

Case series report of LINAC-based Stereotactic radiosurgery of Intracranial meningioma – an institutional experience

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INTRODUCTION

Meningioma has been conceptualized as a collection of “dural endothelioma” that occurred throughout neural axis i.e. brain and spinal cord. This was first described by Harvey Cusing, famous neurosurgeon in 1922¹. Meningioma is the most common primary intracranial tumor. According to The Central Brain Tumor Registry of the United States (CBTRUS) statistical reports 2008-2012, It accounts 36.1% of all primary brain tumor and 53.7% of all primary nonmalignant brain tumors². The frequency of diagnosis raises with age having peak incidence in the 5th and 6th decade of life. Literature supports median age of diagnosis 55years and diagnosed at a rate of ~98 per 100,000 persons³.

ABSTRACT

Stereotactic radiosurgery (SRS) has been widely used for the treatment of intracranial lesions. We have been doing SRS since March 2019. The unique ability of SRS to deliver higher focused dose to the smaller targets preferably in a single exposure in a convenient manner while sparing adjacent critical structures has made a more widely adopted treatment option. This case series is intended to show our institutional experience and procedural technique adapted for treating intracranial meningioma using SRS by Linear accelerators. We present five cases of intracranial meningioma. Four had Grade I meningioma and one patient with Grade III meningioma. One patient had radiological diagnosis only and treated with SRS. Two patients underwent gross total resection and SRS was prescribed on the event of recurrence. Rest two patients had recurrence/progression after subtotal resection and adjuvant radiation. The dose prescription ranged from 13 to 21Gy in one to three fractions which was determined by tumor volume, location, grade, proximity to critical structures, pre-existing neurologic impairment, previous treatment history, time to progression/relapse and the ideal balance of prescription dosage and expected problems. There were no acute side effects from any of the procedures. All five patients had improvement in clinical symptoms in the immediate post-SRS period. One patient who has two-year post-SRS revealed a significant regression in the size of the tumor. This case series summarizes the fact that SRS for intracranial meningioma is safe and effective treatment strategy when appropriate.

Key words: Meningioma, LINAC, Stereotactic Radiosurgery.

Risk factors related to the incidence of meningioma are advanced age, previous history of radiation to head and neck area, female sex, Hormone replacement therapy etc. Neurofibromatosis type-(NF2) and chromosomal aberrations such as mutation of chromosome 22q is also associated with spontaneous meningioma^{3,4}. Familial meningiomas are uncommon. Meningioma is rarely seen in children but a child undergoing craniospinal radiation for the treatment of childhood acute lymphoblastic leukemia harbor the risk of developing meningioma⁵.

World Health Organization (WHO) has classified meningioma into grade-I(benign), grade-II (atypical),

grade-III (anaplastic), which gives information about the tumor aggressiveness and probability of recurrence. This classification is based on mitotic activity (≤ 4 mit/hpf, 4-19mit/hpf, ≥ 20 mit/hpf) and a range of histopathological feature i.e., brain invasion, hypercellularity, small cells with high nuclear to cellular ratio, prominent nucleoli, pattern-less sheet-like growth, and foci of necrosis. Grade I meningiomas are slow-growing and most common type accounting 70-80% of all meningiomas. Metaplastic, secretory, lymphocyte-rich, angiomatous, psammomatous, microcystic, fibrous, meningothelial and transitional are the subtypes of grade I or benign meningioma. Grade II or atypical meningioma, accounting 20%, grows more rapidly and has higher risk of recurrence. The clear cell and chordoid subtypes are considered atypical as well. Grade III or anaplastic meningioma are also called malignant meningioma. They encompass features of frank anaplasia with focal, or diffuse loss of meningothelial differentiation, and their cytology often resembles carcinoma, sarcoma, or melanoma. Grade III meningioma accounts approximately 2-3% and has most aggressive behavior. Rhabdoid and papillary subtypes are classified as anaplastic grade⁶.

Symptoms related to meningiomas is an outcome of irritation of underlying cortex, compression of cranial nerves and brain, hyperostosis, invasion to overlying soft tissue and vascular injury to brain. Small meningioma lesions often remain asymptomatic and discovered incidentally. Larger tumors produce symptoms that vary depending upon location. Symptoms can range from focal seizure, headache, paresis, cranial nerve dysfunction, visual deficit, aphasia, seizure etc⁷.

Diagnosis of meningioma is mostly radiological. Contrast-enhanced MRI has superior capacity to define characteristics such as diffusion, vascular supply information, and perfusion details. When MRI is contraindicated (eg- pacemaker), contrast-enhanced CT is an alternative. Angiography highlights relationship of blood vessels with meningioma. On MRI, meningioma is a iso-intense, well-circumscribed mass with broad dural base on T1W & T2W sequences with homogeneous contrast enhancement. "Dural tail", a helpful imaging sign is seen in 60-72% of meningioma. Meningioma appears hyperdense (occasional isodense) on CT and features of calcifications, hyperostosis of adjacent skull or osseous destruction is also detected in CT scan. To understand the exact subtype and biologic characteristics of tumor, a biopsy is important^{8,9}.

The management decision of Meningioma is dependent upon the size, location, presenting symptoms and histologic features. European Association of Neuro-oncology (EANO) have published a guideline on meningioma management¹⁰. Incidentally diagnosed asymptomatic patients with small sized (<2cm) and radiologically low-grade tumor can be observed with imaging surveillance. Patient with multiple comorbidities and limited life expectancy are also observed instead of active intervention¹¹. Macroscopic complete tumor removal with excision of dural attachment, any abnormal bone, and involves venous sinuses (Simpson grade I), is the ideal is treatment modality as first approach of management. Patients in whom complete resection becomes limited due to eloquent location of the tumor or nearby critical structure, radiotherapy plays vital role in as adjuvant regimen to control the tumor and reduce recurrence.

