Review Article

The stereotactic radiosurgical treatment of common benign brain tumors: pituitary adenomas, vestibular schwannoma and meningiomas

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Introduction: Several treatment options exist following the diagnosis of common benign intra-cranial tumors including microsurgery, radiation and when appropriate medical management. This article will review the current stereotactic radiosurgical trends in the treatment of pituitary adenomas, vestibular schwannomas and meningiomas.

Methods: The medical literature was used to review cutting edge current stereotactic radiosurgical practices in the treatment of benign intra-cranial tumors.

Conclusions: Radiosurgery is a safe and effective alternative treatment option to microsurgery for the management of common benign intra-cranial tumors with excellent control rates and low morbidity.

Keywords: Stereotactic radiosurgery (SRS); Gamma Knife; Cyberknife; pituitary adenoma; acromegaly; prolactinoma; Cushings disease

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The use of radiosurgery for the treatment of central nervous system (CNS) tumors has been around since the conception of Dr. Lars Leksell's Gamma Knife in the late 1960's (1). By early design, the Gamma Knife was framed based and treatment were delivered in a single fraction. However, the definition of radiosurgery has evolved and is currently characterized as the 1 mm precision or less of the stereotactic delivery of multiple beams of radiation onto a target in five fractions or less. As imaging study improved with higher intra-cranial resolution first through the advent of CT and later MRI, more and more stereotactic radiosurgery (SRS) delivery devices have been invented or modified and tumors of all types treated with their response and treatment toxicities studied. We now have a plethora of dose fractionation schemes to choose from without the benefit of randomized trial comparisons. This article will try to address where the advantages and disadvantages of fractionation matter in the treatment of common benign intra-cranial tumors with SRS.

Radiosurgical modalities differences in a nutshell

The most common platforms for radiosurgery delivery are: Gamma Knife (2) and linear accelerator photon based systems. Gamma Knife treatment delivers multiple simultaneous gamma rays tightly conforming onto a radiation target. Often multiple isocenters of varying size are used. Radiosurgery using a linear accelerator based system is also known as linac radiosurgery. Linac radiosurgery can or may not be frame based and also employ multiple photon beams delivered individually through a treatment pathway or arc. Like with Gamma Knife, the beams are also collimated to conform to the target shape. Cyberknife (Accuray Inc., Sunnyvale, CA, USA) a is a frameless robotic linear accelerator based system that can provide continuous imaging of the target in real time and for extra-cranial targets eliminates the need for gated techniques during treatment (3). Proton beam utilizes its brag peak to deliver protons at the treatment depth. Proton systems at this time are not stereotactic delivery systems and as expected they

are less accurate when compared to true stereotactic systems with a 3-5 mm margin of treatment error when covering a target. As a result, when delivering protons, the dose is most often fractionated. Gamma Knife and linac radiosurgery systems are used in practice to deliver single fraction treatment to targets <3 cm when there is a 2-3 mm margin from a radiation sensitive structure. If the tumor abuts or engulfs a radiation sensitive structure like the optic apparatus, fractionation of the dose is best and usually given with an linear accelerator based system or protons. When the target is greater than 5 cm, the beam profile of protons is superior to that of SRS dose delivery systems, IMRT and 3DCRT by better limiting the fall off dose to adjacent normal structures. It should be noted however that the dose disturbance with protons is more pronounced than with photon SRS systems when there is tissue inhomogeneity such as a sinus air cavity near a skull based tumor.

Why fractionate?

In regards to radiosurgery compared to fractionated radiotherapy, the traditional benefits of radiobiology are less obvious and all principles may not apply. Single or multi-fraction high dose to most SRS targets overcome the need for tumor cell redistribution within the cell cycle or re-oxygenation of hypoxic cells (4) for cell death to occur. These latter radiobiology principles are the bases for a protracted radiation course of 5-6 weeks employing standard fractionation regimens (i.e., 1.8-2.0 Gy) for many tumor types (5,6). Also, single or multiple high dose per fraction has been shown to overcome tumor radio-resistance in the treatment of such tumors as melanoma and renal cell tumors. However, the radiobiology of fractionation should not be ignored when normal tissue is embedded within the SRS target. Fractionation even with a high dose per fraction might allow for sub-lethal damage repair of normal tissue minimizing both early and late effects of radiation injury.

