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Clinical Investigation

Multisession stereotactic radiosurgery for large benign brain tumors of >3cm- early clinical outcomes

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Objective: To evaluate the clinical outcome of linear accelerator based multisession stereotactic radiosurgery (SRS) for large benign brain tumors of >3cm.

Methods: Between June 2009 and May 2011, 35 patients having large benign brain tumors of >3cm (≥15 cm^3) were treated by multisession stereotactic radiosurgery. This retrospective study was carried out at Neurospinal & Medical Institute Karachi. There were 17 (48.6 %) males and 18(51.4 %) females. Median age was 36 years (range: 13-65 years). Median target volume was 49.4 cm^3 (range: 15-184 cm^3). The median marginal dose was 25 Gy (range: 20–27.5Gy) prescribed to a median 75% isodose line (range: 65-100 %). Median number of 5 fractions were used ranging 3-5 fractions.

Results: All the patients tolerated treatment very well. 21 (58.3%) patients had remarkable clinical improvement of neurological symptoms, 14 (38.9%) patients had stable symptoms, and only one patient had transient worsening of symptoms. No permanent neurological damage or radiation injury was seen. Radiologically, 9 (25.7%) patients achieved reduction in size of the tumor, 26(74.3 %) patients were having stable disease, and overall control rate was found to be 100 %. Median follow-up time from the end of SRS was 6.4 months (range: 1-22.5months).

Conclusion: Linear accelerator based multisession stereotactic radiosurgery for large benign brain tumors of >3cm is effective and well tolerated.

Key Words: Stereotactic radiosurgery (SRS), multi session SRS, brain tumors, linear accelerator, benign brain tumors, radiation injury.

INTRODUCTION

With the recent advancements in delivery of the radiation therapy, arrival of modern radiotherapy equipments and the latest immobilization devices have increased popularity of radiation therapy and radiosurgery in managing brain tumors and other extracranial tumors.

Stereotaxy technique is the most widely used method of localization of tumors in the brain and is a minimally invasive form of surgical intervention in which three-dimensional coordinate system is being used. First stereotactic frame was described by Horsley and Clarke in 1908 [1]. By using this technique famous Swedish neurosurgeon Lars Leksell pioneered the field of stereotactic radiosurgery in 1951 , when he applied the methodology of stereotaxy to the delivery

of external beam radiations [2]. The first gamma knife stereotactic radiosurgery system became operational at the Sophiahemmet in Stockholm in 1968 [3]. Stereotactic radiosurgery (SRS) is defined as the delivery of an ablative dose of ionizing radiation to the focused target with stereotactic localization to elicit a specific radiobiologic response of the target and sparing the surrounding normal brain tissue. Traditionally this is carried out in a single session [4-5] . Revised Definition of SRS was emerged in 2007 by ASTRO (American Society for Therapeutic Radiology and Oncology), AANS (American Association of Neurological Surgeons), CNS (Congress of Neurological Surgeons). They have jointly agreed to define SRS in a way that includes both traditional single dose SRS, as well as multi-session SRS up to 5 fractions (2-5 doses) [6-7].

Single session intracranial stereotactic radiosurgery has shown a significant role in the management of benign brain tumors having size ≤3cm. Stereotactic radiosurgery has several potential advantages: 1) it appears to produce more tumor shrinkage than conventional radiation therapy [8] ; 2) rapid dose falloff allows for sparing of normal tissues and critical structures (e.g., brain, optic apparatus, brain stem), with minimal radiation-associated adverse effects; 3) shorter treatment duration makes it more convenient for patients; 4) radiobiologically, benign tumors are thought to behave like late-responding normal tissue [9] and, thus may respond better to higher doses per fraction.

When tumor size increases >3cm or critical organ lies very close (<2 mm) to the tumor [10] , single session SRS is usually avoided because of the higher chances of normal tissue toxicity and/or poor local controls. Moreover, when tumor size increases to >3cm, surgical resection becomes an integral part of treatment. But radiation, perhaps fractionated regimen becomes more preferred treatment if surgery is not possible for any reason such as deep seated / eloquent area tumors, or critical organ is encased, invaded, or lying close to the tumor, or surgically unresectable tumor to avoid gross neurological deficit, medically inoperable (elderly patient, known ischemic heart disease in recent past, uncontrolled diabetes mellitus/hypertension) or patient refuses surgery (either because of the high risk involved in surgery or patient preference. In these situation, multisession (multi-dose) SRS becomes an appropriate non-invasive alternative primary treatment option for this group of patients with adequate therapeutic benefits and minimum normal tissue toxicity. Multisession SRS is based upon the basic principles of radiobiology (concept of fractionated radiotherapy- 4 Rs stand for repair, re-assortment, repopulation and re-oxygenation). Adler et al [11], described that the fractionation is the cornerstone of radiation therapy. Multisession SRS gives the liberty to deliver a high dose per fraction while allowing for interfraction normal tissue repair, hence decreasing the risk of late side effects [12]. Also increasing the cell kill from interfraction reoxygenation and reassortment that may improve tumor control. Multisession SRS was evolved with frameless setting. The availability of image-guided radiosurgical technology made it possible to incorporate the principle of multiple sessions into the delivery of radiosurgery. This gives an advantage of combining anatomic precision and conformality of radiosurgery with the biological benefits of fractionation [11]. Moreover, use of larger doses in fewer fractions in treating benign as opposed to malignant brain tumors gives the strong theoretical basis, though no controlled study carried out to prove this [13]. Although comparison between stereotactic radiosurgery and radiation therapy revealed that both modalities have high rates of local controls in treatment of benign tumors. But larger doses per fraction that characterizes radiosurgery resulted in a higher biological equivalent doses and causes greater tumor shrinkage on follow-up studies [14].

