Surgery and radiotherapy: complementary tools in the management of benign intracranial tumors

WALTER D. JOHNSON, M.D., F.A.C.S.,1 LILIA N. LOREDO, M.D.,2 AND JERRY D. SLATER, M.D.2

Departments of 1Neurosurgery and 2Radiation Oncology, Loma Linda University, Loma Linda, California

Historically, radiation therapy has been used extensively in the treatment of malignant and aggressive intracranial tumors, and the importance of its role has been repeatedly verified by prolonged patient survival rates and increased tumor control. As more modern capabilities are employed in surgery and radiotherapy, attention is being directed to the utility of radiation as either primary or secondary treatment of benign tumors. Specifically, primary treatment encompasses irradiation of small benign tumors without biopsy confirmation of tumor type; secondary treatment involves postoperative radiation therapy, with the possibility that less-aggressive tumor resection may be performed in areas that have a higher probability of resultant neurological deficit. Current literature suggests that this is not only a possible treatment strategy, but that it may be superior to more radical resection in some cases, for example, in vestibular schwannomas and meningiomas. This article provides an overview of factors to consider in the use of radiation therapy and reviews the relationships between radiation and surgery, notably the unique complementary role each plays in the treatment of benign intracranial tumors. (DOI: 10.3171/FOC/2008/24/5/E2)

KEY WORDS • Gamma Knife surgery • intensity-modulated radiotherapy • intracranial tumor • stereotactic radiosurgery • stereotactic radiotherapy

Abbreviations used in this paper: CGE = cobalt gray equivalent; CN = cranial nerve; CRT = conformal radiation therapy; CT = computed tomography; GKS = Gamma Knife surgery; IMRT = intensity-modulated radiotherapy; LINAC = linear accelerator; MR = magnetic resonance; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy.
tion team’s task, in short, is to deliver the maximum dose necessary to the targeted volume while minimizing the dose delivered to normal tissues or avoiding exposure of those tissues entirely. This task implies the need to conform the radiation dose to the tumor, which may be accomplished partly by designing a treatment plan that configures the delivery portals precisely and partly by selecting a radiation particle and mode of delivery that permits a high degree of conformation to the intended target volume and spares surrounding tissues. Fortunately, rapid advances in computational and digital imaging capabilities have greatly enhanced the radiation team’s ability to conform targeting more accurately and with more flexibility.

There are 3 fundamental strategies of delivering ionizing radiation to benign intracranial neoplasms—or to any target volume—that surgeons and radiation teams should be aware of: SRS, SRT, and fractionated radiation therapy. The essential difference between these strategies is in the number of fractions, or doses, that the physician uses to deliver the total dose to the patient. In SRS, the total dose is typically delivered in 1 fraction, although the current definition permits a maximum of 5 fractions; in SRT and in fractionated radiation therapy, tens of fractions might be required, depending on the total dose to be delivered, and they are differentiated only by the fact that SRT is delivered stereotactically. The decision regarding the strategy to employ depends primarily on the tissues that will be exposed to radiation by whatever means delivered, falls under this definition. The term is not traditionally associated with fractionated radiation therapy, but it should be understood that modern methods of positioning patients are highly precise and repeatable, such that precise localization of the target in 3D space can be accomplished routinely for fractionated radiation therapy as well, in centers employing the appropriate technology. Although the term tends to be associated with devices designed to deliver radiation to tumors in the head, the concept applies to any method of radiation delivery wherein highly precise, repeatable localization is achieved. Given modern techniques of delivering fractionated radiation therapy, it does not stretch the definition too much to call that modality “stereotactic” as well.

**Techniques Underlying the Strategic Alternatives**

Modern radiotherapeutic practices are made possible by dramatic, relatively recent progress in the development of computer technology that enhances the ability to target and deliver radiation due to refinement in digital neuroimaging capabilities, and also by high-quality digital imaging in MR, CT, and positron emission tomography (or in combination using image fusion techniques). Hence, exquisite target imaging is available, enabling more precise treatment planning, verification, and highly accurate follow-up. Two main methods of delivering radiation therapy with great precision, either of which can be employed in SRS, SRT, and fractionated radiotherapy, have resulted from these advances: 3D conformal radiotherapy and IMRT. The former method refers, quite simply, to radiation therapy that is planned on an image-based, 3D, beam’s-eye-view planning system. The latter method also uses image-based, 3D planning but is delivered via a computerized system that varies the intensity of the beam.