The decision regarding dose and fractionation is determined by lesion size, histology, prior radiation treatments, patient's co-morbidities and the radiobiology principles to protect surrounding sensitive normal tissue. The effects of dose and fractionation on normal tissue can be estimated using the linear quadratic cell survival curve model. In this model, the a/b ratio reflects cell response to changes in radiation fraction size. Tissues with low a/b ratios are more sensitive to larger dose fractions. Pituitary adenomas, vestibular schwannomas and meningiomas all have a low a/b ratio (less than 3) that approximates that of normal brain tissue suggesting a decreased benefit from fractionation and more favored response to single or multi-fraction high dose SRS regimens (7).

CNS imaging studies and treatment set up

Many centers prefer to obtain the MRI the day before Gamma Knife treatment to avoid an often seen imagining artifact from the pins used to hold the stereotactic frame in place. On the day of treatment and following the frame placement, a CT is obtained usually without contrast. For non-frame based linac radiosurgery systems, an aquaplast mask helps immobilize the head and decrease treatment set up time. The CT is obtained and fused to the planning MRI. For treatments with Cyberknife, the software processes live images and calculates offsets based of digitally reconstructed radiographs (DRR's) from the CT and sends the offset data to the robotic manipulator for motion compensation.

Both the linac radiosurgery platforms and the gamma Knife planning systems are capable of a high degree of fused study accuracy. Because of higher resolution than CT, MRI imaging is used to identify the target for SRS treatment planning. Contrast enhancement is given and the MRI cuts are 1 mm throughout the entire brain and skull base structures. For skull based tumors, a T2 weighted 3-D volume sequence is obtained to best visualize the cranial nerves and also delineate the cochlea and semicircular canal when treating a vestibular schwannoma.

Definition of tumor control and SRS success

The vast majority of intra-cranial tumors are slow-growing and often responds slowly to the effects of ionizing radiation. SRS tumor control is defined as no growth or a volume reduction following treatment. In general, SRS control rates for benign tumors are excellent. In most published series, the control rates are 90% or better for non-secreting pituitary adenomas, acoustic schwannomas and grade 1 meningiomas (8). Because of the nature of slow growing tumor, a maximum radiographic response may not be realized for many months to years.

Pituitary adenomas

Introduction

Pituitary adenomas comprise 10-20% for all brain tumors (9). Thirty percent of pituitary tumors are non-secretory and 70% secret excess amount of normal pituitary hormones. Of

the secretory adenomas, 60% are prolactinomas, 20% growth hormone secreting tumors followed by adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) secreting tumors.

Secretory tumors are often discovered by the clinical symptoms they produce. Often they are small on imaging studies compared with non-secreting tumors which often compress the optic apparatus at diagnoses with visual field loss being the patient's presenting symptom. Also, large non-secreting pituitary adenoma can cause hypopituitarism by compressing a significant amount of the normal gland.

A complete neurologic evaluation, pituitary endocrine panel, ophthalmologic exam and radiologic evaluation is required on all patient suspected of having a pituitary adenoma. For tumors other than prolactinomas, surgery is the mainstay of treatment. A transphenoidal surgical approach is the most common procedure performed to relieve mass effect and reduce excess hormone production. Radiosurgery is administered for residual, recurrent tumors or in cases where the patient is not a surgical candidate because of co-morbities (10). In general, secreting tumor require higher SRS doses than non-secreting tumor for cure. Most Gamma knife center attempt delivery of 15 Gy margin dose or greater to the 50% isodose of a non-secreting tumor compared to >20 Gy to the margin dose of a secreting tumor (11). Hormone normalization can take months to years following if at all following treatment (12).

