

LINAC Based Radiosurgery and Radiotherapy for Neurosurgical Diseases: What have we learnt so far

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SUMMARY

Background: Stereotactic radiosurgery uses a single fraction high dose radiation while stereotactic radiotherapy uses multifractionated lower dose focused radiation.

Materials and Methods: Radiosurgery used rigid CRW head frame while stereotactic radiotherapy utilized GTC or HNL relocatable frames. Stereotactic planning and radiation involved Radionics X-plan and LINAC system.

Results: Since December 2001, we have treated 83 lesions from 77 patients using either radiosurgery or fractionated stereotactic radiotherapy. Eighty six percent (86%) of our treated lesions showed favourable outcomes with median follow-up of 32 months (0-7 years).

Conclusions: Our lessons from LINAC precision radiation therapy uphold its value as a promising and effective tool in treating a range of nervous system pathologies.

KEY WORDS:

Linear accelerator, Radiosurgery, Stereotactic radiotherapy, Brain tumours, Arteriovenous malformation

INTRODUCTION

In the 1980s, linear accelerators (LINAC) were introduced as a tool for precision radiation therapy¹. Whilst stereotactic radiosurgery (SRS) uses a single fraction high radiation dose, stereotactic radiotherapy (SRT) uses multifractionated lower dose focused radiation on a stereotactic defined target. The hallmark of radiosurgery is the sharp dose gradient of radiation at the treatment field edges, which markedly reduces the dose of radiation to the surrounding normal brain tissue. On the other hand, fractionated radiotherapy relies on differences in radio-sensitivity and repair capability between normal and neoplastic cells. In general, SRT is helpful in cases in which LINAC radiosurgery has limitations, such as large tumours or those that arise near critical structures, like the optic chiasm or brainstem. We had treated 83 lesions with either SRS or SRT since December 2001. This is our early experience using LINAC radiosurgery and stereotactic radiotherapy to treat certain neurosurgical diseases.

MATERIALS AND METHODS

The stereotactic frames that we used for precision radiation therapy were Crown-Robert-Well (CRW), Gills-Thomas-Cosman (GTC) and head and neck localizer (HNL) accessories (HNL Accessories-Radionics. Inc). Radiosurgery was given by using a rigid CRW head frame while stereotactic radiotherapy utilized GTC or HNL relocatable frames. CT and MRI fusion for tumours or CT and selective cerebral angiography fusion for AVM was used for treatment planning. Stereotactic planning was performed on Radionics X-plan 2.2. Some planning and delivery system used the multileaf collimator (MLC) technology which allowed fixed and dynamic shaping of the radiation field. The radiation therapy was given via LINAC X-Knife and a combination of radionics cones for radiosurgery. In general, radiosurgery was given to lesions less than 4 cm in diameter, more than 2 mm from the optic chiasm and nerves, and lesions which did not abut the brainstem. Stereotactic radiotherapy was given to those lesions which did not fulfill the SRS criteria. The type of lesions in which SRS was used were arteriovenous malformations (AVMs), non-basal meningiomas, vestibular schwannomas, recurrent pituitary adenomas, low grade gliomas, high grade gliomas, metastases and haemangioblastoma. Stereotactic radiotherapy was used in other lesions in which radiosurgery was considered dangerous or inappropriate. Such instances include brainstem lesions, basal or skull base meningiomas which often non-spherical and diffused in shape, optic nerve lesion, vestibular schwannomas which abutting the brainstem, recurrent pituitary adenomas that lie close to the optic pathways, as well as pineal region tumours, lymphoma, clival chordoma and large residual tumors after surgery. In all treated cases, a series of follow-up imaging were acquired every 6 to 12 months, along with the computation of the treated volume. The volumes of the lesions were compared before and after the therapy. In addition to the radiological response, any clinical complications were also noted on our regular follow-up.