Role of radiation is meticulously evaluated considering the tumor type and prior treatment given. Cavernous sinus meningioma and optic nerve meningioma, that are not suitable for surgery, Radiation is the primary treatment modality. RTOG 0539, a prospective trial guided the used radiation in meningioma. Incompletely resected grade-I meningioma having high labeling index (Ki-67), early adjuvant radiation instead of waiting is preferred. adjuvant radiation is generally recommended after gross total excision and strongly recommended after subtotal resection of grade-II meningioma. All grade-III/malignant meningiomas have a definite indication of postoperative radiation.

Stereotactic radiosurgery (SRS) for Meningioma has been in practice since 1990¹². The unique ability of SRS is to limit unwanted doses to the nearby critical structure by utilizing multiple high dose radiation precisely directed to the target. Less treatment time and more patient compliance has led radiation oncologist to treat unresectable meningioma, sub totally resected tumor with SRS. SRS exploits two-target model of radiobiology to control tumor. After exposure of high dose stereotactic radiation, endothelial cell inflammation and apoptosis causing subsequent microvascular dysfunction with synchronous DNA damage and generation of ceramide leads to cell death¹³. SRS was initially used for skull base meningiomas. But now-a-days, there are ample data proving that SRS by both GKRS and Linac unit is a feasible,

safe and effective option with tolerable side effect profile for both definitive and adjuvant treatment in other locations as well. Konziolka et al. described that primary SRS can offer higher rates of tumor control for small to medium-sized symptomatic meningioma (<3.5cm) that are equivalent to Simpson grade-I resection¹⁴. Adjuvant SRS also improves progression-free survival. Condra et al. and Dale et al. in their separate study supported adjuvant radiation has a vital role in improving better tumor control^{15,16}.

In Bangladesh there is no Gamma Knife Radio Surgery (GKRS) unit installed till date. Evercare Hospital Dhaka has been treating patients with Linac-based since March 2019. A Linac unit utilizes non-invasive stereotactic headframe, modern treatment planning systems along with comprehensive QA tests that are the component of a Lina-Based SRS system and has the capacity to generate superior dose-effect than GKRS with maximum dose to the tumor with higher Conformity Index (CI) and minimum dose to the critical structure with higher Gradient Index (GI)¹⁷. In this case series, we intend to share our institutional experience in treating five patients with intracranial meningioma, who underwent Linac Based Stereotactic Radiosurgery in our institution in the preceding years.

Case Presentation 1

A 42-year-old female initially experienced an episode of seizure and loss of consciousness on 3.12.18. She also had occasional blurring of vision with hypertension, hypothyroidism and bronchial asthma. MRI showed a meningioma in left temporal region, she Underwent left temporal craniotomy with zygomatic osteotomy and removal of meningioma on 12.01.2019. Histopathology confirmed Meningothelial meningioma (WHO grade I). Follow-Up MRI after 3 months showed residual lesion of 2.3x1.9cm in left temporal region deep to craniotomy with mild mass effect on adjacent temporal lobe. A further followed up with MRI at 6 months post-surgery showed similar findings but she had persistent complain of left sided facial pain, painful swallowing, and decreased sleep. Subsequently she received stereotactic radiosurgery with marginal dose of 13Gy in single fraction treated on 5th October 2019. Follow up MRI on 18.12.2019 (2.5moths post SRS) estimated hyperdense residual lesion size 2.0x1.6cm with oedema in adjacent temporal lobe with regional mild mass effect and uncal herniation. She lost follow up for two years for

financial constraints and COVID pandemic. Next MRI on 03.10.2021 (2year post SRS). The lesion found decreased in size 2.0x0.8cm with visible dural tail. Encephalomalacia in adjacent temporal lobe involving left inferior and parahippocampal gyrus was noted. This tumor volume is 4.76cc compared to initial tumor volume (GTV) of 7.89CC, an approximately 38% reduction in tumor volume observed.

Case Presentation 2

A 57-year-old lady, with diabetes and chronic kidney disease, had complaints about headache, occasional vomiting and sleep disturbance for few months in 2020. MRI brain on 03.09.2020 showed well defined extra axial intracranial mass (2.45x1.79x3.09cm) in right parasagittal region, radiologically diagnosed as meningioma with mass effect and superior sagittal sinus invasion causing expansion of the sinus and almost complete luminal occlusion. Patient was explained both the option of surgery and radiosurgery as both the modality have similar outcome. She opted for radiation therapy and underwent stereotactic radiosurgery on 14th November 2020 with a marginal dose of 13Gy in single fraction. MRI at 3 month post SRS reported 2.4x1.2cm enhancing mass lesion in right parietal parasagittal region with superior sagittal sinus invasion and focal occlusion within the same. There was minimal mass effect in the underlying brain. She had improvement in headache with no new complaints. Her subsequent imaging after one year on 18.09.2021 reported the lesion being stable sized (2.4x1.6x1.4cm) in right parietal parasagittal region with part of it invading to superior sagittal sinus opacified. MRI on 27.08.2022 (2-year post SRS) reported to have stable-size lesion with no interval changes. She had improvement in quality of life due to less headache and vomiting.

