Chapter

Overview of Radiosurgery for Intracranial Meningiomas

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Abstract

Meningiomas are the second common Central Nervous System (CNS) neoplasm, and are the most common benign intracranial tumor. They approximately constitute up to 30% of all intracranial tumors. They arise from the arachnoidal coverings of brain. Presentation varies and depends on size, number and location of tumors. Symptoms include those related to increased in intracranial pressure, local irritative features including seizure and local pressure effect to eloquent areas, white matter tracts and cranial nerves. Management of meningiomsa is always challenging and multi-disciplinary approaches includes surgery, radiotherapy and possible chemotherapy and immunotherapy. Among radiation therapy treatment, stereotactic radiosurgery (SRS) or stereotactic radiosurgery (SRT) is getting the popularity compared to traditional conformal radiotherapy with comparable tumor control rate.

Keywords: intracranial meningioma, stereotactic radiosurgery, stereotactic radiotherapy, LINAC, Gamma Knife, CyberKnife

1. Introduction

Meningiomas are the second common Central Nervous System (CNS) neoplasm, and are the most common benign intracranial tumor. They approximately constitute up to 30% of all intracranial tumors. They arise from the arachnoidal coverings of brain. Presentation varies and depends on size, number and location of tumors. Symptoms include those related to increased in intracranial pressure, local irritative features including seizure and local pressure effect to eloquent areas, white matter tracts and cranial nerves. Management of meningiomsa is always challenging and multi-disciplinary approaches includes surgery, radiotherapy and possible chemotherapy and immunotherapy. Among radiation therapy treatment, stereotactic radiosurgery (SRS) or stereotactic radiosurgery (SRT) is getting the popularity compared to traditional conformal radiotherapy with comparable tumor control rate. This chapter is intended to discuss the overview of radiosurgery on management of intracranial meningiomas with more focus on the outcome related to location of tumors and different modalities of radiosurgery, and sharing of the local experience of our centre.

2. Epidemiology

The overall age-adjusted incidence is about 8.6 per 100,000 of all primary brain and spinal cord tumors. The incidence rates are correlated with ages, with a median

age at diagnosis of 66 years. Tumors are reported to be 1.5 to 3 times more frequent in women. Under the World Health Organization (WHO) classification of brain tumors, majority of the tumors around 80–85% are grade I, around 15–20% are grade II, with 1–2% confirmed to be grade III malignant [1].

3. Classification

The WHO classification of brain tumors is the most popular classification system according to the histological molecular genetics. According to the 2016 WHO classification of tumors of CNS, there are totally 16 meningioma subtypes (**Table 1**) [2]. Meningiomas can also be classified according to their site of origin, and this classification method allows physician to predict the presenting signs and symptoms associated (**Table 2**).

Meningioma	**9530/0**
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3

Table 1.
2016 World Health Organization (WHO) classification of meningiomas.

Location	**Typical symptoms**
Convexity – frontal	Affective disorders
Convexity – parietal	Seizures, motor or sensory disorder, hemiparesis
Convexity – temporal	Speech disorders, memory disturbance
Anterior cranial base	Loss of olfaction, affective disorders, loss of activity, visual field or acuity loss
Cavernous sinus meningioma	Diplopia, facial pain or numbness, ocular venous congestion
Orbital or optic nerve sheath	Exophthalmos, loss of vision
Sphenoid wing	Loss of vision, diplopia psychomotor seizures, schizoaffective
Ventricular	Isolated hydrocephalus
Tentorial	Hydrocephalus, seizures, visual field loss, ataxia
Posterior fossa	Ataxia, vertigo, hydrocephalus, symptoms related to brainstem compression, unilateral or bilateral cranial nerve palsies

Table 2.
Clinical presenting features according to location.

4. Treatment strategies

Treatment of intracranial meningiomas generally include observation, microsurgery, radiotherapy in terms of fractionated radiotherapy in terms of conventional radiotherapy, intensity-modulated radiotherapy (IMRT) or volumetric arch therapy (VMAT), proton therapy or stereotactic radiosurgery or radiotherapy (SRS/SRT) [3–5]. Chemotherapy is indicated in some selected refractory cases. Microsurgery remains the best option for symptomatic intracranial meningiomas if complete resection can be achieved with low morbidity. Based on the well-known Simpsons grading system, the extent of tumor resection correlates with the tumor recurrence rate (**Table 3**). Nevertheless, total excision together with dural origin is seldom possible, particularly in cases with involvement or encasement of important neurovascular structures around skull base.

Stereotactic radiosurgery or radiotherapy can be of curative intent when adopted as a primary treatment, in postoperative cases when there is residual disease or high risk of relapse especially in WHO grade II or III cases, or of palliative intent when the disease is beyond cure [6, 7]. European Association of Neuro-oncology (EANO) had published their suggested flowchart in treatment guidelines (**Figure 1**) [8]. There was a review of patients with meningioma between 2010 and 2012 under the National Cancer Database. A total of 802 patients were included, of which 173 patients received SRS/SRT (22%) and 629 patients (78%) received external beam

Grade	Definition	10-Year recurrence rate
I	Macroscopically complete removal with excision of dural attachment and abnormal bone	9%
II	Macroscopically complete removal with endothermy coagulation (Bovie or laser) of dural attachment	19%
III	Macroscopically complete removal without resection or coagulation of extradural extensions	29%
IV	Partial removal leaving intradural tumor in situ	40%
V	Simple decompression with or without biopsy	Not available

Table 3.
Simpson grading system on meningioma resection.