RESULTS

Since December 2001, 83 either benign or malignant lesions were treated, using either SRS or SRT at Universiti Sains Malaysia Kampus Kesihatan Hospital. Fifty one lesions received single fraction or stereotactic radiosurgery and 32

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lesions were treated with fractionated stereotactic radiotherapy. There were 42 males and 35 females with their mean age of 39 years old [ranged 11 - 77]. Eighty six percent (86%) of our treated lesions showed growth restraint or total obliteration, preventing them from causing new symptoms with median follow-up duration of 32 months (0-7 years). However, there was a 14% complication rate arising from this modality of treatment. The most disastrous complication (4%) involved benign tumours which changed to higher grade tumours after 4 to 5 years of receiving radiation therapy. These patients died within months of their final diagnosis.

Table one tabulates our irradiated cases according to histological diagnosis, mode of radiation therapy and their dosages and the lesional outcome. Favorable responses were seen in patients harboring brain AVMs, recurrent pituitary adenomas, skull base meningiomas, vestibular schwannoma, pineal tumors, clival chordoma, craniopharyngioma, brain metastases, low grade focal brainstem gliomas, cerebral lymphoma, haemangioblastoma and cervical schwannoma. Mixed response were noted in cases of benign tumours, low grade gliomas and non-basal meningiomas. Two irradiated low grade glioma patients died from malignant change to GBM and one case of WHO grade 1 non-basal meningioma died from anaplastic meningioma (WHO grade 3) within 5 years of SRT. All three cases who died from high grade tumors were initially irradiated for low grade tumors.

A) Analysis based on pathology

Fifteen non-basal meningiomas were treated, SRS was utilized in 8 and SRT in another 7 meningiomas. There were 11 non-basal meningiomas which showed good response, either decreased or static in volume. However, 3 non-basal meningiomas showed poor response towards SRT which appeared larger after the therapy and one patient with multicentric meningiomas had new neurological deficits after cerebellopontine angle (CPA) meningioma radiosurgery. The basal or skull base (cavernous and sphenoidal) meningiomas which were treated with SRT showed good response with reduction in tumoral volume.

For our nine vestibular schwannoma cases, SRS was used in 7 lesions and SRT in 2 lesions. All of them (except one who lost to follow-up) showed a good response towards radiation therapy. However, complications arose in two lesions; tumoral expansion and tumoral bleed, although these two lesions gave no adverse effects to the patients and were treated conservatively. Nonetheless, there was one patient who had SRS of 19 Gy to the tumour (90% isodose line) who experienced a progressive facial nerve palsy.

A total of 22 AVMs cases were treated. All of them were treated with LINAC-based radiosurgery except for one brainstem AVM which was treated with SRT after presenting with symptomatic AVM bleed. Eight AVMs were obliterated. Three AVMs decreased in nidus density and four newly treated AVMs remained static and still under our regular follow-up. The posterior fossa AVMs appeared to be difficult to treat. We had two large posterior fossa AVMs which recurred after combination of therapy using radiosurgery and embolisation.

Eight from our 9 treated recurrent pituitary adenomas (one lost to follow-up) showed a favorable response to the radiation therapy. None of them increased in volume or had resurgence of abnormal hormonal levels. For other lesions, we had favorable outcomes in term of local tumoural control. Lesions of brainstem gliomas which were focal and small (low grade features), cerebral metastases, pineal germinoma, clival chordoma, cerebral lymphomas, craniopharyngiomas, cerebellar haemangioblastomas and two extracranial cervical schwannomas showed either total obliteration, became reduced in their volume or arrested in their growth. However, three low grade gliomas (one received SRS and two received SRT) showed poor response towards radiation therapy. Two patients died because the initial low grade gliomas transformed into higher grade gliomas 4 to 5 years after receiving SRT. In addition, one patient who had SRS for low grade tumor (DNET), developed a new secondary tumor (oligodendroglioma) with a marked cystic lesion causing severe mass effect. Types of therapy and doses administered to different types of pathology are tabulated in Table one. Table two summarizes the complications that we experienced.

B) Case Example of Higher Grade Tumour After SRT

A 37-year old man was diagnosed to have symptomatic right frontal cystic low grade glioma (Figure 1A). He had surgical resection of the tumor and an adjuvant SRT (50 Gy) was given. Three years after that, he died from high grade gliomas, glioblastoma multiforme (Figure 1B).

