direct proximity to the optic nerves or chiasm. For pituitary adenomas with supra and parasellar residual or recurrent tumor and for tumors involving the cavernous sinus fractionated stereotactic radiotherapy (FSRT) is a suitable treatment option, overcoming the limitations of radiosurgery. Because all the patients we treated for pituitary adenoma, presented at our department after at least one attempt at surgical removal in the past and all of them had quite large tumor volumes, we decided to use FSRT. It seemed reasonable to us, to combine the accuracy of stereotactic technique with the radiobiologic advantages of fractionation. Other groups have already reported their experience with FSRT in the treatment of patients with pituitary tumors, mainly NFPAs. They found tumor control rates ranging from 85.3 % to 99.09 % [6, 26, 27, 28, 31]. The tumor control rate of 91.9% achieved in the present series of patients compares well with the tumor control rates reported in the literature by mentioned groups using FSRT.

Radiation induced pituitary deficiency requiring hormonal replacement is one of the main toxicities of concern. It has been reported between 5 % (4.76) and 29 % (28.5) of patients after FSRT [6, 26, 27, 28, 31]. Following radiosurgery, hypopituitarism has been reported in a similar range of 0% to 41 % and a variable median follow-up of 6-60 months [14, 15, 23, 34, 40]. In our study hypopituitarism rates remained mostly unaffected by FSRT: 41 % of patients of decreased pituitary hormonal axis to 3 involved axis, needing hormonal substitution. After FSRT 43 % of patients had evidence of partial hypopituitarism, meaning that one single patient with normal pituitary function before FSRT needed hormonal replacement therapy following FSRT. The percentage of patients with panhypopituitarism

before and following FSRT with a median follow-up of 57 months was constant with 35 % in our series.

Late effects of stereotactic radiotherapy of pituitary adenomas include reduction of visual acuity and visual fields defect. These side effects result from proximity of the adenomas to optical apparatus as optic nerves and chiasm. Sheehan et al reported a decline in visual function in 1 of 42 patients (2.4%) after Gamma Knife radiosurgery [40]. The same group reported about another patient of the same series with deterioration of visual fields despite a decrease in tumor size [40]. Other groups reported that none of their treated patients with NFPAs demonstrated any decline in visual function following stereotactic radiosurgery [23, 34].

Milker-Zabel et al report about 4 of 60 patients (7%) who experienced a reduced visual acuity after fractionated stereotactically guided radiotherapy [26]. Paek et al. described radiation-induced optic neuropathy in 2 of 68 patients after FSRT [31]. The same group found objectively improved visual fields in 28 patients, stable visual fields in 24 patients, and worsened in 2 patients [31]. In our evaluation, visual fields remained stable in 35 patients, were improved in one patient, and worsened in one patient. With respect to visual acuity, we found it was stable in 28 (75, 6 %) of 37 patients, 7 (19 %) showed an improved visual acuity, and 2 (5, 4 %) patients demonstrated some deterioration of visual acuity during the last follow-up visit.

We report here about 37 consecutive patients, who have been treated at our department for a recurrent or residual pituitary adenoma, mostly non-functioning adenoma (29 cases). All patients have been operated at least once before being referred to radiotherapy department. 18 patients underwent one single surgical intervention, 8 patients 2 interventions, 9 patients 3 operations, one patient 4 and another patient even 5 neurosurgical interventions before FSRT was considered and indicated. After treatment was performed at our department, we followed our patients for a median time of 57 months and found a tumor control rate of 92 %, which compares well to other reports about stereotactic radiotherapy of pituitary adenomas. The mostly prescribed dose of 50, 4 Gy seems to lead to a good tumor control rate and at the same time low side effects. We analyzed pituitary function before FSRT and during follow-up separately for all

pituitary axis with respect to the need of hormone substitution therapy and analyzed visual acuity for each eye separately and Humphrey visual fields. As we reported above, pituitary function, visual acuity and field remained mostly unaffected by FSRT.

In conclusion, stereotactic radiotherapy or residual or recurrent pituitary adenomas, both hormone producing and non-functioning, is a highly effective treatment in terms of radiological and clinical tumor control. We also conclude that stereotactic radiotherapy of pituitary adenomas delivered in a fractionated manner is associated with low side effects and can be given irrespective of adenomas dimensions. Very low rates of radiotherapy associated hypopituitarism and visual fields defects have been observed in our patients during follow-up. At the same time visual acuity improved in 19 % and showed some deterioration in only 5 % of the patients.

6.1. Volumetry

We also studied the shrinkage of non-functioning pituitary adenomas after FSRT by implementing volumetric MR imaging. Other studies exist that have determined response rates of pituitary adenomas after radiotherapy. Unfortunately, different definitions were used, such as: tumor shrinkage of $\geq$ 25%, decrease of at least 18% of the pre-therapeutic volume or for multilobular tumors, the longest diameter in one dimension.

Our study presents the findings of volumetric follow-up radiological assessments in a group of patients diagnosed with clinically NFPAs and managed at our centre with stereotactic fractionated radiotherapy. We present an analysis of the data available from 16 patients over a median follow-up period of 63 months. All patients had previously undergone at least one surgical intervention, 2 of them have been operated even 4 times before being referred to radiation therapy. Our data support the effectiveness of SFRT in the treatment of NFPAs, since no recurrence could be detected during the above-

mentioned follow-up period. We observed a 51% mean relative reduction of tumor volume, representing a statistically significant difference between the pituitary adenoma volumes before and after radiotherapy.