Case Presentation 3

A 56-year-old lady had her initial presentation of difficulty in vision in 2017. On evaluation she was found to have loss of vision in the temporal field. MRI brain (04.09.2017) reported well delineated 2.9x2.5x1.5cm, nodular space-occupying lesion in the suprasellar region with subtle intracellular component and predominant right parasellar extension causing regional mass effect. Lesion had mild patchy homogeneous contrast enhancement. Optic chiasma was indented and encased (right >left) with optic nerve involvement.

There was anterior extension of lesion over the dorsum sellae with small dural tail with Encasement of regional internal carotid artery. She underwent endoscopic trans-sphenoidal resection on 27.10.2017. postoperatively she had little improvement in her vision. Histopathology confirmed Psammomatous meningioma (WHO Grade- I). There was no evidence of any residual or recurrence of the disease till 2021 and neither she had any neurological deterioration, new deficit or complaints. recurrence was observed after 04 years by MRI on 19.05.2021, that reported 1.8x1.2x0.8 cm nodular space-occupying lesion in the suprasellar region with right parasellar extension causing regional mass effect with mild postcontrast enhancement. Then she underwent SRS with a marginal dose of 14Gy in single fraction on 15th June 2021. Follow up MRI (04-month post SRS) showed a decreasing trend of lesion (1.5x1.0cm) with mild edema in the right inferior frontal lobe due to radiation. Her most recent MRI done on 24.08.2022 (14 months post-SRS) showed stable sized lesion with resolved edema in right frontal lobe. Patient is asymptomatic with no new complaints.

Case Presentation 4

A 48-year-old lady with hypertension had non-progressive hearing loss in left ear for five years and imbalance in walking for six months and was detected to have left sphenopetroclival meningioma on MRI brain in early 2014. Examination revealed left sided 5th, 7th and 8th nerve involvement. She underwent left temporal craniotomy and subtotal excision of the tumor on 07.03.2014. Tumor in cavernous sinus and part of tumor in posterior fossa was left behind. The biopsy reported as an angiomatous meningioma, WHO grade I with MIB labelling index 2%. Afterwards she received 54 Gy radiation therapy in 30 fractions from 20.05.2014 to 02.07.2014. Thereafter, she was symptom free and dropped out. MRI brain done on 02.01.2020 (6years post treatment) suggested residual or recurrent mass at left temporal region adjacent to cerebellopontine angle and left parasellar region. In June 2020, she reported headache for four months with tinnitus in left ear with vertigo & dizziness. MRI brain suggested increase in the size of residual lesion (i.e. 3.0x2.8.1.5cm in January'21 but 4.0x2.5x1.8cm in August'21) in left Petroclival region which extend along the clivus over the tentorium into middle cranial fossa. The lesion caused mass effect on the left side of the brain stem, invasion into left mackles cave and left cavernous sinus and encasement of left internal carotid artery with intraosseous extension in bony clivus

and left petrous apex. Patient was taken for SRS as evaluation for re-excision at the skull base deemed challenging. Considering the extent of the recurrent lesion and location of the adjacent critical structure, she was planned with hypofractionated radiosurgery with a marginal dose of 21 Gy in three fractions from 19th to 21st August 2021. Her Brain MRI on 09.08.2022(1year post SRS) noted stable appearance of the mass lesion left petrous apex, adjacent greater wing of sphenoid bone and left cavernous sinus. She has complaints of occasional headache, heaviness in head with weakness and left sided facial discomfort. She is given conservative management.

Case Presentation 5

A 62-year-old lady with diabetes and hypotension had initial complaints of difficulty in speech for one-month, occasional headache and heaviness in head with left-sided earache in 2019. MRI brain showed large sized (4 x 4.6 x 6.1cm) extra-axial mass in the left frontoparietal parasagittal location with perilesional edema. The mass was mixed in nature and showed dense contrast enhancement. She underwent left front parietal craniotomy and gross total excision on 14th October 2019. histopathological confirmed meningioma being atypical with focal Rhabdoid morphology (WHO grade-II), MIB labeling index 7%. Later she received adjuvant radiation therapy of 60Gy in 30 fractions from 11.11.2019 to 21.12.2019. She dropped follow up because of a personal problem and COVID pandemic until June 2021, when she developed pain in left ear. MRI brain on 24.05.2021(2-year post treatment) showed multiple extra axial mass at left frontal temporal region. She underwent repeat surgery on 20.06.2021. Histopathological examination reported rhabdoid meningioma (WHO grade-III) with high mitotic index and CNS invasion. Follow up MRI brain on 07.09.2021 showed small residual nation of 2.4 x 1.0cm in left parietal region along with dura. Considering the rhabdoid morphology, aggressive biological behavior of the disease, size of residual lesion and performance status, she was planned for SRS. Pre SRS MR imaging of Brain reported mass lesion in left sylvian Fissure (2.7x1.5 cm), right side of falx with extension to superior sagittal sinus with partial occlusion (0.5x0.7 cm), and right lesser wing of the sphenoid bone producing mild mass effect on right temporal lobe (2.8x 1.3 cm) with features of meningiomatosis in brain. Then she underwent SRS with a marginal

dose of 14~15 Gy to all three lesions in single exposure on 29th September 2021. She was advised to attend close follow-up every three months. She had complaints of sleep disturbance, occasional inability to relate to time, place and orientation along with shock like sensation over the head. Her MRI on 6th April 2022(6month post SRS) showed all the lesions stable sized. But MRI on 23rd July 2022(10months post SRS) had a significant progression in the size of the lesion. The enhancing mass lesion in the left frontal convexity measured 8.2 x 5.1 cm with mass effect on left perimesencephalic cistern, left temporal lobe, partial effacement of the left lateral ventricle and 5.9 mm mild midline (towards right), deformed left cerebral peduncle and invasion into calvarium. Lesion in the anterior falx and. She was on supportive care and expired on 6th October 2022.