We investigated the specific group of patients, who do not underwent surgery and had large benign brain tumors or they may undergo surgical resection but had residual tumors >3 cm. We assume that multisession stereotactic radiosurgery can be used for these type of patients to reduce the normal tissue toxicity without compromising the therapeutic benefits to achieve good local controls equivalent to or superior to existing standard management strategies. Our aim was to evaluate the clinical outcome of linear accelerator-based multisession stereotactic radiosurgery for large benign brain tumors of >3cm.

PATIENTS AND METHODS

Between June 2009 and May 2011, thirty five patients of large brain tumors >3cm (≥15 cm^3) were treated by multisession stereotactic radiosurgery (SRS) with the help of a modern linear accelerator (Synergy-S, ELEKTA, Crawley UK) having 3 mm micro-multileaf collimators (mMLC), on board imager: cone beam CT (CBCT) and robotic couch. This retrospective study was carried out at Neurospinal & Medical Institute Karachi. The study was approved by the ethical review committee of the institution. Written informed consent was obtained from all the patients included in this study. All the potential benefits, complications, and alternative therapeutic options were discussed in detail to every patient before granting consent for multisession stereotactic radiosurgery.

We included only those patients who have benign brain tumors and were ≥13 years of age and their original or residual/recurrent tumor size was >3cm in long-

est diameter or gross tumor volume was ≥15cm^3. They all were assessed and interviewed for surgical resection but found ineligible for surgical resection because of any of the following reasons: deep seated or eloquent area tumors, or critical organ was encased, invaded, or lying close to the tumor, surgically unresectable tumor, medically inoperable (elderly patient, known ischemic heart disease in recent past, uncontrolled diabetes mellitus/hypertension), or patient refuses surgery (either because of the high risk involved in surgery or sometimes because of the regional traditions where patients do not want to open the skull at any cost). Seventeen (48.6 %) patients were male and 18(51.4 %) were females. Median age was 36 years (range: 13-65 years). Nine (25.7%) patients were with various co-morbid conditions and 5 (14.3 %) patients were found surgically unresectable by the neurosurgeon because of high risk of surgical morbidity. Four (11.4%) patients refused surgery at their own will, remaining 17 (48.6%) patients who underwent surgery and had residuals or recurrent tumors larger than 3 cm. Four out of 17 patients who had surgery, also received external beam irradiation. No patient received chemotherapy or SRS. Location of the tumor was CP angle-15 (42.8%), sellar, suprasellar & parasellar- 15 (42.8 %), cerebrum- 4 (11.4%), cerebellum- 1 (2.9%).Characteristics of the patients are described in Table 1. Median target volume was 49.4 cm^3 (range: 15-184 cm^3). The median marginal dose was 25 Gy (range, 20–27.5Gy) prescribed to a median 75% isodose line (range: 65-100 %). Median numbers of 5 fractions were used ranging 3-5 fractions (Table 2). Radiation adverse events were noted at 6 weeks and 6 months from the end of multisession SRS.

Patient selection

Following criteria was used to select the patient having tumor size >3 cm in maximum dimension for multisession SRS. 1) Recurrent / residual tumors: documented radiologic progression of disease after previous treatments. 2) New symptoms or symptomatic deterioration, and surgery was not possible for any reasons mentioned in inclusion criteria. 3) Patients had minimal symptoms related to mass effect at the time of presentation.

Mode of Diagnosis

A histopathological diagnosis was available for 17(48.6%) patients who underwent surgical resection. For 18 (51.4%) patients who had no surgery, the diagnosis was based on a combination of radiographic appearances, tumor location, pattern of contrast enhancement etc.

Clinical Evaluation

Before multisession SRS, detailed clinical assessment was carried out, including history, physical examination in particular a neurological examination, blood tests (complete blood examinations, base line pituitary hormone profile, if required), perimetery in cases of optic apparatus involvement, audiometery in cases of cerebellopontine (CP) angles tumors causing hearing impairment, comprehensive radiologic investigations including thin-slice, plain and contrast-enhanced magnetic resonance imaging (MRI) with specific sequences as needed, and high-resolution computed tomographic (CT) scans with contrast.