DISCUSSION

Stereotactic radiotherapy and radiosurgery are two methods of precision radiation therapy that focuses the radiation given to the stereotactically defined targeted area. It offers an alternative option of therapy for patients with selected range of intracranial pathologies. Precision radiation therapy has been regarded as a non-invasive method of therapy and has been widely used for brain tumours and AVMs. Its non-invasive nature appeals to many of these patients instead of having the open surgery. Neurosurgeons prefer precision radiation therapy, on selected cases, especially for a deep seated lesion. Nevertheless, there are possible complications which may arise from this mode of radiation therapy, such as radionecrosis, development of a secondary or higher grade tumor, endocrinopathy, new neurological deficits and neurocognitive sequelae. Salvati *et al.* recently described a 1.3% rate of radiation-associated glioblastoma multiforme within an observation period of 7 years². Shorter latency period of developing secondary or higher grade tumors were previously reported by Kranzinger *et al.*³. They described high grade gliomas induced after 4 years of receiving radiation therapy for optic glioma and craniopharyngioma. The latency period of developing secondary or high grade tumors in our series appeared short too, between 3 to 5 years.

These high grade tumors (GBM and anaplastic meningioma) which were considered irradiation-induced secondary tumors, however, cannot be distinguished easily from late relapses with malignant transformation. However, certain features of these tumors point to likely their origin of radiation-induced as previously described by Cahan *et al.*⁴ and Donson *et al.*⁵; a) the tumor originates in the previously

Table I: Diagnosis, mode, dosage of radiation therapy and lesional outcomes. (Note: Lost F-up : Lost to follow-up).

Diagnosis	No. Of Lesions (SRS)	Mode of Radiation therapy				Outcome. (Median follow-up time of 32 months)					
		Radio-Surgery (Gy)	Dose Ranged radiotherapy. (SRT)	Fractionated 3D- (Gy)	Dose Ranged	obliterated	Decreased volume	Static	Increased volume.	dead	Lost F-up
1. Non-basal meningioma.	15	8	11-20	7	11.25-45	-	5 SRS 3 SRT	3 SRS,	3 SRT	1 SRT	-
2. Cavernous meningioma.	3	-	-	3	45-46	-	3 SRT	-	-	-	-
3. Sphenoidal meningioma	1	-	-	1	45	-	1 SRT	-	-	-	-
4. Optic nerve meningioma	1	-	-	1	46	-	-	-	-	-	1
5. Vestibular Schwannoma	9	7	14-19	2	24-25	-	4 SRS,	2 SRS	-	-	1
6. Arteriovenous Malformation (AVMs)	22	21	14-22.5	1	36	2 SRT 8 SRS	3 SRS	4 SRS	3 SRS	-	4
7. Recurrent Pituitary Adenoma	9	6	12-20	3	46	2 SRS	3 SRS, 2 SRT	1 SRS	-	-	1
8. Brainstem gliomas	2	-	-	2	45-50	-	2 SRT	-	-	-	-
9. Low grade gliomas	7	5	12-18	2	36-50	2 SRS	-	1 SRT	1 SRS	2 SRT	1
10. High grade gliomas	1	1	15	-	-	-	-	-	-	-	1
11. Metastases	3	2	12-14	1	30	-	2 SRS, 1 SRT	-	-	-	-
12. Pineal tumour-Germinoma.	4	-	-	4	25-56	4 SRT	-	-	-	-	-
13. Clival Chordoma	1	-	-	1	55	-	1 SRT	-	-	-	-
14. Lymphoma	1	-	-	1	10	-	-	-	-	-	1
15. Craniopharyngioma	1	-	-	1	55	-	1 SRT	-	-	-	-
16. Haemangioblastoma	1	1	20	-	-	-	-	1 SRS	-	-	-
19. Cervical Schwannoma	2	-	-	2	24	-	-	2 SRT	-	-	-
Total	83	51	-	32	-	12 SRS, 4 SRT (16 Lesions)	17 SRS, 13 SRT (30 Lesions)	11 SRS, 6 SRT (17 Lesions)	4 SRS, 3 SRT (7 Lesions)	3 SRT (3 patients)	(10 lesions)

Table II: The complications in patients who had precision radiation therapy in our series.