Both 3D CRT and IMRT are conformal modalities. Both can employ photons (x-rays or gamma rays) or heavy-charged particles (mainly protons) to deliver ionizing energy to the target volume. The essential difference between the 2 methods, as the name of the latter suggests, is beam intensity. In the former method (3D CRT), beam intensity remains uniform through the delivery portal; in the latter method, beam intensity is modulated within each portal. Intensity-modulated radiotherapy is characterized by many more delivery portals than 3D CRT; it thus exposes a larger volume of normal tissues to ionizing radiation but relies on intensity modulation to concentrate the high dose in the target and minimize it to the volume of the normal tissue. From the radiation team’s point of view, an essential point to understand about selecting either of these options is that one would prefer to avoid radiation exposure of untargeted tissues as much as possible. As noted, IMRT generally exposes a larger volume of normal tissues to ionizing radiation than does 3D CRT, although intensity mod-

---

Surgery and radiotherapy for benign intracranial tumors

ulation enables the physician to deliver low doses to most of the untargeted tissues. This difference is the result of a trade-off. To achieve the tight conformation of the high-dose region in the targeted volume, IMRT must deliver the radiation beam through many portals. Delivering radiation through many portals must result in radiation exposure of the tissues intervening between the target and the beam’s entrance region, and must also result in radiation exposure of tissues distal to the target, if the radiation beam employed in IMRT cannot be made to stop in or just beyond the target. Noting this effect is not to deny the desirability of achieving a conformal high-dose region, but the fact that a greater volume of untargeted tissue (volume integral dose) receives some radiation dose should not be overlooked. Radiation teams would prefer to avoid such a trade-off if possible.

Another form of radiation delivery, TomoTherapy, is an implementation of 2 types of technology: spiral CT scanning and IMRT. TomoTherapy allows patient positioning, treatment planning, and treatment delivery to occur simultaneously. TomoTherapy can be thought of as IMRT carried to its logical conclusion. An image-guided, moving beam is used to achieve the required high-dose conformation, but with the limitation of using only coplanar beams. The same considerations of volume integral dose apply.

For any of these modalities, treatment planning begins with high-quality neuroimaging. This planning is generally accomplished using CT but may be augmented with MR imaging and positron emission tomography. The resulting images are then used to generate a 3D image of the patient and target volume and thus to determine sophisticated shaping of dose distribution by means of collimation design. Intensity-modulated radiotherapy may achieve intensity modulation by either constructed complex physical compensators or by means of multileaf collimators.

Patient positioning and stabilization is of primary importance during treatment planning and delivery. Patients are immobilized most commonly by means of either a face mask or some type of body molding that ensures identical patient positioning during each treatment session. These immobilization methods are designed for patient comfort and, for the most part, are fairly well tolerated during treatment. After the patient is immobilized, radiotherapy simulation is initiated. First, planning imaging is obtained with virtual simulation using 3D imaging techniques. Then the images are used to digitally define the gross tumor volume (the tumor volume delineated on imaging studies); the clinical target volume, encompassing the visualized tumor plus adjacent areas at risk; and the planning target volume, which is a slightly enlarged clinical target volume that includes a margin of error for patient motion, setup errors, and LINAC alignment errors. In some planning systems, a fourth dimension is added to compensate for some of the latter factors, such as patient motion. Once planning is optimized and treatment devices are fabricated and calibrated, treatment commences.

Radiation Sources

A variety of radiation sources, such as photons (high-energy x-rays or gamma rays) or charged particles (electrons or protons, for example) may be used to accomplish the objectives of the therapy plan. X-ray beams are generated by high-energy LINACs, and gamma rays are generated from a natural source, such as cobalt-60. The photons that comprise x-rays and gamma rays have no mass or charge. They deposit energy exponentially as they pass through tissue; depending on the depth of the intracranial target volume, a single photon beam may deposit a significant part of its energy before reaching the target and will continue to deposit energy beyond the target. This fact underlies the practice of using multiple beams to accumulate the desired total dose in the target volume, a practice that is carried to its logical conclusion in IMRT. If photons are used in such applications, however, the dose in distal normal tissues cannot be eliminated and the volume integral dose is greater than that obtained with other delivery modes.