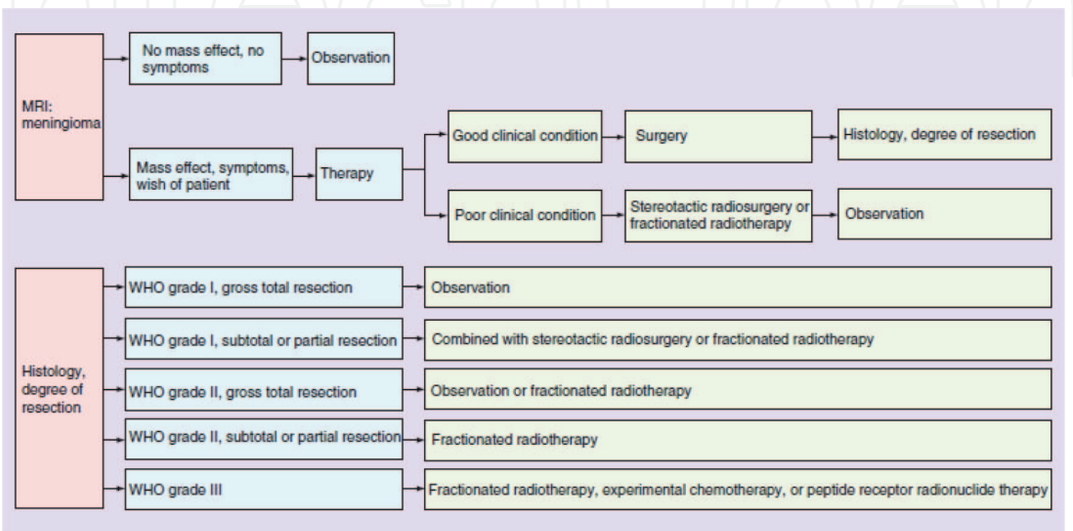


Figure 1.
The European Association of Neuro-oncology (EANO) treatment guideline flowchart for intracranial meningioma.

radiation therapy (EBRT). The 3-year overall survive rate of 2 treatments were similar (97.3% in SRS/SRT group and 93.4% in EBRT group) [9].

This chapter is intended to have an overview of radiosurgery as treatment of intracranial meningiomas.

5. Radiobiology of radiosurgery

Radiosurgery, invented by Prof. Lars Leksell, has been regarded as a significant treatment of choice in patients with intracranial neoplasm, since December 1967, when the first patient suffering from craniopharyngioma was treated with the prototype Gamma Knife at the Sophiahemmet Hospital in Stockholm, Sweden. Radiosurgery is the use of ionizing radiation to treat patients with neoplasm by delivering a precisely measured dose of irradiation to a defined tumor. The main aims include the followings:

1. to eradicate tumor

2. to arrest tumor progression

3. to relieve complaining symptom

4. to achieve better quality of life

5. to prolong survival

The difference between radiosurgery and radiotherapy generally is the size of the treatment volume, and the dose delivered during that single session. While volume is important, it is the radiosurgery team in achieving a precise and accurate radiation plan. Radiosurgery allow high dose per fraction which results in a higher biologically equivalent dose to the target without increasing the risk of complications in

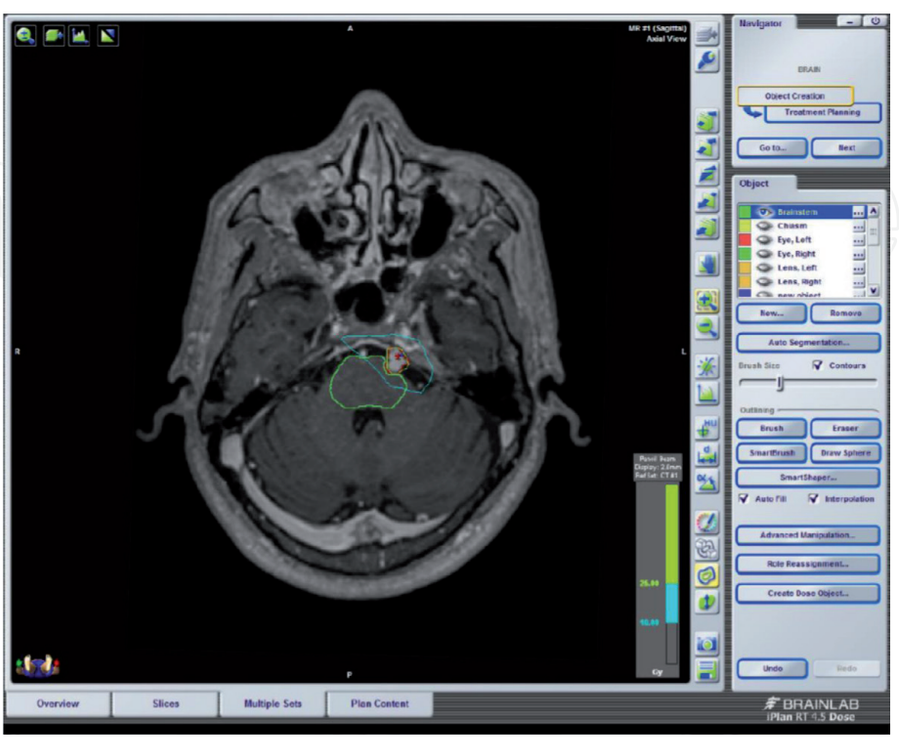


Figure 2.
LINAC stereotactic radiotherapy 25 Gy in 5 fractions for treatment of left petroclival meningioma in our centre.