SRS dose for non-secreting pituitary adenomas

92-100% controls are seen with SRS treatments of pituitary non-secreting tumors. For single fraction Gamma Knife a dose of >15 Gy delivered to the 50% isodose is given. Law's *et al*. analyzed 16 retrospective studies in which 1,229 patients were treated with SRS with a mean calculated tumor control rate of 95% (13). In one series 68% of the tumors decreased in size and several reports described improved visual function after SRS associated with tumor shrinkage. When treating with a linear accelerator based system, the prescription isodose is usually higher (70-85%) requiring an increase in the tumor peripheral dose so as to be radiobiologically equivalent to this single fraction dose. Also, depending on the tumor proximity to the optic chiasm, the single dose fraction is restricted to <10 Gy to avoid injury.

Using the linear-quadratic model of the cell survival curve, it is possible to estimate the biologically equivalent doses between different fractionation schemes (14). The biologically equivalent dose for a pituitary adenoma given an external bean radiotherapy dose of 45-50.4 Gy in 25-30 fractions of 1.8 Gy per fraction is 72-83 Gy when the a/b equals 3. The equivalent 1 or 5 fractions SRS dose is 15 and 27 Gy (5.4 Gy ×5), respectively. Unfortunately, the linear-quadratic model does not integrate the biological effects of SRS on normal tissue and tumor volumes, dose build-up within a target or vascular response to radiation and thus can only be used as a guideline for dose consideration and selection. When a single fraction is used, most center deliver 15 Gy or greater to the 50% isodose to the margin of a non-secreting pituitary adenomas. If the tumor engulfs or abuts the optic apparatus, our center prescribes a dose maximum of 5.4 Gy ×5 fractions. Given that this fractionated dose is reasonably equivalent to 45 Gy over 25 fractions and maybe low to control a secretory pituitary tumor, a protracted fractionated course using IMRT, 3 DCRT or protons to 50.4 Gy at 1.8 Gy per fraction should be considered particularly if the dose to the medial temporal lobes can be spared.

SRS treatment for ACTH secreting tumors/Cushings disease

The use of a 24-hour UFC (urine free cortisol) is the gold standard to define cure for Cushings disease. Others couple this lab result to resolution of clinical stigmata or a series of normal post treatment cortisol levels (range, 5.4-10.8 mircogr/dL or 150-300 nmol/L). The latency period following SRS is 14-18 months and hormone normalization is observed in 17-83% of patients treated (12).

SRS treatment for GH secreting tumor/acromegaly

Remission is defined by a normal serum IGF-1 level and a GH levels less than 1 ng/mL in response to a glucose challenge. Biochemical remission rates range between 20-96% at 2 years following single fraction treatment with SRS with does greater than 20 Gy (15,16).

SRS treatment for prolacintomas

Remission is defined as a normal serum prolactin level. Biochemical remission rates with SRS using single fraction doses above 20 Gy range from 0-84% at two years post treatment (17).

Hoybye *et al*. showed that SRS may falsely elevate the prolactin level for years after treatment postulating injury of the infundibulum.

Anti-secretory medication and its effect of radiosurgery effectiveness

Several groups report a significantly lower hormone normalization rate for function pituitary tumor patients receiving antisecretory drugs at the time of radiosurgery (18,19). It is postulated that the anti-secretory drugs interfere with phases in the tumor cells cycle making them less radiation sensitive. As a result of these published studies, many centers hold antisecretory drugs 6-8 weeks before and after radiosurgery.

Complication following SRS for pituitary adenomas

SRS is ideal for tumors invading the cavernous sinus. Cranial nerves other than the optic apparatus are reasonably radio-resistant, resulting in fewer long-term complications than aggressive microsurgical resections of tumor residing in this location. SRS to small lesions in the cavernous sinus can often spare the pituitary stalk, optic chiasm and residual pituitary gland. The incidence of optic apparatus injury is a function of nerve volume within the high dose region. The optic apparatus may also be more sensitive to injury by prior surgery, prior radiation or compression. Since secretory tumors require higher radiation doses for control than nonfunctioning tumors, in some cases it may be necessary to deliver higher doses to the optic apparatus and accept an increased risk of potential injury for tumor control. Laws *et al.* reviewed 34 studies of SRS which included 1,567 patients. Sixteen cases (1%) had decreased visual acuity and 21 cases (1.3%) had trigeminal or oculomotor palsy (15). Acute radiation reactions are rare and include limited hair loss, skin reactions, headaches and nausea. Delayed radiation complications include a less than 1% risk of vascular or hypothalamic injury. Hypopituitarism varies with tumor size and location and occurs in 0-70% of cases. Although, there have been no reported cases of a radiation-induced malignancy with SRS given for a pituitary adenoma, the expected occurrence is <1%.