Type of lesions	Complications							
	Higher grade gliomas/ tumours	New tumour	New neurological deficits	Facial nerve palsy	Tumour expansion	Lesional bleed	Recurrent	Endocrinopathy
Low grade gliomas/tumors	2	1 (DNET-Oligo)						
Meningioma	1 (Non-basal)		1 (CPA)					
Vestibular Schwannoma				1	1 (at 6 months only)	1		
AVMs						1	2 (Posterior fossa)	
Pineal tumour								1

(Note: CPA: Cerebellopontine angle; DNET: Dysembryoplastic neuroepithelial tumor; Oligo: Oligodendroglioma WHO grade 2; Non-basal: Superficial, not skull base)

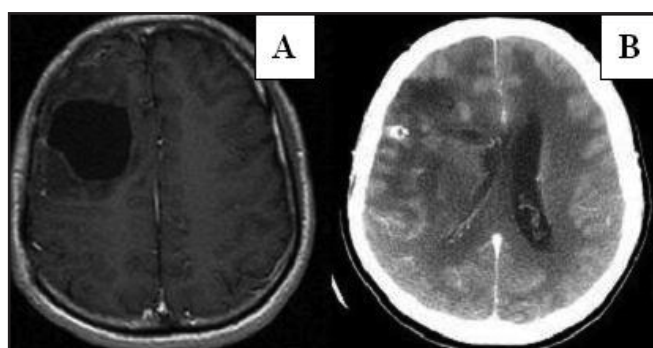


Fig. 1: A: The initial right frontal pilocystic astrocytoma on contrasted MRI. B: Features of high grade glioma (glioblastoma multiforme) developed 3 years after receiving stereotactic radiotherapy.

irradiated region; b) shorter latency periods and c) aggressive clinical course in irradiated-induced high grade tumors, which were fatal in our case series within few months after the final diagnosis.

Interestingly, all three cases who initially harbored low grade tumours and later died from higher grade tumors, had SRT rather than SRS. The dose spillage effect (volume outside prescribed dose) may play a role to cause normal brain cells turning into neoplastic cells. Loeffler *et al.*⁶ and Shamisa *et al.*⁷ had reported the importance of extension of radiation. There are persistent borders of radiation whereby the cells that received non lethal dose of radiation (normal or tumor cells) appeared capable of progressing toward malignant transformation by accumulating series of mutations. The application of relocatable immobilization systems like GTC

frame may have contributed to inaccuracy in our radiation targets and therefore leads to this dose spillage effect. For SRS, accuracy in radiation delivery is thought to be better than SRT. In our series, none of our SRS-treated low grade gliomas developed higher grade gliomas and interestingly, two of our SRS-treated low grade gliomas disappeared after the therapy. Furthermore, none of our SRS-treated brain AVM developed secondary tumor adjacent to the treated nidus volume. The precision attained in SRS planning and radiation delivery of these cases may have contributed to our success without causing unexpected complications. Nowadays, we prefer surgery as a first choice of therapy for symptomatic accessible low grade tumours in young patients. Residual low grade tumours were observed and the recurrences were treated with re-surgery rather than radiation therapy. For inaccessible or inoperable low grade tumors, either observation or symptomatic therapy is our first choice (especially in elderly). If they fulfill the criteria for SRS, radiosurgery may be an alternative mode of therapy to consider.

Other complications shown in Table two are tumoural expansion and bleeding for vestibular schwannomas. These complications had been previously reported by many authors^{8,9}. New neurological deficits are worrisome for patients with CPA tumors which lay close to the brainstem. In this situation, SRT is a preferred mode of therapy. Another difficult situation to handle is posterior fossa AVMs. We failed to eradicate two large posterior fossa AVMs by using radiosurgery and embolisation. Kelly *et al.*¹⁰ has reported better results with multimodality therapy: radiosurgery, embolisation and surgery in combating this type of AVMs. For these two large recurrent posterior fossa AVMs, our preference is still non-invasive methods; radiosurgery and embolisation.

CONCLUSIONS

LINAC precision radiation therapy is a good tool in neurosurgery to treat some CNS pathologies. Nonetheless, the neurosurgeons should be aware of the complications which can arise from this type of therapy. Those complications are preventable and could be minimised by selecting the right mode of precision radiation therapy and avoiding imprecision in radiation delivery.

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