Description	Constraint	1 fraction		3 fractions		5 fractions		8 fractions		Source	Did point (and magnitude of risk if previously quantified)
		Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)		
Optic pathway	DMax (0.1 cm^3)	—	<8	—	<15	—	<22.5	—	—	AAPM [13], Hiniker et al. [14]	AAPM: grade 3+ optic neuritis
											Hiniker et al.: 3 fraction: 0.8% and 5 fraction: 1.6% risk grade 4 radiation-induced optic neuropathy when limited to 0.05 cm^3
Cochlea	Mean	<4	<9	—	<17.1	—	<25	—	—	AAPM [13], Tamaru et al. [15]	AAPM: grade 3+ hearing loss
Brainstem (not medulla)	DMax (0.1 cm^3)	<10	<15	<18	<23.1	<23	<31	—	—	AAPM [13]	Grade 3+ cranial neuropathy
Spinal canal* (including medulla)	DMax (0.1 cm^3)	<10	<14	<18	<21.9	<23	<30	<25	<32	AAPM [13], Grimm et al. [16], UK SABR Consortium [17], LungTECH [18]	AAPM: grade 3+ myelitis

Description	Constraint	1 fraction		3 fractions		5 fractions		8 fractions		Source	Did point (and magnitude of risk if previously quantified)
		Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)		
											Grimm et al.: single and 3 fraction optimal doses to 0.1 cm^3 limit risk of grade 2–4 myelopathy to ≤0.4%
	D1 cm^3	<7	—	<12.3	—	<14.5	—	—	—		AAPM: grade 3+ myelitis
Cauda equina and sacral plexus	DMax (0.1 cm^3)	—	<16	—	<24	—	<32	—	—	AAPM [13]	Grade 3+ neuritis
	D5 cm^3	—	<14	—	<22	—	<30	—	—	AAPM [13]	Grade 3+ neuritis
Normal brain (whole brain – gross tumor volume)	D10 cm^3	<12	—	—	—	—	—	—	—	Group consensus	Radiation necrosis
	D50%	<5	—	—	—	—	—	—	—	Group consensus	Cognitive deterioration
Lens	DMax (0.1 cm^3)	<1.5	—	—	—	—	—	—	—	Group consensus	Cataract formation

Description	Constraint	1 fraction		3 fractions		5 fractions		8 fractions		Source	Did point (and magnitude of risk if previously quantified)
		Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)		
Orbit	DMax ($0.1\ cm^3$)	<8	—	—	—	—	—	—	—	Group consensus	Retinopathy

DMax is the near-point maximum dose, defined in this case as D0.1 cm^3, which is the minimum dose to the 0.1 cm^3 volume of the organ receiving the highest dose.
D1 cm^3, D5 cm^3 and D10 cm^3 are the minimum doses to the specified volume of the organ (1 cm^3, 5 cm^3, 10^3) that receive the highest doses.
D50% is the median dose to the volume (equal to the minimum dose to the 50% of the volume receiving the highest doses). *For treatments of the spine itself, these constraints should be applied to the cord planning organ at risk volume (PRV).*

Table 4.
UK consensus on central nervous system dose constraints.

surrounding. Mechanism of radiation related tumoricidal activity include DNA injury together with induction of apoptosis and vascular endothelial damage [10]. The advantages compared to other radiotherapy modalities include maximal conformity, rapid dose fall-off at radiation beam edges and minimal spatial inaccuracies in patient set-up, with generally very low radiation related toxicity (**Figure 2**) [11].

In current radiosurgery principle, the generally applied prescription dose is 12–16 Gy to the tumor margin at 50% isodense line [12]. Treatment dose need to be balanced with the radiation tolerance thresholds to those Organ-at-risk (OAR). A guideline with UK Consensus on normal tissue dose constraints for stereotactic radiotherapy was published as reference (**Table 4**) [19].

6. Radiosurgery techniques and current devices

Dose selection is the basic but upmost significant step in planning of radiosurgery treatment. It is always a balance between the expected level of treatment success and complications risks at various doses so as to select the most optimal dose for the individual patient. The paired sigmoid dose–response curves illustrate the balance between increasing the desired response and increasing complications with higher radiation treatment doses, with the so-called therapeutic window is the area between the two curves (**Figure 3**). Another essential principles in radiosurgery planning are conformity and selectivity. Traditionally, stereotactic radiosurgery (SRS) refers to stereotactically guided delivery of focused radiation to a defined target volume in a single session. Most of the procedures are performed in stereotactic frame-based manner. Modern development of radiosurgery technique allows the fixation of patient's head on couch without the stereotactic frame i.e. frameless. Thus the concept of fractionated stereotactic radiosurgery (FSRS) evolved, or in better terminology, stereotactic radiotherapy (SRT).

Current choice of radiosurgery devices can be divided depends on the application of clinical beams. LINAC Radiosurgery makes use of either linear accelerators-based system or robot-assisted e.g. CyberKnife, while Gamma Knife Radiosurgery employs Cobalt (Co)-60 as the source (**Figure 4**). Both treatment of choices are effectively in treatment of intracranial meningiomas.