Conclusions/author's note

Radiosurgery is an effective treatment for patients with pituitary adenomas with minimal risks. SRS provides control of tumor growth in the vast majority of cases and hormone normalization in some secretory tumors. Although, the likelihood for hormone normalization for secretory tumors is less than 50% in the vast majority of published studies, this SRS data is similar to the post-operative surgical series. Both SRS and surgery in these patients may help reduce or eliminate the need for costly anti-secretory dugs and their side effects. Therefore, SRS is indicated postoperatively as adjuvant therapy if residual secretory or non-secretory tumor persists, at the time of interval growth or when biochemical markers establish recurrence. Ongoing studies will determine the optimized dosing schedule and help further lessen the risk of injury to adjacent or embedded sensitive normal tissue within the SRS target volume.

Meingiomas

Meningiomas arise from the dura lining the brain and spinal canal. Most of the tumors are benign and located intracranially. The benign tumors in general have a typical radiographic appearance with smooth boarders and no evidence of parenchymal brain invasion. Less than 10% of meningiomas are atypical or malignant. There are many conditions where SRS may be offered to a patient without histologic or grade conformation: (I) the patient presents with a radiographic skull based symptomatic non-surgical amendable meningioma; (II) on imaging MR, there has been a significant change in tumor size which could very soon cause neurological compromise and the patient has been offered or refuses surgery; (III) the tumor was subtotally resected or recurred after a gross total resection and; (IV) tumor histology was atypical or malignant and the cavity width is less than 4 cm on post-operative imaging.

Meningiomas can present as a challenge to both the surgeon and radiation oncologist depending on the tumor size and location. Skull based tumors particularly of the cavernous sinus often involve nerve(s) and blood vessels making complete resections not possible (19). The surgical risk of convexity tumors adjacent to the venous sinus can include neurologic deficits from possible venous injury. However, large tumors of the convexity with or without venous sinus involvement may lead to prolonged edema following radiosurgery and commit the patient to months of oral steroids and their ensuing side effects post treatment (20). Fortunately, many meningiomas are benign, small and can be completely resected or given SRS with a high degree of tumor control and minimal injury. In addition, many centers have found that combining surgery with radiosurgery for subtotally resected tumors is a welcome compromise with a high degree of tumor control while mitigating both radiation and surgical risk.

Meningioma tumor response to SRS

Most Gamma Knife center use a dose of 14 Gy to the 50% isodose to achieve tumor control rates above 90% for WHO grade 1 tumors (21). When using linac radiosurgery and treating to a higher prescription isodose (i.e., 70-80%), the margin dose to the tumor is higher (i.e., 16 Gy) and, when delivering multiple fraction to reduce the risk of injury of involved or adjacent normal tissue, 5 Gy ×5 fractions is an approximate radiobiological equivalent dose (14).

Complications following SRS for meningiomas

The nerves within the cavernous sinus tolerate the SRS dose for meningiomas reasonably well and side effect risks resulting from nerve or vascular injury is minimal (22). In fact, some author report the possibility of pretreatment ocular palsy correction months following SRS. Post-radiosurgery complications can be related to direct injury of involved or adjacent radiation sensitive structures such as the chiasm. To avoid injury, single dose fraction to the optic apparatus should be restricted to <10 Gy. Post-operative symptoms such as headaches or nausea can result from edema sometimes observed after convexity tumors are treated (23). These symptoms can be reduced with steroids. However, if steroids are needed and many weeks to 2-4 months have passed other measures need to be taken to avoid chronic steroid use side effects. An alternatives to steroids or removing of the tumor surgically includes hyperbaric oxygen therapy or the use of avastin (24,25).