Stereotactic Radiosurgery Technique

CT simulation was carried out after preparing an immobilization device for a particular patient. Either head fix or thermoplastic sheet was used for brain, head & neck immobilization. Thin-slice (2 mm) high resolution CT images were obtained in all patients for planning purpose after the intravenous administration of 1-1.5 mL/kg body weight non-ionic contrast ultravist -370 (Bayer healthcare- 1ml= Iopromide 0.769gm, 370 mg I /mL), using a siemens emotion-6, 6 slicer CT scanner.

High-resolution, thin-slice contrast enhanced CT images give an excellent visualization of tumors in reference to bones (e.g. cranial base tumors and the adjacent critical anatomy). Then Dicom CT images were transferred through digital link to treatment planning systems PRECISE and ERGO++. MRI scans with and without contrast were taken for all patients having different specific sequences for various pathologies. These MR images were transferred to ERGO++ treatment planning system.

Then radiation oncologist delineates the target and adjacent critical structures after having fusion of CT/MRI images with or with out the help of radiologist. GTV (Gross tumor volume) was drawn by taking gadollinum enhanced tumor volume on T1 weighted MRI. Non-isocentric dose optimization was carried out by the treatment planning software to generate an acceptable treatment plan after multiple planning iterations. Best fit isodose line to the peripheral margin of GTV was selected to label it as prescription isodose line (Figure 1 to Figure 5 represent the patient with treatment planning). Later the approved plan was transferred to MOSAIQ (record & verify system), from there to machine (desktop pro). Images and counters were

Table 1. Characteristics of the patients (N = 35)

Median Age	36 Years (range: 13-65)
Gender	17(48.6%) male 18 (51.4%) female
WHO* Performance Status	0-5 (14.3%) I-10 (28.6%) II-09 (25.7%) III-10 (28.6%) IV-1 (2.9%)
Co-Morbids	09(25.7%) with various co-morbid conditions 26(74.3%) without co-morbid
VP Shunt	Yes- 17 (48.6%) No- 18 (51.4%)
Previous Treatment History	17 (48.6%) had surgeries done 04 (11.4%) had EBRT** as wel with surgery. None received chemo or SRS
Location of the tumor	Cerebellopontine angles- 15 (42.8%) Sellar, suprasellar & parasellar- 15 (42.8 %) Cerebrum – 4 (11.4%) Cerebellum- 1 (2.9%)
Side wise location	12 (34.3%) left sided 09(25.7%) right sided 14 (40.0%) midline
Mode of diagnosis	17(48.6%) histopathology 18 (51.4%) radiologic diagnosis
Distribution of primary tumor (diagnosis)	Meningioma- 13 (37.2%) including 1 recurrent tumor. Pituitary adenoma- 10(28.6%) including 3 recurrent tumors. Acoustic schawanoma – 5 (14.3 %) including 2 recurrent tumors. Trigeminal schwanoma-2 (5.7%) Glomus Tumor- 1 (2.9%) Recurrent. Craniopharyngioma- 1 (2.9%) Recurrent. Hemengioblastoma- 1 (2.9%) Recurrent. Giant Cell Tumor- 1 (2.9%) Recurrent. Neurofibroma- 1 (2.9%)

*WHO=World health organization

**EBRT= External beam radiotherapy

transferred to XVI (x-ray volume imager) and DRRs (Digitally reconstructed radiographes) were transferred to I-view GT (Display software for electronic portal imaging device). When patient enters the treatment room, after fixation, CBCT (cone beam CT) takes the images and XVI reconstruct and displays the images in 3-D visualization. Then reference CT scan sent from the treatment planning software to XVI was matched with the images taken by the CBCT just before the treatment. This process of matching is called "registration" of the images, that can be carried out manually or automatically, either on soft tissue density or bone density or combination of both. If deviations were recorded then corrections (shifts) were made and finally treatment was

Table 2. Dosimetery of the patients (N=35)

Tumor Volume (cm^3)	Median- 50.45 (15-184)		
Total Dose (Gy)	Total Dose (Gy)	Frequency	Percent
	20	4	11.4
	22.5	2	5.7
	23.25	1	2.9
	23.75	1	2.9
	24	2	5.7
	25	24	68.6
	27.5	1	2.9
	Total	35	100.0
	Median- 25 Gy(20-27.5 Gy)		
Dose per fraction(Gy)	Dose per Fraction (Gy)	Frequency	Percent
	4	4	11.4
	4.5	2	5.7
	4.75	1	2.9
	5	24	68.6
	5.5	1	2.9
	7.75	1	2.9
	8	2	5.7
	Total	35	100.0
	Median -5 Gy(4 -8 Gy)		
Number of fractions	Number of Fractions	Frequency	Percent
	Three Fractions	3	8.6
	Five Fractions	32	91.4
	Total	35	100.0
	Median – 5 fractions (3 -5 fractions)		
Prescription Isodose line (%)	Prescription Isodose Line (%)	Frequency	Percent
	65	1	2.9
	70	5	14.3
	73	1	2.9
	75	13	37.1
	78	1	2.9
	80	11	31.4
	100	3	8.6
	Total	35	100.0
	Median- 75 % (65% -100 %)		
Minimum Dose to target(Gy)	Median- 23.31 Gy (15.5-25.4 Gy)		
Maximum Dose to target(Gy)	Median- 33.63 Gy(21.59-42.84 Gy)		
Mean Dose to target(Gy)	Median-30.70 Gy (20.41- 35.92 Gy)		