From 2019 to 2021, five patients of meningioma were treated with stereotactic radiosurgery at our hospital. All of them were female. The location of the tumor was diverse. A skull base was a common site for three patients. Four patients had previous surgery, two of them had previous history of adjuvant radiation therapy, one of them underwent re-excision on the event of recurrence. One patient in our case series had her diagnosis determined by MRI only and subsequently underwent primary stereotactic radiosurgery without prior surgery. A comprehensive history taking, clinical assessment, survey of past clinical records was made before advancing for treatment. Table 1 sums up the demographic profile and treatment characteristics of all patients.

Radiotherapy Techniques & Treatments

All patients treated on the Linac-based stereotactic framework at Evercare Hospital Dhaka. They have been sent to our department for consultation as postoperative recurrence of disease with symptoms, or meningioma not amiable for surgery. Once the agreement is for SRS from both the radiation oncologist and patient, Informed High risk written consent is obtained from patient & family members before setting up the procedure. Three clamp double layered, thermoplastic mask were used for immobilizing the patient in supine position. Afterwards, a non-invasive localizer box ("Z" shaped) is used to acquire the isocenter of the treatment plan through nine stereotactic external coordinates on each axial slice coordinates. This external localizer box is essential in reproducing set up and locating the

smaller targets to the accuracy of sub-millimeter during treatment delivery. Once the mold work is complete, subsequently patient is sent for image acquisition. A thin sliced contrast enhanced delayed CT scan of 1 millimeter thickness maintaining stereotactic localizer box in situ is obtained. Next, high-resolution Gadolinium-enhanced MRI (T1 Fat Sat) of similar thickness was acquired in the same setup position defined during mold work. Both CT-scan and MRI were carefully co-registered in the treatment planning system before target delineation. Radiation Oncologist, Neurosurgeon, and Neuroradiologist joined to delineate the target tumor and the Organ at Risk (OARs) as the volume of interest and structure of avoidance. GTV (gross tumor volume) and/or CTV was contoured on CT and/or MRI images. Target volume was edited taking into account of the pre-operative volume and natural anatomic barrier. Later PTV (Planned Target Volume) was created by adding a margin of 1-2mm around the GTVs or CTVs. Once the prescription dose was determined, Treatment planning was performed by medical physicists using the Monaco treatment planning system (Elekta, Version 5.3). Treatment plans were reviewed vigilantly by treating Radiation Oncologist and Medical Physicist against The Radiation Therapy Oncology Group (RTOG) guided consensus dose constraints, Conformity index and Homogeneity index, and Dose Gradient Index. DVH and Dose painting color was also analyzed for hot and cold spots inside and outside the target volume before final approval. patient- specific QA was carried out to ensure dosimetric as well as collision-free physical reproducibility of the treatment plan on the machine. Finally, Prior to radiation delivery, reproducibility of the patient position was confirmed utilizing KVCT and hexapod 6D couch to guarantee submillimeter precision.

The Tumor dose ranged from 13-23 Gy. Patients who received stereotactic radiosurgery in one fraction was prescribed with a dose of 13-14 Gy. One patient underwent treatment in three fractions. she was prescribed 23 Gy in three fractions in 3 consecutive days. All SRS patients were given prophylactic steroid, antiemetic and mannitol prior to SRS. medicines used

Table 1: Demographic profile and treatment characteristics of all patients.

Case no	Age /sex	PS	Tumor location	Most recent Symptoms	Diagnosis confirmation	WHO Grades/ subtype	Pre-SRS treatments	Tumor volume GTV (cm ³)
1.	42/F	1	Lt. temporal region	Lt. sided facial pain	Histopathology	Grade I/ Meningothelial meningioma	Surgical excision x1	2.814
2.	57/F	0	Rt. posterior Para-sagittal region	Severe headache & vomiting	Radiological	-----	None	4.674
3.	56/F	0	Suprasellar region	None	Histopathology	Grade 1/ Psammomatous meningioma	Surgical excision x1	0.819
4.	49/F	1	Lt. Sphenopetroclival region	tinnitus in Lt ear with headache and dizziness	Histopathology	Grade 1/ angiomatous meningioma	Surgical excision x1 Radiation x 1	9.743
5.	64/F	1	Multiple site in anterior cranial fossa; Lt. sylvian fissure, rt. lesser wing of sphenoid bone, right side of fax.	Pain in Lt ear.	Histopathology	Grade 3/ rhabdoid meningioma	Surgical excision x1 Radiation x1 Repeat surgery x1	GTV1- 2.827 GTV2 – 1.314 GTV3 – 0.405

to decrease the risk of intense edema. Steroids and antiemetics tapered off within three weeks. Figure 1 shows the size residual lesion and Figure 2 shows the color wash display of the dose distribution of the same patient with DVH.

The table 2 illustrates the quantitative and qualitative dosimetric characteristics of each patient.

Toxicity Evaluation

Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) has been used to describe toxicities. Acute toxicities/early side effects were defined as toxicities observed within three months of radiation therapy.

Early side-effects

The treatment was well tolerated for all patients. None of the patients had any major treatment related complications during immediate and the post-procedural period. Patients had grade 1 fatigue and occasional nausea. None of the patients develop any new neurological deficit.