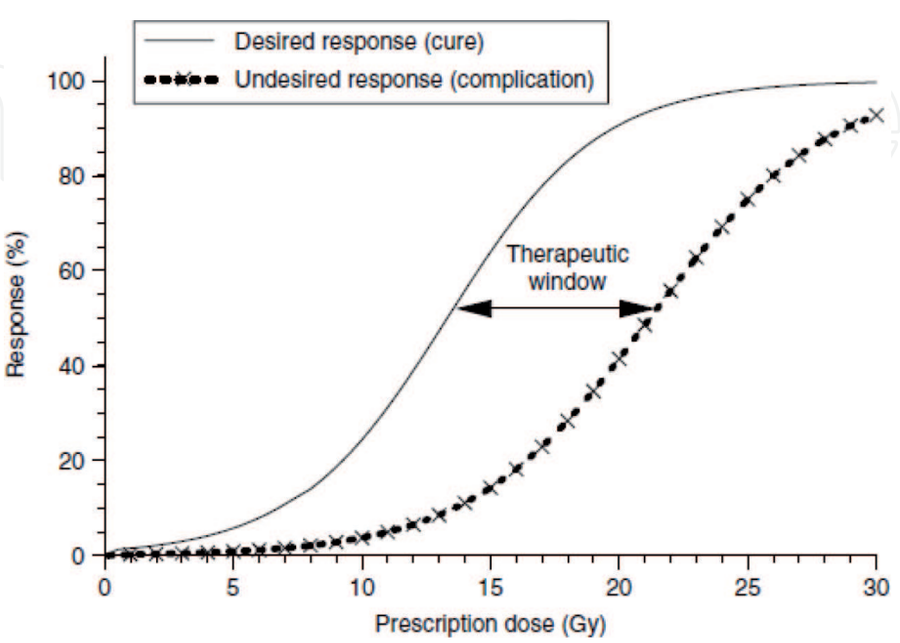
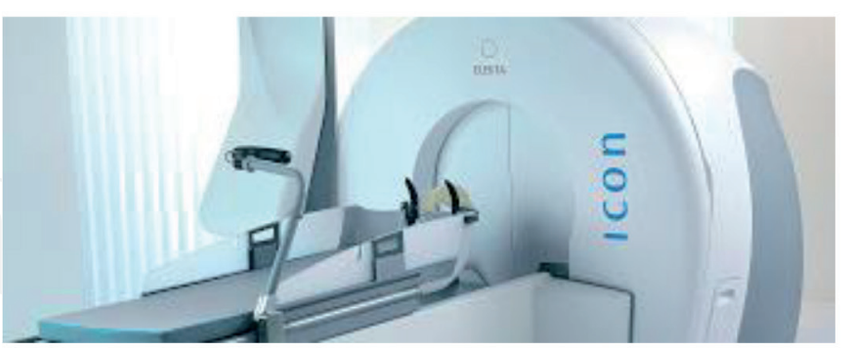


Figure 3.
Paired sigmoid dose–response curves for both desired response and complications.

(a)

(b)



(c)

Figure 4.
Models of radiosurgery system in Hong Kong (a) LINAC in our centre (b) CyberKnife in private hospital (c) Gamma Knife Icon in private hospital.

7. Patient selection

The practice of radiosurgery is guided by the treatment purposes, the nature and extent of the lesion, proximity of the lesion to critical organs at risk and patient factors such as general condition, comorbidities and symptoms. In our centre, potential candidates for consideration of radiosurgery for treatment of meningiomas will all be discussed and reviewed in regular multi-disciplinary team meeting. The whole radiosurgery team includes neurosurgeon, clinical

oncologist, radiation physicist and nurse as case manager. The following are considerable factors:

1. Patient factors – age, pre-morbid status, presenting symptoms or incidental finding, any past history of head and neck radiation

2. Tumor factors – size, number, location, relationship to organ-at-risk (OAR) e.g. optic nerve, optic chiasm, retina, brainstem, hippocampus, cochlea, any tumor growth during observation period [20]

In general, meningioma with diameter >3 cm with deteriorating clinical condition will be suggested to consider surgical excision instead of radiosurgery.

8. Treatment outcome

8.1 Gamma Knife vs. LINAC radiosurgery

Gamma Knife Radiosurgery was one of the most popular treatment modalities in centres worldwide. Professor Douglas Kondziolka in Pittsburgh had an early study on 946 patients between September 1987 and December 2004. The actuarial tumor control rates was 93% at 5 years and 10 years for benign types, and 83 +/−7% in 5 years and 72+/−10% for atypical and malignant types. Adverse radiation effect ranged from 5.7 to 16% [21]. Outcome of gamma knife radiosurgery of meningioma in 10 years were reviewed by Lippitz et al. 86 Swedish patients were included between March 1991 and May 2001. Totally 130 tumors were treated in 115 treatment sessions. Local tumor control was achieved in 87.8% with recurrence adjacent but outside the initial radiation field was found in 15.1% of patients. A significant lower rate of in-field local recurrences was seen in meningiomas treated with a prescription dose of >13.4 Gy (7.1% vs. 24%, p=0.02) [13]. Seo et al. had another review on 424 patient after Gamm Knife Radiosurgey from 1998 to 2010. The median tumor volume was 4.35 ml and the median marginal dose was 14 Gy. The actuarial tumor control rates were 91.7% at 5 years and 78.9% at 10 years [22]. Morever, Jang et al. showed overall tumor control rate of 95% with 15% peritumoral oedema in 628 pateints from January 2008 to November 2012, whom had received Gamma Knife Radiosurgery with maximal dosage 27.8 Gy and marginal dosage 13.9 Gy [17].

There are numbers of published papers from centres employing LINAC Radiosurgery in treatment of meningiomas with promising treatment outcome. UCLA group had a review of their early results in using LINAC system in treatment of 161 patients between May 1991 and July 2003. SRS with peripherial dose of 12–22 Gy (mean 15 Gy) was given to 26 lesions and SRT with dose ranged from 23 to 54 Gy (mean 48 Gy) was given to 7 cases. Tumor control rate was 92.3% in SRS group and 100% in SRT group, with 2 patients in SRS group suffered from worsening of neurological deficit [23]. Gallego et al. reported the results in using of LINAC Radiosurgery for treatment of 82 patients with cavernous sinus meningioma from 1992 to 2005. The mean volume of tumor was 17.96 ± 13.67 cm^3. Tumor volume reduced in 74.4% and remained stable in 14.6% [14]. Kaul et al. in Germany had retrospective review of 297 patients with LINAC Radiosurgery. The overall progression free survival was 92.3% at 3 years, 87% at 5 years and 84.1% at 10 years [16].