Figure 1. Treatment setup for a case of young female with CP angle meningioma treated on synergy-S.

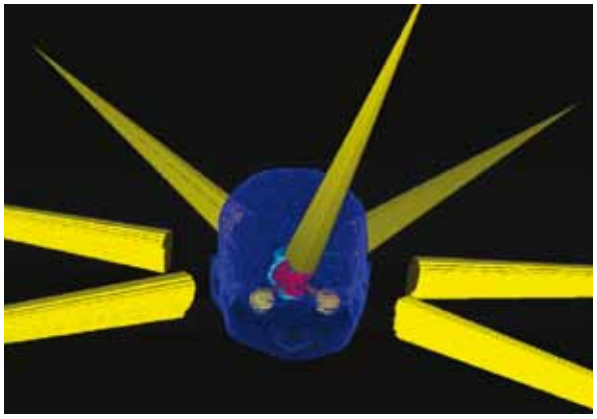


Figure 2. Beams Eye view, 7- beams treatment planning targeting on red colored GTV.

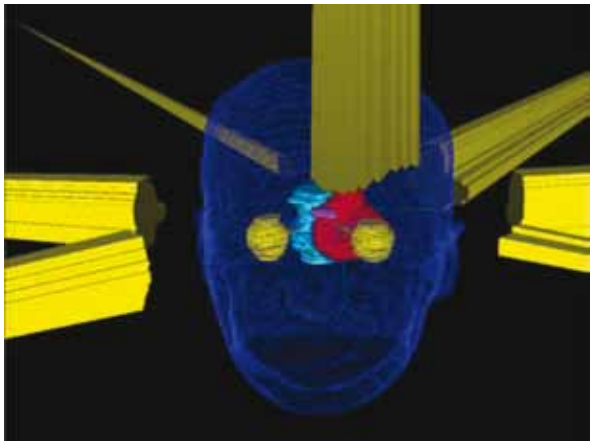


Figure 3. Various Structures drawn. In blue color body marked, red colored GTV, brain stem in light blue color, optic chiasma in purple color, yellow colored round eyes. While 7- beams direction shown out side the body.

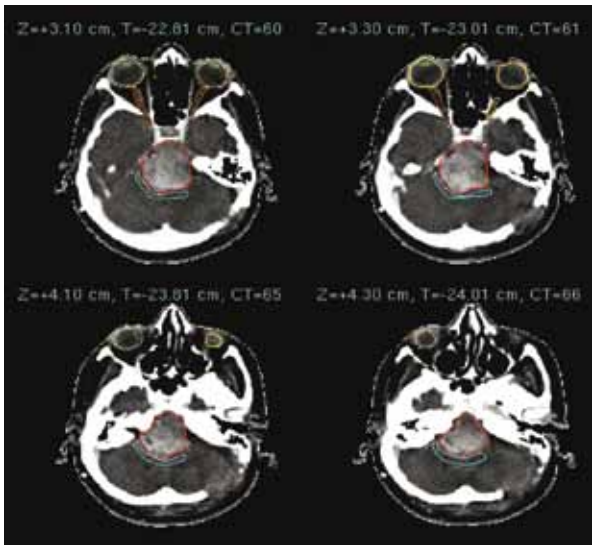


Figure 4. CT scan slices showing CP angle meningioma in red lining, while compressed brain stem in light blue color.