These results compare to the good treatment responses of pituitary adenomas to radiotherapy reported by other investigators. In the study by Schalin-Jäntti et al a 29% decrease in pretreatment tumor volume was achieved at 19 months after SFRT in 30 patients with pituitary adenomas [38]. For the subgroup of patients with NFPAs (n=20), the authors report after median follow-up of 4.5 years, 30% stable disease and 70% partial response. After a median follow up of 32 months, Selch et al report that tumor size was stable in 26 and decreased in 13 patients with pituitary adenomas (n=33 non-functioning, 6 functioning) after stereotactic fractionated radiotherapy [39]. Park et al report a volume reduction in 29% of 21 pituitary adenomas after gamma knife radiosurgery, through 25 months of follow-up [33]. Another group reporting about MR imaging of pituitary adenomas after gamma knife stereotactic radiosurgery, observed during a mean follow-up of 36 months 41% average reduction of tumor volume, with 77% of tumors having at least 25% reduction in volume [43].

Even if the follow-up studies of pituitary adenomas after stereotactic radiotherapy are based on serial MR imaging, there are limitations regarding exact tumor volume assessment. Most of the studies estimate tumor volume by approximating it from largest diameter or by using the formula proposed by Lundin [24].

Schalin-Jäntti et al even assume in their report, that in 4 of 20 patients with NFPAs, tumor shrinkage was even greater than reported, but this was not measurable because of irregular shape [38]. To our knowledge, this is the first follow up study for pituitary

adenomas following stereotactic radiotherapy, reporting exact volumetric data of tumor response to FSRT.

Interestingly we found an inverse correlation between time after radiotherapy and relative tumor reduction. A similar finding is reported by Tung et al with incremental reductions in tumor volume on annual follow-up MR imaging, beginning at 1 year after radiotherapy [43]. Selch et al report that in their study the largest tumor dimension decreased by more than 50% in 2 patients after 24 and 48 months after stereotactic radiotherapy [39]. Such a gradual reduction in tumor volume may be explained by radiobiologic effects, considering radiation induced DNA damages with cell reduction becoming apparent only after subsequent cellular division or programmed cell death [41]. The cytotoxic effects of radiation therapy may become evident over a longer period in slowly growing tumors, such as pituitary adenomas. Another effect contributing to the observed tumor volume reduction over time might be due to chronic ischemic effects of radiation induced vasculopathy.

As late recurrence in NFPAs is well recognized and it is known that a re-growth may be clinically asymptomatic), the need for close radiological follow-up seems evident to us [19],[17]. In this context, it is important to find the ideal time interval for MRI examinations. Therefore, time dependency of tumor shrinkage is important. Coulter et. al report in their retrospective radiologic follow-up study of 41 patients with NFPAs that the time in which 50% of the tumors attained a “no change” status was 30 months and 90% of the adenomas attained this state in approximately 88 months [7]. The majority of patients in our study were examined by 3-D MRI from 24 to 72 months after radiotherapy. We did not assess tumor volumes at very early and early time points such as 6, 12 or even 24

months after radiotherapy; however, the time interval after radiotherapy was extended to up to 100 months. This offers the advantage to study long-term follow up. In our study the mean relative tumor shrinkage was 26%, 47% and 62% for the patients treated by SFRT at $\leq$ 36, 36 – 72 and > 72 months after radiotherapy. We observed a statistically significant inverse correlation between time after radiotherapy and relative tumor reduction ($p=0.039$). We conclude that further tumor shrinkage takes place in pituitary adenomas even 6 years after radiotherapy.

We saw a discrepancy comparing the results measured by 3D MRI with the regular diagnostic MRI reports. In only 31% of the patients the tumors measured in three dimensions revealed a size reduction compared to 100% in our volumetric study. This shows that 3D MRI is more sensitive to alterations in size and indicates that in patients with newly diagnosed pituitary adenomas who decided for a watchful waiting strategy, volumetric MRI can be useful to differentiate between tumor progression and stable disease.

In conclusion, we think that volumetric evaluation of tumor size after radiotherapy of pituitary adenomas using 3D T1Gd-MRI is a highly precise method to measure tumor regression. In all pituitary adenomas a size reduction was detected, representing 100% radiological response.

We report 26%, 47% and 62% reduction in tumor volume of NFPAs at $\leq$ 36, 36 – 72 and > 72 months after radiotherapy. During long-term follow up, we observed a time dependency of tumor shrinkage, with incremental reductions in tumor volume at longer intervals after radiotherapy.

The two parts of the study were publicized in the Red Journal Magazine and in the Strahlentherapie Onkologie Magazine :

1. Tumor Shrinkage assessed by Volumetric MRI in the long term Follow-up after Fractionated Stereotactic Radiotherapy of Non-functioning Pituitary Adenoma**.**

Christine Kopp, Marilena Theodorou, Nektarios Poullos, Vesna Jacob, Sabrina T. Astner, Michael Molls, Anca-Ligia Grosu,

International Journal Radiation Oncology Biol Phys.2012 12 Mar 1;82(3):1262-7

2. Fractionated Stereotactic Radiotherapy in the Treatment of Pituitary Adenomas.

Christine Kopp, Marilena Theodorou, Nektarios Poullos, Sabrina T. Astner, Hans Geinitz, Bernhard Meyer, Michael Molls, Anca-Ligia Grosu.

StrahlentherOnkol 2013 Nov;189(11):932-937

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8. Shortcut list

Gy Gray

SFRT stereotactic fractionated radiotherapy

RS radiosurgery

LC local control

FU follow-up

CT computer tomography

MRI magnetic resistance imaging

GTV gross tumor volume

CTV clinical target volume

PTV planning tumor volume

SD stable disease

PR partial response

PD disease progression

OS overall survival

i.v. intravenous