8.2 SRS vs. SRT

There is always debate on the indications or effectiveness of single fraction therapy in SRS or multiple-fraction therapy in SRT [15]. Huang et al. had a retrospective review of 228 patients with 245 tumors treated with radiosurgery between March 2006 and June 2017 using LINAC radiosurgery using Novalis system. 147 (64.5%) patients were SRS group with total dose of 12–16 Gy in one fraction as treatment protocol and 81 (35.5%) were SRT group with 7 Gy/fraction/day for three consecutive days to 21 Gy as total dose. The actuarial local control rate between two groups was not statistically significant during the total 10-year follow-up period (96.86% vs. 100%, p=0.175, in 2-year, 94.76% vs. 97.56%, p=0.373, in 5-year, 74.4% vs. 91.46%, p=0.204, in 10-year), and with comparable radiation-related side effects [24]. Wegner et al. from Pittsburgh also had a review on 56 patients with either SRS or SRT for meningioma treatment from 2008 to 2017. They concluded that fractionation had improved local control compared with single session (91% vs. 80% at 2 years, p=0.009) with minimal radiation-related toxicity [18].

Hypofractationated therapy by CyberKnife in meningioma treatment was reviewed by French group. Meniai-Merzouki et al. collected 126 patients with 136 meningiomas undergone treatment between December 2008 and June 2016 with median prescription dose of 25 Gy (12–40) in a 5 median fractions (3–10). They showed that the subgroup with more fractions (25–40 Gy in 5–10 fractions) had significant higher progression free survival that the subgroup with less fractions (21–23 Gy in 3 fractions), and only 2% of patients experienced radionecrosis at 24 months [25]. Di Franco et al. reviewed the treatment outcome of stereotactic radiosurgery and fractionated stereotactic radiotherapy with CyberKnife from January 2013 to April 2017. They achieved 100% local control for 28 patients at 12 months, 89% local control for 19 patients at 24 months and 9 patients at 36 months [26]. Smith et al. also reported 100% crude local control rate for large meningiomas with mean treatment volume 14.7 cm^3 (range 0.79–64.5 cm^3) with hypofractionated CyberKnife with dose of 22.5–30 Gy in five fractions [27]. Study of Oermann et al. in 38 patients treated with five-fraction CyberKnife showed similar response rate to SRS but have low peritumoral oedema around 13.2% [28]. Other centres employ fractionation in terms of 1–5 fractions. Bria had treated 73 patients with median volume of 5.54 cm^3. 60 patients had WHO grade I, 11 patients had WHO grade II and 2 patients had WHO grade III. Treatment median dose was 17.5 Gy with median of three fractions. The Actuarial local control at one year was 95% in WHO grade I, 71% in WHO grade II and 0% in WHO grade III. There was no acute significant toxicity and only one late toxicity noticed [29].

Fractionated treatment is also getting its popularity in centers using Gamma knife, particularly after the introduction of the sixth versions of Leksell Gamma Knife System, ICON®. In a retrospective review of 70 patients with large-volume meningiomas (>10 cm^3) that had undergone gamma knife treatment by Han et al., the single session group having 42 patients with median tumor volume 15.2 cm^3 (range 10.3–48.3 cm^3) and median prescription dose of 12 Gy (range 8–14 Gy) was compared with fractionated group having 28 patients with median tumor volume 21 cm^3 (range 10.2–54.7^3) and median prescription dose of 7.5 Gy in 2 fractions (range 5–8 Gy), 6 Gy in 3 fractions (range 5–6.5 Gy) and 4.5 Gy in 4 fractions. The fractionated group had higher progression free survival rate at 5 yars (92.9% vs. 88.1%) with lower complication rate (7.1% vs. 33.3%) compared with patients with single session treatment [30]. Another smaller series by Park et al. showed satisfactory tumor control after fractationated Gamma Knife radiosurgery with functional preservation for large skull base meningiomas in 23 patients with mean volume of tumors of 21.1+/−15.63 cm^3 (range 10.09–71.42) [31].

Meta-analysis study by Fatima et al. in 2019 had reviewed a total of 1736 patients from 12 retrospective studies. Treatment modalities included Gamma Knife surgery, linear accelerator and CyberKnife. Results showed SRT group had better radiographic tumor control, progression-free survival at 4–10 years, with significantly lower risk of clinical neurological deterioration during their follow-up (OR 2.07, 95% CI 1.06–4.06, p=0.03) and of immediate symptomatic oedema (OR 4.58, 95% CI 1.67–12.56, p=0.003) [32].

Regarding the radiation-induced oedema after radiosurgery, Milano et al. had reviewed 26 studies from 1998 to 2017. Symptomatic oedema was reported in 5–43% of patients among all oedema in 28–50%. The average time to oedema onset time ranged from around 3 to 9 months. Possible factors correlated with radiation-induced oedema included greater tumor margin and/or maximum dose, greater tumor size and/or volum, non-base of skull location particularly parasagittal, no prior resection for meningioma, and presence of pretreatment oedema [33].

9. Radiosurgery in special circumstances

9.1 Meningioma eligible to microsurgery

Microsurgery is the first choice if therapy is indicated and aims at radically removing the tumor if possible. However, the benefits of surgery have to be seriously balanced against the possible interventional related anesthetic risks. Also some patients, though having meningiomas eligible to surgery, refuse surgery due to personal reason. Ruge et al. analyzed 188 patients with 218 meningiomas that undergone LINAC radiosurgery with median tumor volume 4.2 cm^3 (0.1–22) and mean marginal radiation 13+/−3.1 Gy. The estimated 2-, 5-, 10- and 15-year regional recurrence rates were 1.5%, 3.0%, 6.6% and 6.6%, which provides reliable long-term local tumor control with low rates of mild morbidity [34].