Late side-effects

Till the case series is written, one patient died due to aggressive nature of the disease. Of rest four patient two patient completed 2 years post SRS (case1 &case2).

Case 1 was found to have encephalomalacia in adjacent temporal lobe involving left inferior and parahippocampal gyrus reported on follow up MRI, which is expected. She is asymptomatic and currently on follow up only. Other two patient (case3 &case4). have completed 12-14 months post SRS. Till now they are free of any late complications.

Follow up Evaluation

All patients were reassessed within two-week post procedure to find out any acute complications. Later all are assigned for planned follow up schedule, which is to attend OPD review for symptom review, clinical examination, and neuro-radiological evaluation at three on first follow up to six months to one year interval on subsequent follow up. Till the report has been written, two patients completed two-year post SRS follow up. They are on a regular follow up schedule. One patient died recently in October’22 due to disease progression. Rest two of our patients completed 12-14 months post SRS follow up.

Table 2: Patients Dosimetric Characteristics

S. N.	Case 1	Case 2	Case 3	Case 4	Case 5
Dose (Gy) /No. of Fractions	13/1	13/1	14/1	21/3	15/1
PTV D _{max} (Gy)	17.49	17.14	18.44	31.52	17.79
PTVD ₉₅ (Gy)*	13.37	11.29	13.47	22.21	PTV1- 14.77 PTV2- 15.64 PTV3- 15.69
PTVD ₉₉ (Gy)**	10.64	10.55	12.94	20.30	PTV1- 14.36 PTV2- 15.31 PTV3- 15.36
HI [#]	1.25	1.47	1.32	1.34	PTV1- 1.14 PTV2- 1.10 PTV3- 1.11
CI ^{##}	0.96	0.73	0.88	0.98	PTV1- 0.90 PTV2- 0.99 PTV3- 0.99
GI ^{###}	0.986	0.90	0.95	0.99	PTV1- 0.96 PTV2- 0.99 PTV3- 0.99
Hot spot (%)	134	132	131.7	150	118.6

* PTVD₉₅ (Gy) – Volume of PTV receiving 95% of prescribed dose.
 ** PTVD₉₉ (Gy) - Volume of PTV receiving 98% of prescribed dose.
 # HI - Homogeneity Index is the ratio of the maximum dose in the target volume (Imax) to the reference isodose volume (RI) i.e. value of less than 2.0 is the RTOG/Formula E about the acceptable limit of HI. $HI = D5/D95$; where D5 = minimum dose in 5% of the Planning Target Volume (PTV), indicating the “maximum dose”, and D95 = minimum dose in 95% of the PTV, indicating the “minimum dose”. The lower (closer to one) the index, the better is the dose homogeneity.
 ## CI- Conformity Index is an important metric for determining how tightly the prescription dose is conforming to the target. The ICRU report 62 defines conformity index as $CI = TV/PTV$ where TV is the treated volume enclosed by a given isodose surface (e.g. 100%, 50%) and PTV is the planning target volume (near 1.0).
 ### GI - The Gradient Index defined as the ratio of the 50% isodose (V50) volume to the prescription isodose volume (PIV).

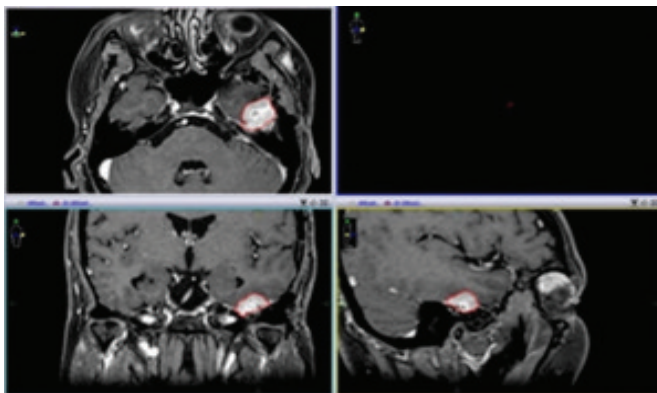


Figure 1: Showing 2.3x1.9 cm post-surgery residual lesion of Case no1

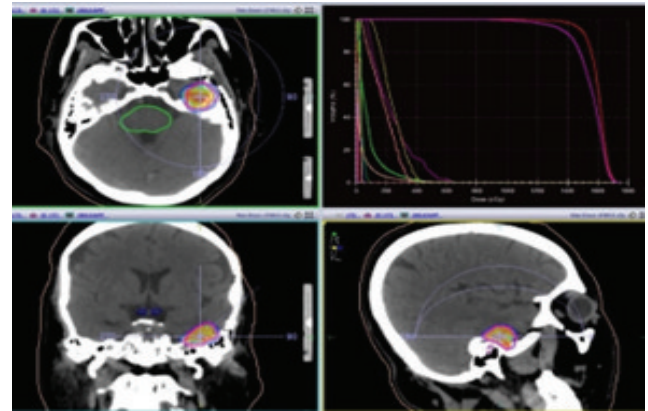


Figure 2: Showing dose distribution of 13Gy SRS plan delivered to Case No1 and Dose Volume Histogram

Clinical Response

All patients were free from any unfavorable event in a 24hour post-procedural period. Initial Follow up was done after 2 weeks and then 3-6months of radiation therapy. No patient experiences any immediate treatment-related complications, neither they developed any new complaints. All the patients had improvement in their symptoms that was persisting prior to the procedure. One patient had a significant radiological response at two-year post SRS (illustrated in fig 3&4). Another patient is found to have stable disease at two-year post SRS period. Two patient is having stable sized lesion at 1year post SRS. One patient Grade 3 Meningioma, had very notorious disease behavior. She had progression of disease within 10month of SRS and expired.