Throughout the history of radiation therapy, a variety of subatomic particles and ions have been used for therapy, including electrons, neutrons, negative pi mesons (pions), and heavy-charged particles such as protons, helium ions, and ions of heavier atoms such as carbon. Pions are no longer used, and neutron beams are not used for treating intracranial tumors, but any of the other particles may be employed. Most centers around the world use photon beams for all radiotherapeutic applications, including treatment of benign intracranial tumors, but an increasing number of centers have the option to use heavy-charged particles (in most cases, proton beams). Protons and photons are similar in terms of their radiobiological effect in tissue, but are vastly different in terms of their physical dose distribution; the latter quality is the basis for their employment in centers that use them.

Protons are the nuclei (ions) of hydrogen atoms. They thus have both mass and charge; their mass enables them to pass through tissue to reach their target without being deviated substantially, and their charge enables the physician to direct them magnetically. In some delivery systems, such as those employing scanning beams, this property of protons can thus be used to attain the required conformation in tissue. In addition, protons have the intrinsic property of depositing the bulk of their energy near the end of their travel. This point, called the Bragg peak, can be placed in the desired target volume by modulating the energy of the proton accelerator to accommodate the required depth in tissue (Fig. 1). Distal to the Bragg peak, protons deposit no energy. Thus, the physician can control the proton beam in 3 dimensions, which is impossible with photon beams. These properties enable the physician to place the conformal high-dose region where desired and to spare nearby normal tissues to a greater extent than is possible with photons. Proton 3D CRT plans routinely achieve the target-volume conformity seen with photon IMRT plans but with a much-reduced volume integral dose. That is, much more of the surrounding normal tissue is spared radiation exposure.

Protons are not the only heavy-charged particles used. Some centers, mainly in Japan, employ beams of carbon ions. These particles also have a Bragg peak but are more massive owing to a greater number of protons in each particle. They thus have a potentially greater radiobiological effectiveness in tissue, in terms of more intense ionization density per track length (higher linear energy transfer); this property results in more lethal cell damage in all cells irradiated by such beams. Clinical research into the optimal applications for these particles is required. Protons, which,
like photons, are low linear energy transfer particles, allow
irradiated normal cells a greater opportunity to effect cell
repair, thus exploiting the greater capacity for repair of nor-
mal cells than tumor cells.

Specific Technologies of Delivering Radiation to Treat Intracranial Tumors

Given the exquisite proximity of intracranial structures
to each other and the great need to eliminate or minimize
radiation exposure of all structures except for those that are
diseased, stereotaxis has always been a prime concern in
treating intracranial neoplasms, benign or otherwise. The
development of SRS, SRT, and modern fractionated radia-
tion therapy arose from this concern.

Historical Perspectives of Stereotactic Radiation

Stereotactic radiation treatment for intracranial tumors
was first performed using the proton beam. Leksell, in
Sweden, reported on the use of the Uppsala research beam
for intracranial SRS in the late 1950s and Kjellberg used
the Harvard Cyclotron Laboratory research machine for
similar purposes in the 1960s, as did Fabrikant on the West
coast. The Harvard experience continued for several
years and that group accumulated a large patient database.
Some of these early attempts made in the era before mod-
ern 3D imaging were limited to treatment of intracranial
structures that could be well localized without benefit of
such imaging; pituitary adenomas were notable examples.
These attempts established the value of a proton beam in
which the high-dose region could be configured to encom-
pass the target without greatly damaging the nearby struc-
tures.

The Gamma Knife

When the Uppsala research cyclotron became less avail-
able for therapy, Leksell, a neurosurgeon, introduced the
Gamma Knife. Initially conceived and developed for the

treatment of movement disorders, it quickly became adapt-
ed for use in intracranial tumors and arteriovenous malfor-
mations. Since that time, it has been used to treat >
200,000 patients worldwide with a wide variety of intracra-
nial disorders.