9.2 Meningioma close to optical apparatus and skull base vital structures

Management of meningioma at anterior skull base close or adhered to optical apparatus is always challenging in radiosurgery considerations (**Figure 5**).

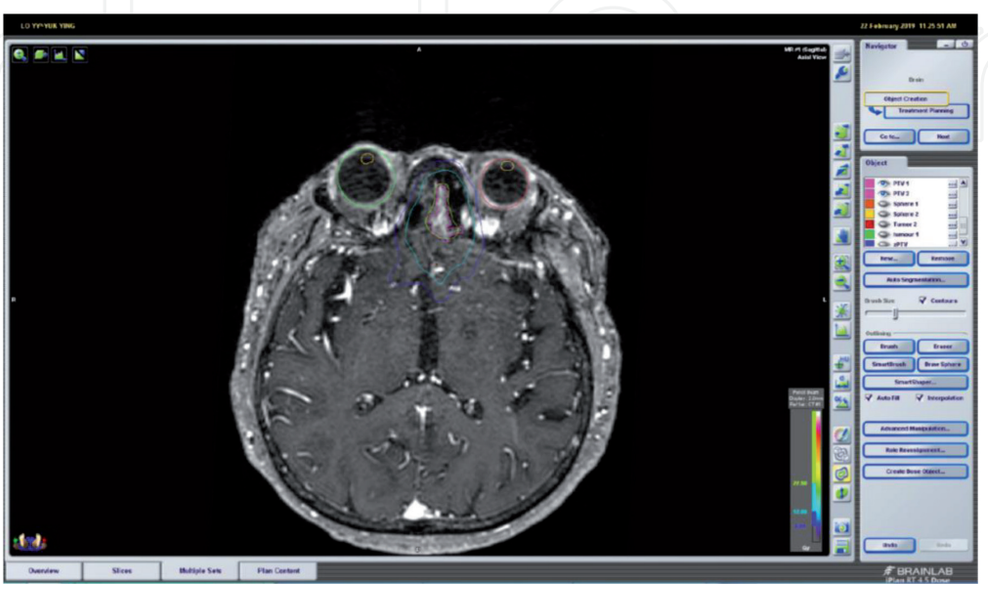


Figure 5.
Treatment of anterior cranial fossa meningioma near bilateral optic nerves using LINAC 27.5 Gy in 5 fractions in our centre.

Tumor control has to be balanced by risk of high-dose radiation exposure leading to optic neuritis and radiation-induced neuropathy. As mentioned, vision preservation can be achieved by confounding the maximum radiation exposure of optic pathway to 8–10 Gy per session. Su et al. in Taiwan treated 4 patients with large tumor volume by volume-staged Gamma Knife Radiosurgery. In stage I, the treatment was focused on the basal part of tumor (mean volume 13.2 cm^3, range 3.9–54.7 cm^3) with marginal dose of 13.5 Gy (range 12–15 Gy), followed by smaller upper portion of tumor close to the optical apparatus (mean volume 4.3, range 1.5–16.2 cm^3) with marginal dose of 9 Gy (range 9–10 Gy) in stage II. 34–46% tumor reduction was observed during the median follow-up period of 100.5 months with no new visual deterioration [35]. A study from Williams et al. on parasellar meningiomas treatment with Gamm Knife Radiosurgery had reviewed the tumor control together with any radiation induced neurological deficit. Totally 138 patients were reviewed from 1989 to 2006. The mean radiation volume was 7.5 cm^3 (range 0.2–54.8 cm^3). Radiographic progression free suvivial at 5 and 10 years were 95.4% and 69%. Only 4% of their patients had radiation related optic neuropathy [36].

Starke et al. had also similar promising findings in Gamma Knife Radiosurgery treatment for other skull base meningiomas. Around 10% of their cases had deterioration in neurological symptoms [37]. His group in another review specifically focus on posterior fossa cases in 152 patients. The radiographic progression free survival at 3, 5, and 10 years to b 98%, 96%, and 78% respectively. 9% of study patients showed deterioration in symptom. They concluded the predicative factors of new or worsening symptoms were clival or petrous-based location [38]. In Austria, Kreil et al. had a review of 200 patients with skull base meningimas with a follow up of 5–12 years. The tumor volume ranged from 0.38 to 89.8 cm^3 (median 6.5 cm^3), and the median dose was 12 Gy (7–25 Gy). They achieved actuarial progression free survival rate of 98.5% at 5 years and 97.2% at 10 years with only 1% radiation induced oedema and 4.5% neurological deterioration [39]. The promising tumor control with low new neurological deficit in Gamma Knife Radiosurgery can also be demonstrated in centres using LINAC system. Villavicencio et al. in Brigham and Women's Hospital had reviewed 56 patients with treatment for skull base meningiomas. The minimal peripheral dose ranged from 12 to 18.5 Gy (mean 15 Gy). The actuarial progression free rate was 95% in median follow-up of 26 months (range 6–66 months) [40].

In cases where skull base meningiomas had extension into the internal auditory meatus, the concern will be more towards the facial nerve function and hearing preservation after radiation. Pollock et al. had reviewed 16 patients from 1992 to 2002. The median tumor margin dose was 15 Gy. They achieved 63% tumor reduction in size at medial follow-up period of 36 months. No facial nerve palsy was reported, and 1 patient had worsened facial sensation. The actuarial incidences of hearing preservation was 93% at 1 year, 84% at 2 years and 42% at 5 years [41].