Conclusions/author's note

Before the mid 90's, minimal effective dose for benign tumor control was not known. Most Gamma Knife centers treated all tumor, benign and malignant, with the same single high fraction dose for a given tumor size. For tumors less than 2 cc's, this dose was often as high as 18-20 Gy. The dose was based on a maximum for tumor volume to avoid necrosis (26). Surprisingly, it wasn't uncommon to observe complete disappearance of small meningiomas less than 2 years post treatment. With the current effective, considerably lower dose recommendation, excellent tumor control is achieved but rarely if at all a partial or complete tumor response observed. The trade off one could argue was less toxicity for a decrease in tumor size. Indeed, in many cases controlling growth maybe the goal. However, there are some cases in the skull base where tumors compressing the nerve(s) should be eradicated to reduce symptoms such as in the case of tumors on the 5th nerve casing ipsilateral face pain or on the 6th nerve resulting in ocular palsy. This is a reasonable proposal in my estimation given the fact that our data with treating secretory pituitary tumors in the cavernous sinus that require doses of >20 Gy are tolerated well.

Also, it is fortunate that atypical and maligniant meningiomas are rare (<10% of all meningiomas). Nevertheless, at our center we make is a policy to treat the operative cavities of completely resected grade 2 or 3 meningiomas. We will uses single SRS or fractionate if the cavity size is larger than 4 cm in maximum diameter. When gross disease remains post operatively, the dose we deliver is equal to that given for a malignancy as outlined by RTOG 90-05 (27).

Vestibular schwannomas

Vestibular schwannoma, acosutic neuroma and acoustic neurilemoma are names used interchangeably and refer to a rare slow growing benign tumor usually arising from the vestibular branch and less often the cochlear branch of the 8th cranial nerve. They account for 8% of all intra-cranial tumors (28). The tumor is usually unilateral and can occupy the internal auditory canal, cerebellopontine angle or both from the over production of schwann cells arising from the myelin sheath coating then nerve's branches.

The most common presenting symptom is a decline in hearing on the tumor side (29). Other less common presenting symptoms which can become more apparent as the tumor enlarges includes tinnitus, headaches, balance disturbance, dizziness, facial numbness and facial weakness.

Treatment options for vestibular schwannomas to prevent worsening symptoms from an enlarging tumor mass include surgery, SRS or observation for slow growing minimally symptomatic patients with hearing loss (30). If the patent elects close observation at the very least annual scans and hearing test are preformed. The appropriate timing for treatment intervention is before new symptoms develop thus preventing serious consequences from further tumor compression of the underlying nerves and artery. Fortunately, most of these tumors grow slowly (31), giving the patient time to become comfortable with their decision to treat at diagnoses or continue with serial follow ups.

The three most common surgical techniques for removal of a vestibular schwannoma are the retrosigmoid, translabyrinthine and the middle fossa approaches (32). Today surgery is reserved for large tumors compressing the brainstem, sudden or rapid changes in hearing loss at

diagnosis or if the patient refuses radiation.

SRS dose management, results and complication

SRS has equal excellent control rates and similar or less side effects than surgery (33) and removes the risks associated with an invasive procedure such as blood loss, infection, cerebral fluid leak and surgical nerve trauma not to mention the costs of hospitalization. Indeed, tumor control rates with SRS are well above 90% with chronic complications <10% (34), a decline in hear being the exception at <50% in long term follow up (35). Doses with Gamma Knife are typically 12.5-13 Gy at the 50% isodose while if possible restricting the cochlear dose to 6 Gy or less. Single fraction Linac radiosurgery is used with reported equal success for tumor control to Gamma Knife published reports but higher long-term complications including facial weakness and numbness have been observed (36,37). A common dose schedule followed by the Stanford Cyberknife and other has been 18 Gy given over 3 fractions of 6 Gy each to the 70-85% isodose (14,38). The rational to fractionate was postulated that it might further reduce injury to the embedded 7th and 8th nerve as well as the cochlea by adhering to the traditional radiobiologic principles of fractionation particular that of sub-lethal damage repair. Center who have compared fractionated regimens to single fraction treatments have found no statistical difference when comparing tumor control or toxicity (39). This was the results we also found with our patient population who received single fraction Gamma knife compared with multi-fraction Cyberknife.