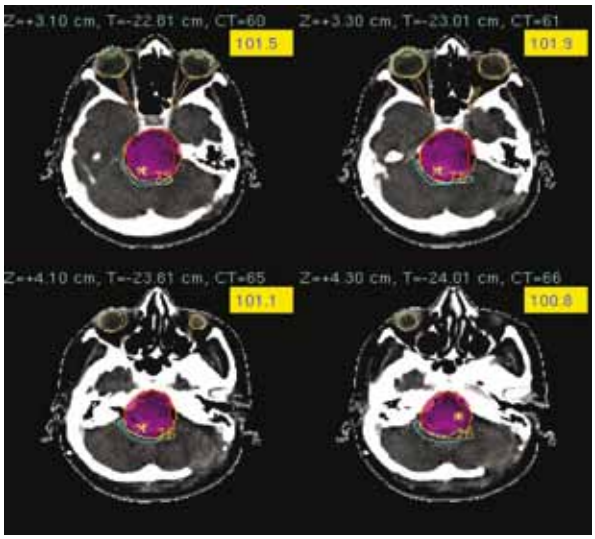
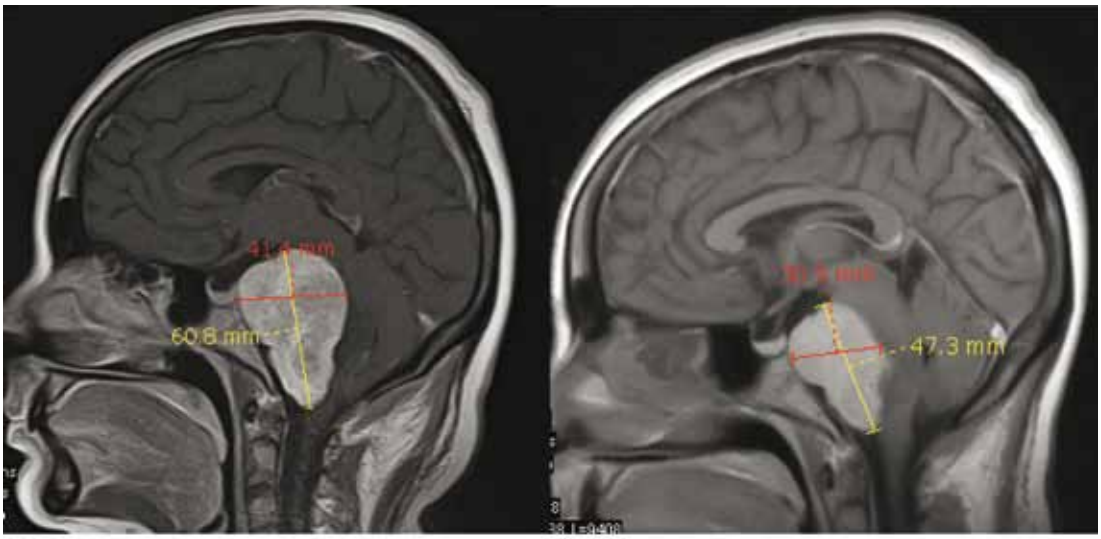


Figure 5. CT slices showing wel conformed treatment plan. 75% prescription isodose line superimposing outer border of GTV with minimal fall off on adjacent normal structures.

executed. The length of treatment ranges between 15 min- 45 min depending upon the complexity of the plan. After completion of treatment, patients were discharged with oral glucocorticoides for about 2 weeks.

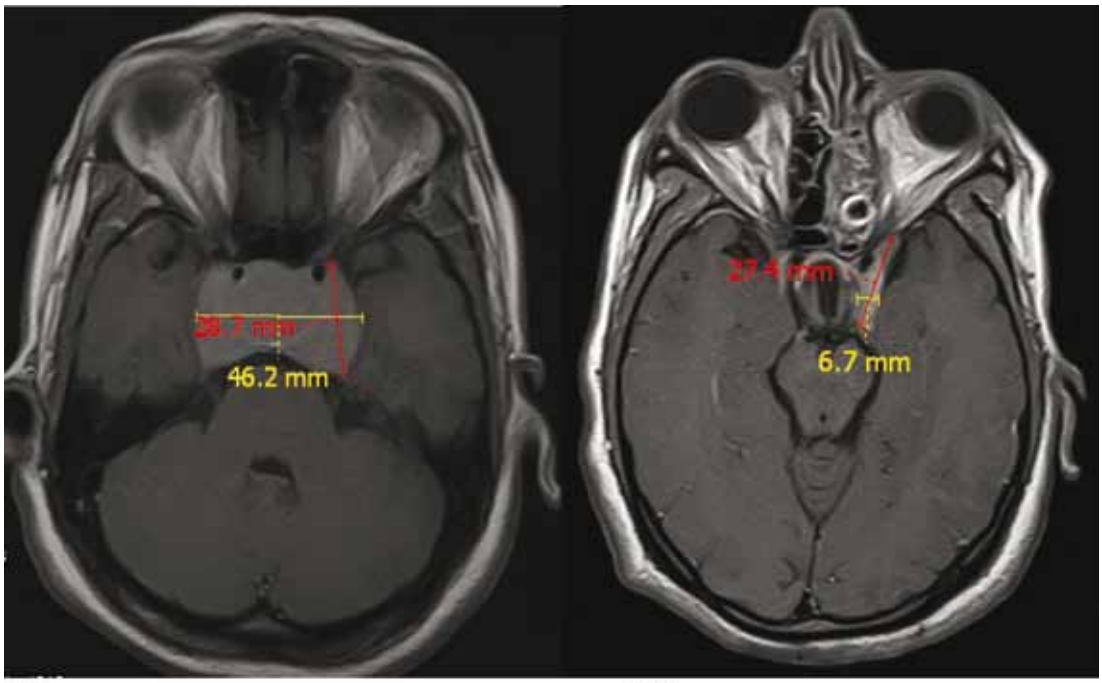
Dose Selection

Multiple factors were considered at the time of dose selection. The dose and fractionation decision was