9.3 Cavernous sinus meningioma

Meningiomas at cavernous sinus are cases always have dilemma with clinical management due to its complex anatomy and its specific location in the antero-lateral skull base (**Figure 6**). Despite the advancement in microscopic and endoscopic surgical technique, still a complete radical excision with minimal anantomo-functional preservation remains very challenging. UCLA De Salles group had proposed a radiosurgery grading system for this specific group of tumor (**Table 5**) [42]. Pittsburgh group reviewed 79 patients with cavernous sinus meningioma between October 1987 and December 1995. The median marginal tumor dose was 15 Gy. The achieved actuarial tumor control rate was 95+/−2.8% at 5 years an 88.2+/−7% at 12 years with 12.7% patients experienced adverse radiation effects [43].

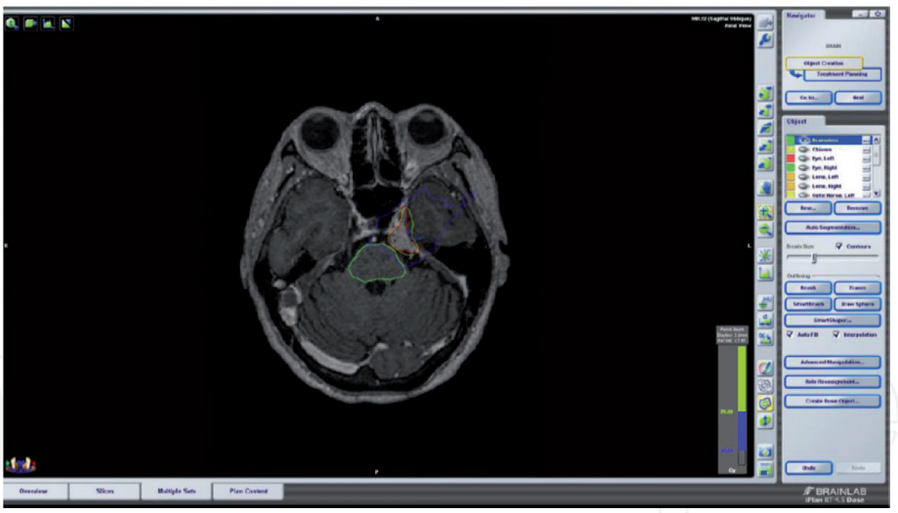


Figure 6.
Meningioma involving cavernous sinus and petrosal apex was treated by LINAC stereotactic radiotherapy using 25 Gy in 5 fractions in our centre.

Grade	Meningioma radiological aspect in MRI T1 contrast images
I	Confined to the cavernous sinus
II	Involvement of the petroclival region without brainstem compression
III	Extension to and compression of the optic nerve, chiasm or tract
IV	Involvement of the petroclival region with compression of brainstem
V	Extensive involvement of both cavernous sinus

Table 5.
Radiosurgery grading system for cavernous sinus meningiomas by UCLA.

Takanashi had reviewed 101 skull base meningioma patients with Gamma Knife Radiosurgery performed from 1991 to 2003. Among those cases, 38 cases are cavernous sinus in location with mean dose delivered to the tumor 14.5 to 15.2 Gy. The overall tumor control rate were 95.5% in the mean follow-up of 51.9 months (range 6–144 months) [44]. Fariselli et al. had proposed a multidisciplinary treatment algorithm involving microsurgery and stereotactic radiosurgery [45]:

1. Small and asymptomatic intracavernous meningiomas – for observation first, radiosurgery in case of progression

2. Larger meningiomas with lateral wall of cavernous sinus involvement – microsurgical resection

3. Large extra-intracavernous meningiomas – combined approach with resection of extracavernous part, followed by radiosurgery for residual tumor part

4. Pre-operative radiosurgery for tumor devascularization is still controversial

9.4 Large tumor volume

The consensus of tumor size in consideration of radiosurgery for meningioma is generally around 30–35 mm in diameter. Tumor volume greater than

8 cm^3 is believed to have poor outcome compared. Starke et al. retrospectively reviewed the Gamma Knife Radiosurgery outcome of 75 patients with mean follow-up of 6.5 years (range 0.5–21 years) whom had tumor volume more than 8 cm^3. The actuarial rates of progression-free survival were 90.3% at 3 years, 88.6% at 5 years and 77.2% at 10 years. Factors associated with tumor progression included [46]:

1. Presentation with any cranial nerve deficit from III to VI

2. History of radiotherapy

3. Tumor volume greater than 14 cm^3

10. Local experience

Our centre, the Queen Elizabeth Hospital in Hong Kong, have conducted a 10-year review of the patients who received LINAC-based SRS or SRT for intracranial meningioma from July, 2009 to June, 2019. We investigated the tumor control rate in the 1-, 2- and 5-years intervals. Tumor control was defined as a static or shrunken tumor. Functional outcome was determined by modified Rankin scale (mRS).

40 patients were included with 45 tumors irradiated. 42% of the tumors were parasagittal or parafalcine, followed by 20% petrous or petroclival and 18% convexity. 48% of the tumors were WHO grade I while 52% were WHO grade II. In 48% of the cases, Simpson I/II excision was achieved while in the remainder, Simpson III/IV was achieved. In 27% of the tumors, radiosurgery were done as primary treatment while 73% as postoperative adjuvant treatment.

In the recent 25 cases, we switched from frame-based to frameless radiosurgery, using the LINAC system. Mean radiation dose was 22.4Gy (SD: 7.2). Mean target volume was 5.0 (SD: 6.1) while mean treatment volume was 6.0 (SD: 6.8), with mean treatment-target ratio being 1.8 (SD: 1.0). Mean coverage was 96.3%. Mean conformity index was 1.7 (SD: 1.0).

Tumor control rate was achieved in 82%, 79% and 66% in 1-, 2- and 5-years intervals respectively. More than 80% patients enjoyed mRS 0–1 over the study period. SRS was associated with better tumor control in the 1- and 2-years interval compared with SRT. However, it was confounded by smaller target volume. Other teletherapy metrics were found to have no significant association with the outcome.