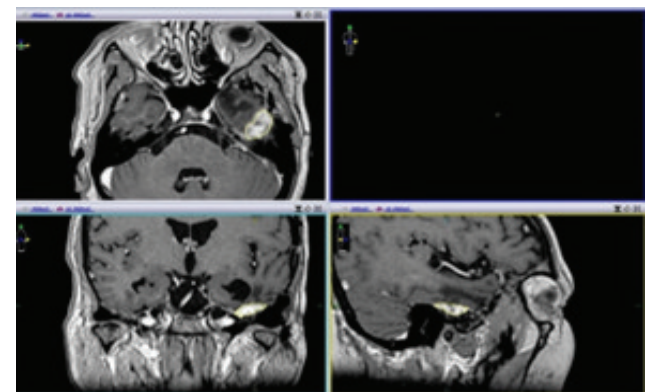


Figure 3: Illustrating volume reduction at 2 years of post SRS

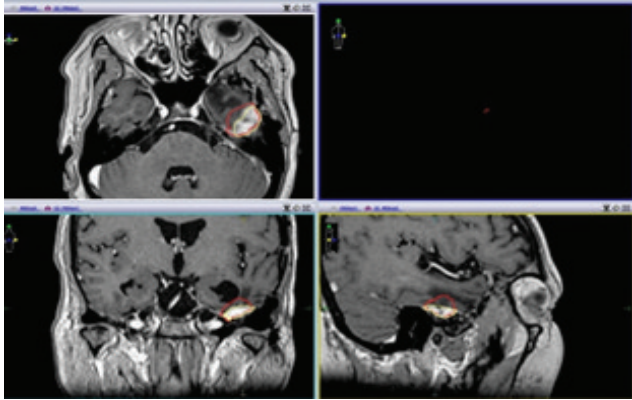


Figure 4: Depicts the regression of lesion size from 2.8 cc to 1.3cc at 2 years of post SRS

DISCUSSION

Meningioma is most common benign intracranial tumor that contributes more than 1/3 of all primary brain tumor and half of all primary nonmalignant brain tumor². Meningiomas are typically found more in females and the occurrence rate raises with age with a highest incidence reported in 5th and 6th decade of life. Most common area of cranial meningioma are Skull base (43-51%), along the convexity (20-37%) and parasagittal region (13-22%). Besides meningioma is less commonly found in intraventricular, orbital or any other ectopic location¹⁸.

In our case series all the patients were female, and majority of the patient belong to 5th and 6th decade of life. Among five patients three patients had their tumor located in skull base and rest two location was in parasagittal region To segregate tumor behavior and the prognostic indices, the World Health Organization has classified meningioma in 15 subtype and three categories namely WHO I, II and III⁶. The decreased survival and increased recurrence rate are directly related to the increments in Grade of meningioma. WHO grade I or low-grade meningioma is most common meningioma, having most indolent behavior, contribute almost 80% of all meningioma. Grade II & III meningiomas has a more aggressive clinical consequence have an approximate prevalence of ~20% & 1~2% respectively⁶. Literature also supports that meningioma (whichever sub-type) with high proliferation index i.e. Ki-67 has a more violent clinical course with higher risk of recurrence and death¹⁹. In our case, four patients had histopathological confirmation of their disease. Three of them had Grade 1 meningioma with different subtypes and one of them had grade 3 rhabdoid meningioma.

The rhabdoid meningioma had a recurrence within a short interval of about 19 months despite undergoing GTE (gross total excision) and adjuvant radiation. Despite receiving SRS, she again had a progression of disease within 10 months period. This depicts the aggressive behavior and poor treatment response for the higher-grade disease.

Presenting symptoms of meningioma had wide range and variation as that is mostly related upon size and location of tumor. Most common symptoms include headache, focal neurologic deficit, Seizure, weakness, vertigo. Meling et al. has more specified the symptoms for skull base and non-skull base tumor. They explained that skull base meningioma more commonly present with neurologic deficits. On the contrary seizure is frequent feature for non-skull base meningioma²⁰. Meningioma in anterior cranial fossa have symptoms when the tumor is considerably larger in size. The symptoms include visual impairment, headache, sensory loss, seizure or change in personality and behavior. Suprasellar meningioma may have presentation of loss of vision or minimal hormonal abnormalities^{18,21}. In our case series, headache was the common presenting symptoms. one patient experienced seizure due to the meningioma temporal lobe. Patient with suprasellar meningioma had visual field defect. Patient with meningioma in skull base/left sphenopetroclival region had gradual hearing loss with neurologic deficit in trigeminal, facial and vestibulocochlear nerve.

Early diagnosis of Meningioma can be made on MRI and contrast enhanced CT scan. They have typical “dural tail” enhancement at the edge of tumor. Surrounding edema adds suspicion for higher grade (WHO Grade 2&3) histology. Somatostatin receptor II directed PET with ⁶⁸Ga-DOTATATE or ⁹⁰Y-DOTA-TOC test has a high sensitivity and specificity for detecting meningioma¹⁰. This test is also useful if the extent of the tumor or the diagnosis of recurrence is uncertain but yet to be available in the country. Although post-operative histopathologic confirmation is not mandatory in diagnosis, but it benefits by understanding the subtypes, to do molecular analysis, also to exclude other pathology. EANO guideline advocated that tissue examination does offer possible scope for future targeted therapy²². In this series, four patients had surgical intervention.

