Stereotactic Radiosurgery and Fractionated Stereotactic Radiotherapy: Background, Definitions, Applications

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Stereotactic radiosurgery has emerged in recent years as a key treatment technique for a number of intracranial lesions, whether malignant or benign. In this issue of *IMAJ*, Attia and colleagues present a review of this treatment modality in general, as well as of their own experience [1]. The group from Sheba Medical Center is to be commended for their pioneering role in the introduction of this technology to Israel. Other groups include our own at Hadassah-Hebrew University Hospital, where we inaugurated a stereotactic radiosurgery program in March 2004.

Based on our experience in Israel and earlier work in U.S. medical centers, as well as on literature in the field, we would like to discuss several terms and concepts that are relevant to radiosurgery and radiation therapy in general. We add a special focus on fractionated stereotactic radiotherapy, another valuable modality for treating various benign and malignant intracranial lesions. We also comment on the indications for radiosurgery and on treatment outcomes as presented by Attia et al. in their review.

Radiation therapy plays a crucial role in the management of a variety of benign and malignant intracranial tumors. The goal of radiotherapy is to deliver a therapeutic dose to all neoplastic or abnormal cells while preserving normal neural tissue [2]. The concept of protracted radiation treatment using a low dose or multiple small fractions was developed based on animal studies and clinical experience over the past 75 years [3]. Today conventional radiotherapy uses multiple fractions over a period of weeks to permit lesion obliteration, with minimal damage to normal tissue during and after the course of treatment. Typically, conventional radiotherapy delivers photons to a target area in the brain, including a margin surrounding the lesion, with dose falloff outside the target volume.

Stereotactic radiosurgery, a term introduced by Lars Leksell in 1951, refers to a single fraction of high dose irradiation delivered to a limited target volume of tissue with sharp dose falloff beyond the target. This technique was developed initially as a non-invasive approach for functional neurosurgical procedures, with radiation directed to targets only a few millimeters in diameter. Leksell believed that interruption of neural pathways might be beneficial in treating epilepsy and Parkinson disease. Today, target location in SRS is defined by image-guided stereotaxy. A large single fraction is delivered by means of multiple, collimated beams. This large dose of irradiation is sufficient to produce focal, irreparable damage in all cells within the high dose target volume. Target destruction is a result of direct cell damage and vascular occlusion, eventually resulting in focal necrosis.

Stereotactic radiosurgery was conceived to be more analogous to conventional surgery than to conventional radiotherapy. As with other neurosurgical procedures, it is precisely localized. Ablation is limited to a well-defined volume with steep dose falloff in adjacent tissue. In order to achieve this precise localization, SRS has historically been limited to small focal targets. As the target volume becomes larger, the amount of normal brain receiving an elevated dose of irradiation also increases. The observations of Kjellberg et al. [4] and the integrated logistic formula of Flickinger and team [5] define an inverse relationship between tolerable dose and the target volume for single fraction irradiation. This consideration of normal tissue tolerance effectively limits radiosurgery for tumor control to targets with a maximum diameter of 3–4 cm. Larger tumors have traditionally been treated with conventional fractionated radiotherapy. Invasive frames, with pins that penetrate the scalp and rest on the skull, provide patient immobilization and target localization for SRS.

Fractionated stereotactic radiotherapy is a combination of SRS and conventional fractionated radiotherapy. Like conventional radiation treatment, FSR involves small doses given daily and, like SRS, it involves small volumes of tissue with relatively sharp dose gradients. FSR is particularly suitable for lesions located in or in close proximity to critical anatomic structures, like the optic nerves or the optic chiasm, for which treatment with a single high dose fraction of SRS would result in unacceptable risk of severe long-term damage due to the radiobiological sensitivity of late responsive tissues to large fractions of ionizing radiation. As a result of the relative sparing of normal brain parenchyma surrounding the lesion in comparison to conventional three-dimensional radiotherapy, FSR is also an attractive treatment option for large lesions such as skull base me-

SRS = stereotactic radiosurgery
FSR = fractionated stereotactic radiotherapy

ningiomas [6] and large vestibular schwannomas [7]. For these indications, fractionation permits radiobiological and spatial selectivity – favoring a biological response in target tissue by the precise stereotactic delivery of more radiation dose to the lesion than to the adjacent brain. Craniopharyngiomas and large recurrent pituitary adenomas, which are generally located near the optic apparatus, the pituitary gland, and the hypothalamus, are therefore also excellent candidates for treatment with FSR [8]. Large skull-base metastases in non-operable patients, low grade [9,10] and high grade gliomas [11], large arteriovenous malformations [12], and AVMs in eloquent areas have also been treated with FSR. Although additional follow-up is needed to weigh the long-term efficacy of FSR in treating these lesions, early results are encouraging. Unlike SRS, FSR is usually possible with the use of a non-invasive relocatable frame that immobilizes the patient and localizes the target volume in a reproducible manner.