11% of the patients required reoperation, while 7% developed radionecrosis or radiation-induced edema. Multiple meningiomata was associated with poor tumor control in 5 years (20% vs. 82%, $p=0.025$). It may reflect the underlying pathology of the entire intracranial meninges, making local irradiation ineffective in overall intracranial control. Parasagittal or parafalcine locations predicted reoperation (21% vs. 0%, $p=0.026$). We observed that these tumors more likely recurred and caused symptoms which required surgical decompression. On the other hand, tumors inside the superior sagittal sinus were often not removed in operation. The residual tumors may progress, with nurture by the surrounding vasculature. Moreover, sometimes there is technical difficulty to plan effective radiation dose to cover the adequate dura origin in this location.

Overall, neither histology grading nor the extent of resection predicted tumor control rate when they were analyzed as ordinal scale in our study.

11. International recommendations

International Stereotactic Radiosurgery Society (ISRS) had a systemic review on stereotactic radiosurgery for intracranial noncavernous sinus benign meningioma in 2020. Totally 2844 relevant studies from January 1964 to April 2018 were reviewed. The 10-year local control rate ranged from 71–100%, and the 10-year progression-free-survival rate varied from 55–97%, based on prescription dose 12 Gy to 15 Gy. ISRS had summarized the following recommendations based on this review [47]:

11.1 Level II evidence

1. SRS may be proposed as a primary treatment modality for an asymptomatic or mildly symptomatic meningioma, and should be considered when a complete surgical excision cannot be achieved or is not amenable

2. After surgery, when a residual tumor is not evident or is minimal, a wait-and -scan approach appears to be reasonable with a regular radiological follow-up. At the time of recurrence or progression, SRS should be taken into consideration as a treatment modality. Some studies suggest that the recurrence/progression rate is lower when SRS is delivered as the primary treatment as compared to an adjuvant treatment and this remains to be confirmed

11.2 Level III evidence

1. Single-fraction SRS with a dose of 12 to 15 Gy appears to be sufficient to manage benign intracranial meningioma. A prescription dose of at least 14 Gy would be advisable

2. Hypofractionated stereotactic radiotherapy (HSRT) may be considered for the treatment of large or/and critically located meningioma. Optimal practice has yet to be defined, however, 25 Gy in 5 fractions is a common approach

3. SRS generally entails a low risk of neurological deterioration. Patients may experience a clinical improvement without tumor shrinkage

ISRS also had published a review of 49 full-text articles from January 1963 to December 2014. The 5-year progression-free survival (PFS) rates was 86–99% and 10-year PFS was 69–97%. The followings are recommendations for management of cavernous sinus (CS) meningioma in level III evidence [48]:

1. SRS/SRT is recommended as a primary/upfront treatment option for an asymptomatic, or mildly symptomatic CS meningioma.

2. Resection should be considered for the treatment of larger and symptomatic CS meningioma in patients both receptive to, and medically eligible, for open surgery

3. SRS/SRT delivered to a CS meningioma has a low risk of complications; most cranial nerve functions are preserved or improved due to tumor shrinkage, and carotid artery stenosis after SRS is rare

4. When no residual tumor is observed, or only a small tumor lining on dura of the CS exists postoperatively, serial neuroimaging studies is not unreasonable. At the time of recurrence or progression of residual tumor, SRS/SRT should be considered

5. In patients with a CS meningioma that has rapidly and substantially recurred after prior treatment, a subtotal surgical resection or biopsy may b considered. More aggressive features of the tumor (transformation of the tumor from WHO grade I to a higher grade) should be ruled out. These tumors have a predilection for progression and postoperative SRS/SRT with a higher dose should be strongly considered

6. The technique for SRS or SRT delivery will depend upon the tumor histology, tumor volume and proximity of the tumor to adjacent critical structures (e.g. the optic chiasm). SRS using single session marginal doses of 11 to 16 Gy offers a local tumor control rate of 90% or higher at 5 year post-SRS

National Comprehensive Cancer Network (NCCN) also had proposed guidelines for CNS tumors. Radiotherapy is recommended in the following clinical scenarios with Level 2A evidence [49]:

1. Small (<30 mm) asymptomatic tumors at presentation, if grade II and subtotally resected or grade III regardless of resection volume, and grade I when sub-totally resected with "potential" symptom

2. Large (>30 mm) asymptomatic tumors if grade III, and if grade II or incompletely resected grade I.

3. Following surgery for any grade III and should be considered for any grade II tumors or large (>30 mm) incompletely resected grade I.

4. Surgically inaccessible tumors or surgically contraindicated patients

12. Future directions

Planning of radiosurgery in meningiomas usually concentrated on the main tumor bulk as overall treatment volume. Lovo et al. recently try to include tumor dural tails of 143 patients with histologically confirmed or radiologically assumed WHO Grade I meningiomas in the radiosurgery treatment plans. All the final prescription isodose line in treatment plans were focused on tumor coverage and measurement of the dose received at maximum distance (MaxDis) of the dural tail and the midpoint distance (MPDis) from the prescription isodose line to the maximum dural tail distance. The dural tail of meningiomas were identified in at least three consecutive sections of the MRI T1-weighted sequence with contrast in 1 mm slice thickness. Tumor control was achieved in 96% of patients [50].

13. Conclusion

Intracranial meningiomas are one of the most common neoplasm in clinical practice. Management should be based on patient's factors and tumor factors. Multi-disciplinary approach in treatment modalities decision is essential to achieve the best treatment outcome. Use of Radiosurgery in terms of Gamma Knife, LINAC or CyberKnife, either in single fraction or multiple fractions, should be subjected to individual centre's preference and experience.

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