At our center, between 2007 and 2013, 49 patients with acoustic neuromas (ANs) received fractionated stereotactic radiosurgery (Group A) and 30 patients with ANs received single fraction radiosurgery (Group B). Median f/u for Group A was 39 months and for Group B 18 months. The average fraction number in Group A was 3 and in Group B 1. The mean dose for Group A was 18 Gy and for Group B 12.5 Gy. The mean tumor volume and prescription isodose for Group A was 2.4 cc's and 73%, respectively and Group B 1.8 cc's and 50%, respectively.

The fraction regimen chosen was not based on tumor volume. Instead, patients who presented with symptoms other than mild hearing loss were encouraged to proceed with the fractionated regimen.

For Group A patients who received fractionated radiosurgery, tumor control was observed in 92% and 65% had no change in useful hearing. Post treatment, 22% of the patients noted the new onset of headaches, 11% imbalance, 4% tinnitus, 6% facial spasms, 2% facial weakness and 7% facial numbness.

For Group B patients who received single fraction radiosurgery, tumor control rate was 90% and 67% had no change in useful hearing. Post treatment, 3% of the patients noted the new onset of headaches, 7% imbalance, 10% tinnitus, 3% facial spasm, 3% facial weakness and 0% facial numbness.

Considering the principles of radiobiology, our algorithm postulated that if a patient had progressing cranial nerve deficit(s) at presentation, the underlying cranial nerve injury could be less affected by a SRS fractionated regimen than a single fraction treatment. Tumor controls rates and hearing outcomes in our two patient treatment populations were similar. The benefits if any of a multi-fractionated stereotactic treatment regimen in the treatment of an AN were not able to be determined in this study when compared to a single fraction regimen.

Unlike with microsurgical techniques, immediate hearing loss is uncommon after SRS. Nevertheless, SRS treatment is not without hearing toxicity. Thirty to 40% of patients with useful hearing treated with SRS, loose hearing over 6-24 months (40). Other chronic side effects include a less than 5% risk of injury to the facial/trigeminal nerve function as well as headaches, imbalance and tinnitus.

Other than hearing loss, 10% of patients receiving SRS experience acute treatment complications or worsening of pre-treatment symptoms from treatment related tumor edema with further compression of the nerves or artery. This edema appears as tumor enlargement on a post treatment MRI. The edema can occur weeks after treatment and persist up to 18-24 months. Steroids might minimize the tumor swelling and reduce side effects. Surgery is to be avoided since the tumor size will decrease as the edema resolves usually resulting in a return to the patient's base-line symptoms. Radiographic treatment success is a stable or reduced tumor size with central loss of contrast enhancement seen on subsequent MRI's. Imaging studies are routinely obtained at 6 months, 12 months, and then every other year thereafter. All patients are advised to obtain audiological testing at the time of their MRI studies.

In addition, if the presenting symptom includes imbalance, these patient are sent to physical therapy for a baseline evaluation. They are also instructed to do balance exercises which can help this often incapacitating albeit temporary worsening side effect until the tumor swelling resolves.

Author's note

Radiosurgery is the new accepted standard in the treatment

of vestibular schwannomas less than 3 cm with excellent control rates and minimal toxicities. Because the dose for tumor control is low compared with other tumors both benign and malignant, SRS dose fractionation regimens have not been observed in our center or elsewhere to reduce toxicity compared with single fraction SRS treatment.

Conclusions

There is a plethora of medical literature reviewing SRS in the treatment of common benign tumors. Radiosurgery has been shown to be a safe and effective alternative treatment option to microsurgery for the management of small pituitary adenomas, vestibular schwannomas and intracranial meningioma with excellent control rates and low morbidity.

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Footnote

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