Thereby, they had report of WHO grading and subtyping. One patient had her treatment with radiological diagnosis. Her tumor location was in right parasagittal region in the motor area. She has a radiologically approved low grade lesion and location of the tumor in motor area and was reluctant for surgery, she preceded for her treatment with radiological diagnosis. Management of meningioma include many options such as, watch-and-wait strategy, surgical intervention (gross total resection or subtotal resection), definite Radiation therapy radiation therapy or combined approach of surgery and radiosurgery. EANO issued guideline on diagnosis and management of meningioma. for the first time in 2016¹⁰. this guideline has been updated in 2021. The given flowchart in Fig. 5 has been published in the EANO guideline in 2021, which provides an easy understanding off meningioma management ²².

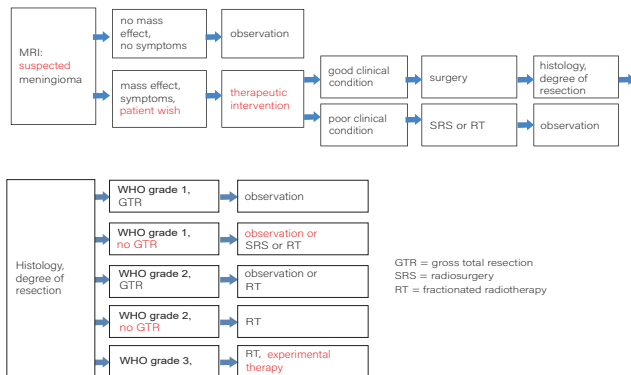


Figure 5: EANO recommendations for management of WHO grade 1-3 meningiomas²².

Watch-and wait strategy has been long advocated approach for all Low-grade meningioma. Later, prospective observation insisted investigators to understand the predictor of tumor growth and select the patient who should be advised for early intervention and minimize observation failure. Lee et al. has illustrated novel weighted scoring system Asan Intracranial Meningioma Scoring System (AIMSS) for estimation of risk of rapid growth in untreated intracranial management²³. Authors described old age, male sex, neurological deficits at presentation, tumor in eloquent area of brain, non-existence of calcification, peri-tumoral edema, hyperintense and isointense signal on T2W MRI is directly related with the rapid tumor growth. Authors concluded that AIMSS score (as described in the table.3) ≥ 4 for tumors ≤ 2.5 cm (approximate volume of 8.18 cm³), score ≥ 6 for tumors between > 2.5 cm and ≤ 4.0 cm, and a score ≥ 8 for tumors > 4.0 cm in diameter (approximate volume of 33.49 cm³)

need early treatment. Authors also defined annual growth rate (AGR) $\geq 2\text{cm}^3$ as rapid growth of tumor requiring immediate therapeutic intervention. On the flip side $\text{AGR} < 2\text{cm}^3/\text{year}$ is found to exhibit a linear static growth pattern. EANO guideline suggested newly diagnosed asymptomatic or small ($<3\text{cm}$) meningioma or slow growing meningioma may be kept under close observation. Zhao et al. also recommended observation for old patients with compromised physical condition²⁴. In our case series all the patients were having symptoms that was compromising the quality of life (QOL)for which early intervention was mandated.

Table 3: AIMSS score for Intracranial Meningioma

Parameter	score
Tumor diameter (cm)	
≤ 2.5 (approximately 8.18 cm ³)	0
>2.5 to ≤ 4.0	3
>4.0 (approximately 33.49 cm ³)	6
Calcification	
present	0
absent	2
Peri -tumoral edema	
present	1
absent	0
Signal on T2W -MRI	
hypointense	0
hyper are isointense	2

The primary treatment for majority symptomatic meningioma, observation failure meningiomas, large sized meningiomas or meningioma's expecting to have rapid growth is surgical resection. the extent of surgical dissection has commonly been described using Simpson grading since 1950²⁵. This grading scale uses a graduation from 1-5 to describe the extent of resection (EOR) that emphasizes the relation of EOR and outcome in term of rate of recurrence. Simpson's 1dissection means to removes all tumor, along Dural attachments, involved bone. but Simpson's 5 is a decompression/ biopsy only. European Organization for Research and Treatments of Cancer (EORTC), Radiation Therapy Oncology Group (RTOG) and modern neurosurgery has adopted Simpson's classification to describe the

extent of resection into either gross total resection/GTR (Simpson 1–3) or subtotal resection/STR (Simpson 4–5)²⁶. As shown in the table below (Table-4).