The Gamma Knife is a large, cast-iron sphere containing
multiple cobalt-60 gamma-ray sources (currently 192) into
which a patient’s head is introduced through a metal en-
trance door. These sources are housed in individual beam
channels within the central core and are directed conver-
gently toward the isocenter. Collimation is provided by
means of a collimator helmet containing a separate collim-
ator for each cobalt source. Initially the patient is immo-
obilized in a rigid stereotactic head frame, and then the
patient undergoes high-resolution imaging (CT, MR imag-
ing, or angiography), which is used for targeting and treat-
ment planning. Once this planning is optimized, the pa-
tient’s head, still rigidly fixed within the frame, is in-
troduced into the collimator helmet and the stereotactic
frame is oriented within the helmet in such a way that the
beam channels and collimators align with the specific tar-
get site. Creating several different isocenters that are then
treated in sequence during the treatment session attains tar-
get conformity. The Gamma Knife can achieve target accu-

racy to as small an area as 0.3 mm, and offers the advan-
tages of single-session treatments, high special accuracy,
and a long history of use and treatment experience.

The CyberKnife System

A more recent development, the CyberKnife, is a
LINAC-based, robotic SRS system that is capable of treat-
ting tumors anywhere in the body with submillimeter accu-

racy, thus minimizing exposure of adjacent normal tissue
to the high dose delivered to the target. Using advanced
image-guidance technology and computer-controlled rob-
otics, the CyberKnife continuously tracks, detects, and
corrects for tumor and patient movement throughout the
treatment. It uses a proprietary stabilization “couch” that
maintains patient positioning without the need for fiducial
screw placement or a stereotactic frame. While the Gamma
Knife creates a stereotactic space within the cranial frame,
the CyberKnife transforms the entire treatment room into
3D (stereotactic) space, thus enabling the use of precise
image guidance for the patient’s entire body. When coupled
with computer-controlled robotics, this image guidance
enables complete and precise treatment. In addition, the
CyberKnife has patented a method of tracking respiration
and heart movement that synchronizes treatment delivery
to the motion of the tumor throughout the respiratory or
cardiac cycle. This is especially helpful for patients with
lung tumors, for example, that would previously require
patients to hold their breath to facilitate appropriate radia-
tion treatment, but is also useful for treating intracranial
sites. The CyberKnife also continually updates its correla-
tion model with each new x-ray image, automatically cor-
recting for any changes in the patient’s breathing patterns.

It is able to deliver high-dose photon radiation in either sin-
gle or multiple fractions with highly precise and accurate
targeting even in patients with geometrically complex

tumors.

Modern Proton-Beam Radiotherapy

As previously noted, the intrinsic properties of proton
beams enable the radiation team to substantially reduce the
amount of energy deposited outside of the target volume in
normal healthy tissue. Protons can be used for SRS, SRT,
and fractionated radiation therapy. Modern means of plan-
nifying and delivering proton radiation therapy make this
modality, for all practical purposes, another form of stereo-
tactic treatment. During the past several decades, > 46,000
patients have been treated with proton-beam radiotherapy
at centers equipped for this type of therapy.

There are several advantages of using heavy-particle ra-

diation. As noted previously, primarily there is greater
controllability due to the particle’s higher charge and mass.
This characteristic allows not only control in targeting tu-
mor volume, but also in targeting the tumor margins, thus
minimizing damage to adjacent tissue. While other types of

W. D. Johnson, L. N. Loredo, and J. D. Slater
Most meningiomas are demonstrated an ac... reported overall local tumor control of... reviewed 219 cases of... Surgery and radiotherapy for benign intracranial tumors...

Menin... the normal-tissue-sparing effects of dose fractionation while still delivering the high total dose to a conformal vol-... Surgery and Radiation in the Treatment of Specific Tumor Types

In cases in which a histological diagnosis cannot be obtained, advanced neuroimaging enables clinicians to predict tumor type with reasonable accuracy based on characteristic imaging properties and/or MR spectroscopy. This advanced neuroimaging thus permits the use of radiation, by means of SRS, SRT, or fractionated radiation therapy, as the primary treatment for benign intracranial tumors. Furthermore, for large tumors requiring surgery, evidence of durable local tumor control enables surgeons to perform less-aggressive tumor resection in areas at a higher risk for neurological injury, with the expectation that radiation therapy can be employed subsequently.