(A) (B)

Figure 6. (A) Gadolinium enhanced T1 weighted MRI brain, sagittal view of 40 years old lady having huge left cerebellopontine angle residual meningioma with grade III brain stem compression after initial surgery. Its size was about 60.8 mm x 41.4mm at the time of multisession SRS. (B)-Gadolinium enhanced T1 weighted MRI brain, sagittal view of left cerebellopontine angle meningioma, that has reduced to 47.3 mm x 30.5 mm at 9 months follow-up after multisession SRS without any signs of radiation injury. The patient had remarkable symptomatic (power, speech, imbalance and visual problems) improvement.



(A) (B)

Figure 7. Gadolinium enhanced T1 weighted MRI brain, axial view in a 28 years old lady, showing a huge residual growth hormone secreting pituitary adenoma 46.2x28.7mm at the time of multisession stereotactic radiosurgery, optic chiasm was not identified. (B)-Gadolinium enhanced T1 weighted MRI brain, axial view showing remarkable shrinkage of tumor, optic chiasm was visible, only small residual thickening 6.7mm x 27.4mm on the left side at 15 months follow-up after multisession SRS, she had excellent clinical(headache, visual)improvement. Growth hormone level was dropped to 518 ng/ml from 1825 ng/ml of pre SRS levels at 3 months follow-up.

individualized for each patient and was usually based upon the following factors: type of tumor, tumor volume, location of tumor, proximity of the critical organs, and history of previous irradiation and duration since last irradiation. Prescription isodose was finalized after reviewing the plan and selecting the best fit isodose line to the peripheral margin of the contoured gross tumor volume (GTV). Usually we kept an interfraction time of approximately 24 hours.

Dose selection for multisession stereotactic radiosurgery of large brain tumors was calculated by biologically effective dose (BED) using conventionally fractionated radiotherapy as a point of reference, assuming an α/β ratio of 3. Following formula was used,

$BED = nd \{1 + d / \alpha/\beta\}$

Where as

n= total number of fractions

d=dose per fraction

$\alpha/\beta = 3$

The median tumor volume in this series was 49.4 cm^3 (range, 15–184 cm^3). The median total dose to the tumor margin was 25 Gy (range, 20–27.5 Gy), administered in 3 to 5 sessions (median, 5 sessions). While median maximum dose of 33.63 Gy (range: 21.59-42.84 Gy), median of mean dose was 30.70Gy (range: 20.41 -35.92 Gy). Radiation doses were prescribed to the 65% to 100% isodose line (median, 75%). Dose selection was made with the help of a literature review [11, 15-20]. Critical structure constraints were used as follows: Optic apparatus maximal dose was kept < 7 Gy per session [15], brain stem should not receive ≥8 Gy per session [21].

Follow-up

Clinical evaluation for first follow-up was carried out at 3 months after radiosurgery, patients were asked to visit the clinic or to update us about the health and to get MRI of the brain with and without contrast, then every 6 months for first two year and annually thereafter. For those patients who did not live locally, clinical follow-up was carried out by telephone interview and some times, in conjunction with local physicians and patient was asked to send the CD of MRI / CT - Dicom images to us to make a comparative report and to update our follow-up record. Perimetery, audiometery or pituitary harmone profiles and other test may be requested, if have been done at the time of radiosurgery.

Imaging (MRI/ CT) response was evaluated with the help of the radiologist. Tumor volume was assessed by measuring the tumor in three dimensions in axial, coronal, and saggital images (i.e., anteroposterior, lateral, and vertical) corresponding to the region of tumor enhancement. These values were recorded and used in the following formula for an idealized ellipsoid: (volume = $4/3\pi$[length/2 x width/2 x height/2]) to assess radiologic response over time and scored as smaller, larger or stable in size. These values were compared to the absolute measures of tumor volume determined by the treatment planning system after countering at the time of radiosurgery. T2-weighted MRI scans were carefully observed for any high signal perilesional edema. Following observations were summarized in the final report prepared by treating physician and radiologist: volume at the time of radiosurgery, volume in the follow-up images and their size comparison, extent of loss of central enhancement, extent of necrosis, comparison of extent of perilesional edema, any mid line shift and other radiologic features.

RESULTS

Tumor Control

Tumor control was defined as no increase in tumor size (stable), tumor size reduction by at least 20% (smaller), tumor size increase by at least 10%(larger).

The median follow-up time was 6.4 months (range: 1-22.5months). Nine (25.7%) of 35 patients demonstrated a decrease in tumor volume (smaller) of greater than 20% on imaging. Tumor remained stable in 26 (74.3%) of 35 tumors. There was no increase in size of the tumors in any patient. On the basis of the last available radiology reports, the rate of tumor control was 100%. The representative cases of tumor reduction shown in Figures 6 and 7.