The accuracy of SRS and FSR largely depends on imaging. High resolution magnetic resonance imaging (we use 3D T1+GD with 0.5 mm slice thickness) is used to provide detailed anatomic mapping with adequate image resolution for defining critical structures such as the optic pathway, and for target volume definition. MRI, however, may lack the spatial fidelity of computed tomography because it is subject to distortion artifact. In addition, radiation dosimetry is based on electron density, which can only be obtained from CT image data. For those two reasons, a CT data set is obtained with the patient's head fixed to a stereotactic frame. MRI-CT fusion is then performed to combine the spatial accuracy of CT with the target definition sensitivity of MRI [13]. MRI-CT fusion can be especially useful in cases of poorly enhancing tumors that are not well visualized by CT alone, e.g., low grade glioma, vestibular schwannoma, meningioma, and small brain metastases. The use of metabolic images such as PET-FDG with MRI co-registration for precise radiosurgical targeting has also been described [14].

Vestibular schwannoma

The treatment of vestibular schwannoma (acoustic neurinoma) remains controversial. There is a general consensus that microsurgery is the best approach in young patients, while radiosurgery will be the appropriate choice in older, less healthy patients with small lesions. Questions remain regarding mature patients, aged approximately 50–65, without significant background disease, and patients at any age with tumors larger than 3 cm in diameter. In the hands of an experienced surgical team with state-of-the-art neurophysiologic monitoring, surgical outcomes have continued to improve and patients have a very good chance of excellent results, especially those with small and medium-sized tumors. Recurrence after radical surgery is extremely rare. Operating on patients who failed radiosurgery may be more difficult and carries a greater possibility of causing facial nerve deficit.

In patients with giant tumors (more than 4 cm in diameter), a good subtotal removal followed by radiosurgery can be a reasonable option to avoid facial neuropathy. It should be stressed that an adequate subtotal removal in these cases still demands the best surgical skills and experience and should be performed in centers with a large case load.

Meningioma

We agree with Attia and co-workers [1] that a small cavernous sinus meningioma that is growing after a period of observation should be treated with stereotactic radiosurgery. Larger parasellar or suprasellar tumors with optic nerve and or optic chiasm involvement should be treated in two stages. First they should be operated to clear the tumor away from the optic pathways and decrease tumor volume. Single-shot radiosurgery should be considered a reasonable second stage of treatment at this point. If surgery is not possible for any reason, we strongly recommend the FSR approach.

For parasagittal meningiomas, radiation therapy is not the best choice of treatment. Radiation therapy does not provide adequate local control of tumor, and elicits short- and long-term radiation side effects. Surgery remains the best approach in these patients, even if more than one procedure is necessary. Radiosurgery should be considered in high risk patients with recurrent parasagittal meningiomas and sinus wall involvement.

Brain metastases

Brain metastases are the most common type of brain tumor, and their optimal management is still the subject of much controversy. The authors rightfully point out that surgery, radiosurgery, and whole-brain radiotherapy are all legitimate treatment options. Nevertheless, in contrast to the lack of level 1 evidence for other types of radiosurgery targets, valuable data from a series of prospective randomized trials are available for brain metastases. For example, two of three trials have found surgery plus whole-brain radiotherapy to achieve a better overall survival than WBR alone [15–17]. In a more recent study in patients with a single brain metastasis, surgery followed by WBR was superior to surgery alone. Surgery combined with WBR was found by Patchell and team [18] to provide a substantial benefit in local and whole-brain control, although there was no statistically significant increase in length of survival or functional independence. The RTOG 95-08 trial, published by Andrews et al. [19], is a seminal study on the role of radiosurgery in the management of brain metastases. In this study 333 patients with one to three brain metastases, and without uncontrolled primary tumor, were randomized to WBR only (with a total dose of 37.5 Gy in 15 fractions), versus WBR followed by a radiosurgery boost. Patients with a single metastasis who were randomized to the stereotactic boost group showed a significant survival benefit [9]. In patients with multiple metastases there was a much better performance scale and less steroid use, but no survival advantage for the combined treatment.

Unfortunately Attia and group do not provide details about their treatment policy for patients with brain metastases, or any

AVM = arteriovenous malformations
WBR = whole-brain radiotherapy

results, and we are left with only the information that "more than 400 patients with brain metastases have been treated." While the authors are to be commended for such a large clinical experience, it would have been very useful to address critical questions of treatment strategy, as well as indications for radiosurgery in terms of number of metastases, performance status, age of patient, status of primary tumor (controlled versus uncontrolled), and assignment of radiosurgery doses with respect to tumor volume/maximal diameter and isodose prescription. It would be of similar interest to assess treatment results in terms of local control, brain control, and survival. In the absence of such data their article does not provide results from their institution, but is merely a short review on radiosurgery in general.

Conclusions

Stereotactic radiosurgery has become a tool of major importance as an alternative for surgery and conventional radiotherapy in the management of patients with various intracranial lesions. Fractionated stereotactic radiosurgery combines the precision of stereotactic radiosurgery with the radiobiological advantages of fractionation. The development of a non-invasive relocatable head frame, and high speed computers together with the modification of existing linear accelerators have greatly increased the feasibility and popularity of this treatment modality. This technology may also minimize the rates of acute and long-term complications in comparison to the rates associated with conventional radiation therapy and SRS. This is an important consideration, especially in pediatric and young adult patients. However, experience with this technology has limited follow-up. It has yet to be seen whether control and toxicity remain favorable over the long term when compared to SRS. Future studies will help define the role of FSR in managing neurosurgical patients who have a variety of intracranial lesions.

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Do not resent growing old. Many are denied the privilege.

Irish Proverb