Table 4: Simpson grades of resection and corresponding EORTC/RTOG definitions of extent of resection (EORTC=European Organization for Research and Treatment of Cancer. RTOG=Radiation Therapy Oncology Group)

Simpson's Grade	Definition	Extent of resection
Grade I	Gross total resection of tumor, Dural attachment, and abnormal bone	Gross total resection
Grade II	Gross total resection of tumor, coagulation of Dural attachment	Gross total resection
Grade III	Gross total resection of tumor without resection or coagulation of Dural attachments or extradural extensions (eg- invaded or hyperostotic bone)	Gross total resection
Grade IV	Partial resection of tumor	subtotal resection
Grade V	Biopsy of tumor	-----

For large sized meningioma producing significant clinical symptoms, surgery provides immediate decompression and improvement of symptoms. But for meningioma in surgically inaccessible region i.e. cavernous sinus or selected candidate who are medically inoperable or do not wish to undergo surgery, radiation therapy (SRS/ HF-SRS/FSRT) has the role producing promising outcomes²⁷. But whether or not Small surgically accessible tumor that is suitable for GTR can safely and effectively treated by SRS has been a subject of investigation. Ruge Maximillian et al. in their cohort analysis of 188 patient explained SRS as a highly effective treatment option for small meningiomas eligible for complete surgical resection. Authors explained that SRS improves patient compliance by reducing the event of hospitalization, duration of post-surgical leave from work as compared to surgical excision²⁸. Similarly, Pollock et al. observed no distinct difference in PFS (both >95%) between SRS and GTR²⁹ In our case series one patient had her tumor located in right posterior para-sagittal region was suitable to GTR but received SRS as primary treatment because of patients' preference to noninvasive SRS option. Role of adjuvant radiation therapy is well established in Grade II and Grade III meningioma in adjuvant setting as these subtypes is more invasive in nature and posed higher risk of recurrence. Adjuvant local radiation produces better local control²². Grade I meningioma after gross total resection

are continued with close observation. If subtotal resection is done due to critical location or probable post GTR adverse effect/deterioration of neurologic symptoms, then a combined subtotal resection with radiosurgery or fractionated radiation provides more comprehensive management of tumor with reduced risk of complications¹⁰. SRS also benefits as salvage approach in recurrent or progressive disease where reintervention with surgery becomes challenging for the radiographic characteristics (tumor location, size, growth pattern and extent of involving vital structures), patients' neurologic status, surgeon's reservation and patient's choice. Aim of salvage radiotherapy is to control the progression of recurrent/progressive disease. Da Li et al. highlighted the fact that immediate reintervention of recurrent /progressive disease is more beneficial than untreated clinical course which leads to fatal progression³⁰. In our case series two patient of Grade, I meningioma treated with SRS for recurrence after gross total resection. Another two underwent stereotactic radiosurgery as a salvage approach on the event of recurrence/progression of their disease during their Post-surgery (STR), post-radiotherapy follows up state.

SRS is used for small meningiomas (<3cm) , small volume (<10-15cc) with ≥ 2 -3mm distance from neighboring critical structures i.e. optic apparatus. Otherwise, Fractionated Stereotactic radiotherapy (FSRT) is a valid alternative for large meningiomas and close critical structures The size and volume of the lesion, its closeness to nearby vital structures, and the characteristics of previous radiation treatments, all are considered while determining the radiosurgery prescription dose. Ganz et al., in his study described minimum peripheral dose for single session SRS ≤ 10 Gy is related with a great probability of failure. But a peripheral dose ≥ 12 Gy provides better control³¹. Consequently prospective trial approves a dose of 13-15Gy suffices for Grade I meningiomas^{14,32}. Sethi et al. assessed dose-response relationship and described prescription dose range escalation to 16Gy to 20Gy for high grade meningiomas, when feasible, can provide improved local control and overcome radio-resistance³³. Ding et al. in their series review for radiosurgical management of WHO Grade II and III intracranial meningiomas described median marginal dose of 16-20 Gy for WHO Grade II and 18-20Gy for WHO Grade III has improved progression free survival¹⁶. In last few years,

the idea of fractionated radiosurgery (FSRT) has developed for better tumor control and tumor shrinkage, low risk of symptomatic oedema alongside preserving the neurologic functions³⁴. This technique has been used to skull base meningiomas, notably perioptic tumors, skull base meningioma. In most cases, two to five fractions with dose of 4-10 Gy per fraction, resulting in total doses of 18-25 Gy are used^{35,36}. In this case series prescription dose ranged from 13-15 Gy for single fraction plan. One patient received hypo-fractionated SRS as salvage approach with a dose of 21Gy in three fractions. This patient had her recurrence in left sphenopetroclival region in post-surgery and post radiotherapy state.

Factors influencing the outcome of stereotactic radiosurgery for meningioma includes tumor location, tumor size, WHO classification of tumor, patients age, presence of symptoms/deficits prior to SRS, initial extent of tumor resection, radiation dose, and other clinical factors such as life expectancy and complications^{37, 28}. To assess local control after SRS, many authors described using linear management, modified MacDonaldis Criteria, Response Evaluation Criteria for Solid Tumor (RECIST) or Volumetric analysis. Pinzi et al. in their meta-analysis opted volumetric analysis as the most reliable method to detect meningioma volume changes after SRS³⁸. Authors also described that symptom control with SRS was effective estimating about 92.3%. Toxicity was related to large tumor volume. In our case series, We made use of volumetric analysis to understand the disease control status for the first case who completed 2 years post-surgery had approximately 38% reduction in tumor volume. Second case is observed to have almost stable sized disease at 2-year post SRS. Third and fourth case has documented stable disease at their 1 year Post SRS follow up state. The fifth case was found to have stable size lesion in her 6 months post SRS follow up though, she had rapid progression of disease afterwards that was apparent in 10month post SRS MRI.

CONCLUSION

SRS is an effective and appropriate treatment option for suitable intracranial meningiomas. It is a convenient and non-invasive approach bearing promising clinical outcome. Tumor histology, previous treatment, time to recurrence, location of tumor, patients' neurologic status

plays critical role in deciding treatment plan as well as outcome of disease. Our case series reports significant volume reduction in one patient while most of the other lesions remained stable. A longer follow up is required for appropriate radiological assessment of local control and late side effects.

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