Clinical Outcome

Complete disappearance of pre-radiosurgical neurological symptom was observed in 8 patients (22.9%), partial disappearance of pre-radiosurgical neurological symptom was seen in 13 (37.1%) and pre-radiosurgical neurological symptoms were stable in 13(37.1%) patients. One (2.9%) patient had worsening of symptoms after 3.5 months of treatment, that was relieved by using glucocorticoids till 5 months after SRS (Table 3), but the imaging studies showed stable disease with out any findings of radiation adverse effects.

The visual problems, eye movements, and improvement in modified House Brackmann grading score of fascial nerve palsy was observed in most of the patients.

Table 3. Response , Follow-up Status and Cause of Death

Median Follow up Time after treatment	6.4 months (1-22.5 months)		
Symptomatic Response		Frequency	Percent
	Complete Disappearance	08	22.9
	Partial Disappearance	13	37.1
	No change in symptoms	13	37.1
	Symptoms worson	01	2.9
	Total	35	100.0
Radiologic Response		Frequency	Percent
	Smaller	09	25.7
	Stable	26	74.3
	Larger	0	0
	Total	35	100.0
Follow-up Status		Frequency	Percent
	Smaller	08	22.9
	Stable	19	54.3
	Dead	08	22.9
	Total	35	100.0
Cause of death		Frequency	Percent
	Non Tumor Related (non brain)Death	06	17.1
	Not Known	02	5.7
	Total Number of Death	08	22.9
	Alive	27	77.1

Acute & Late Radiation toxicity

All patients tolerated treatment very well. No acute adverse radiation effects were observed till 6 weeks. Radiation related late side effects at 6 months were also not found in any patient.

In this series, 6 (17.1%) patients died from unrelated causes. Two (5.7%) patients died of unknown causes. Tumor was controlled and no disease progression or treatment-related side effects were seen in any of these patients.

DISCUSSION

Surgical resection is the main stay of treatment for most of the benign brain tumors [22-24]. Complete resection is always the goal of a surgeon, but if its not possible (e.g. perioptic, base of skull lesions, deep seated lesions) then adjuvant/salvage treatments are required in the form of radiation therapy. Single session intracranial stereotactic radiosurgery (SRS) has now become the successful treatment for most of the benign brain tumors having size ≤3cm [25-29]. If tumor size is >3 cm then surgical resection will remain an integral part of the management. Clinical dilemma comes in when surgery is not possible and/or single session SRS is not the feasible option because of increased normal tissue toxicity. Multisession stereotactic radiosurgery is the suitable answer to lower down the normal tissue toxicity with out compromising the therapeutic benefits.

The most important concern of treating benign tumors with radiation therapy is the malignant transformation and the development of second primary tumors related to therapeutic radiation. Evans et al [30], reported 0.5 – 3% risk of radiation-induced tumors after 30 years of radiotherapy for benign diseases. The lifetime risk of malignancy in the general population is 33-40 %. The relatively small risks of second primary tumors and malignant transformation in comparison

with the benefits of radiation treatment for benign CNS tumours, Evans et al [30], supported the use of radiation in such group of patients as in our study providing that those patients should be aware of the potential risks of tumor induction.

Clinical Improvement

Tuniz et al [18], reported that 20.6 % of the patients were having any improvement in preradiosurgical neurological symptoms while 73.5 % patients were having no change. In their series two patients had facial spasm relieved in 4-6 weeks and two had persistent nausea and vomiting relieved in 6 months. Paravati et al [21], reported about the subgroup of 26 patients with benign lesions out of which 21 were symptomatic at the time of fSRS (fractionated sterotactic radiosurgery). They found complete recovery of preradiosurgical symptoms in 66.6 % of patients. While 33.3 % patients had partial recovery from their preradiosurgical symptoms. Kim et al [31], reported preservation of visual functions in 96 % of the patients after multisession gamma knife radiosurgery for benign perioptic lesions. In this series, they observed improvement in 31.81 % of visual acuity and / or visual field defects, 63.63 % had stable or no change in visual functions and about 4 % experienced deterioration of visual acuity and visual fields. In our study complete symptomatic response was found in 22.9% of patients and partial improvement in preradiosurgical symptoms was found in 37.1 % of the patients, while 37.1% patients were having no change. Only 2.9 % had transient worsening of symptoms. Overall symptomatic response was 97.1 % which is consistent with the studies mentioned above.

Tumor Control

Paravati et al [21], have shown >20% reduction in 34.6% of the patients and Tuniz et al [18], have reported >20% tumor size reduction in 41.66 % of the patients. Benign tumor overall control rate was 100% in both the series. Kim et al [31], reported tumor volume decrease in 77% of the patients and 18 % had stable size. Overall control rate was 95 %. Only 5 % were found to have progression in tumor growth. While in our study, >20% tumor size reduction has been seen in 25.7 % of the patients, remaining all patients were having stable tumor size. Overall tumor control rate was 100%, which is equivalent or better than the mentioned studies. Where as the incidence of >20 % tumor size reduction is slightly lower than other two studies [18, 21], we assume that it is because of short follow-up time in our study and long term follow-up may result in more shrinkage of tumor size. Median follow-up time in Paravati et al [21], study was 24.7 months (range: 0-58 months), Tuniz et al [18], study was 31 months (range: 12-77months) and Kim et al [31], study was 29 months (range: 14-44 months). Where as in our study, median follow-up time was 6.4 months (range: 1-22.5 months).

Radiation Tolerance

Paravati et al [21], documented only 2 patient having RTOG grade III reactions, no patient experienced grade IV reaction. 3 Patients experienced grade II and 8 patients experienced grade I side effects. Late effects were seen in 3 patients at a median of 9 months after SRS, their symptoms were resolved in median interval of 3.5 months. 3 other patients had fascial spasm at 3-6 months after SRS and resolved with in 2 months. These findings were observed in all the patients included in the study having benign as wel as malignant tumors.

Tuniz et al [18], reported 2 patients with fascial spasm at 4-6 months after radiosurgery, improved partially at 4-6 weeks with glucocorticoides. No new permanent neuropathy was observed. Two patients had subacute worsening in symptoms resolved at 6 months. Four patients had radiologic signs of radiation injury. These imaging changes observed at mean time of 6 months after radiosurgery. All above resolved at median time of 6 months after radiosurgery. In our study, we had only one patient with worsening of symptoms at 4 months after radiosurgery, have been taking glucocorticoides till 5 months then relieved and had no signs of radiation injury on imaging. We did not find any patient with fascial spasm. Late effects were not observed in any of the patient included in our series.

Dose Selection & Fractionation

Iwata et al [20], used two types of fractionation schedules. 21 Gy (range:17-21 Gy) in 3 fraction and 25Gy (range:22-25Gy) in 5 fractions for large non functional pituitary adenomas with median tumor volume of 5.1 ml (range : 0.7-64.3 ml) and found both the regimens effective for tumor control and safe for optic apparatus and neuroendocrine functions. Tuniz et al [18], used 24 Gy (16-25 Gy) delivered in median of 3 fractions (range: 2-5 fractions) prescribed at median of 78 % isodose line (range: 67-83% isodose line) for the median tumor volume of 19.3cm^3 (range; 15.8-69.3cm^3). They also found these fractionation doses effective and safe. Paravati et al [21], used median marginal dose of 22 Gy (15-50 Gy) in median of 3

sessions (range: 1-5 sessions) for the median tumor volume of 9.63 cm^3 (range: 0.64 – 103 cm^3). Adler et al [11], used total marginal dose of 20.3 Gy (range: 15-30 Gy) at mean isodose line of 80% (rang:70-95%). 38.77% patients were treated in 5 fractions, 4.08% were treated in 4 fractins,34.69 % received 3 fractions, and 22.44 % patients were treated in 2 fraction. Kim et al [31], used cumulative median marginal dose of 20 Gy (range: 15-20 Gy), prescription isodose was 50%(range: 46-50%). 95.4 % patients were treated in 4 fraction with 12 hours interval in each session, only 4.5 % patients were treated in 3 fractions with 24 hours interval in each session. We used 25 Gy (range: 20-27.5 Gy) in median of 5 fractions (range: 3-5 fractions) prescribed at median of 75% isodose line (range: 65-100% isodose line) for the median tumor volume of 49.4 cm^3 (range: 15-184cm^3). Only three patients were treated in three fraction schedule which was carried out on alternate days. While remaining 32 patients were treated in 5 fractions with 24 hours interval in each fraction and the dose was varied in relation to volumes: larger the volumes, lower the total and per fraction doses.

Unrelated Deaths

Tuniz et al [18], reported two (5.88%) unrelated deaths in their study. Adler et al [11], reported 4.08 % unrelated death. While we experienced 8 (22.9%) deaths. Cause of death was known for 6 patients, and was not tumor related. Two patients died of chest infection (new event), two died of uncontrolled diabetes mellitus (known comorbid), one with chronic renal failure (known comorbid) and one with CSF leakage as surgical complication. It is important to take special care of comorbid conditions, monitoring of blood sugar and blood pressure particularly when patients are using glucocorticoides.

CONCLUSIONS

With this early clinical outcome we conclude that linear accelerator based multisession stereotactic radiosurgery for large benign brain tumors of >3cm is effective and very well tolerated. Follow-up period was short for evelauation of the benign lesions and late side effects of larger fraction size radiation therapy. Higher non-tumor-related death rate indicates that the management of comorbid conditions is necessary to improve the clinical outcome. Further studies are necessary to determine the optimal dose and fractionation schedules with longer followup.

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