Meningiomas

Meningiomas account for ~ 20% of intracranial tumors, roughly 94% of which are regarded as benign. According to the Central Brain Tumor Registry of the United States, meningioma was the most frequently reported benign tumor from 1998 to 2002 (at ~ 30%), with ~ 8600 new cases expected in the US in 2002. Meningiomas occur in a female/male ratio of ~ 2:1, with peak age incidence between 50 and 70 years.

Since Cushing’s description of a wide variety of meningioma subtypes, this variety has been simplified to the present WHO classification (Table 1). Most meningiomas are unilateral, although some large tumors may cross the midline at either the parasagittal region or at the skull base. Multiple tumors are uncommon, with reported rates of 5–9%. Metastases are rare, but when they do occur they are mainly reported in lung and bone. Intracranial locations of meningiomas are varied but tend to be close to dural venous sinuses and the tentorial edge.

The classic approach to meningioma treatment has been tumor excision. The standard of care for convexity meningiomas continues to be gross-total resection, as this treatment course continues to offer the greatest likelihood of attaining permanent tumor-free survival. Gross-total resection has been shown to result in 5-, 10-, and 15-year overall survival rates of ~ 85, 75, and 70%, respectively, and 5-, 10-, and 15-year progression-free survival rates of 90, 80, and 67%, respectively. In many tumors that infiltrate surrounding structures (such as the major venous sinus or tentorium), however, gross-total resection is either not feasible or invites an undue risk of neurological compromise to the patient. Postoperative adjuvant low-dose radiation therapy results in excellent long-term progression-free survival and low morbidity.

Recently, Friedman and colleagues demonstrated an actuarial local control rate of 100% at Years 1 and 2 and 96% at Year 5 following LINAC-based radiosurgery for meningiomas. Flickinger and colleagues reviewed 219 cases of meningiomas diagnosed using imaging criteria that were then treated using GKS, and found an actuarial tumor control rate of 93% at 5 and 10 years. Kondziolka and colleagues also reported a 93% tumor control rate at 5 and 10 years after radiation treatment, with a 96% satisfaction rate. Lee and associates recently updated this patient series and found no significant change in tumor control rates. Milker-Zabel et al. reported overall local tumor control of 93.6% following IMRT for meningiomas of the skull base, with a mean follow-up of 4 years in 94 patients.

Radiation teams at Loma Linda University, who employ proton SRT or fractionated radiation therapy for patients with benign, atypical, and malignant meningiomas, are assessing the results of their interventions. Results have not yet been published, but indications are that proton SRT or fractionated radiation therapy achieves local control rates for benign meningiomas similar to those reported in surgical patient series and SRS patient series (Fig. 2).

A challenging issue in deciding on treatment for these patients is patient selection. It is apparent that elderly patients and those with comorbidities are excellent candidates for radiation therapy. Treatment of younger patients, which in the past has been believed to be the province of surgery, is now open to question; either modality may be suitable as primary treatment, depending on factors associated with individual presentations. As noted earlier, although radiation teams have historically been reluctant to irradiate tumors without histological confirmation of tissue type, characteristic imaging properties and/or evidence seen on MR spectroscopy offer the opportunity for a definitive diagnosis in the absence of histological confirmation, thus permitting the use of SRS, SRT, or fractionated radiation therapy.

FIG. 2. Axial (left and center) and coronal (right) T1-weighted MR images with Gd enhancement showing a subfrontal meningioma. Colors represent dose planning prior to proton-beam therapy.
therapy as primary treatment for meningiomas in patients of any age. And in large tumors requiring surgery, the ability of radiation to effect local tumor control enables surgeons to perform less-aggressive tumor resection in areas with a higher risk for neurological injury, given the expectation that radiation therapy can be employed thereafter. It is generally true that younger patients are healthier, have smaller tumors, and display more rapid recovery, and thus are optimal candidates for surgery. In these patients, clinical decisions are probably more likely to include the extent of surgery, with small remnants possibly left in the sagittal or cavernous sinus, optic apparatus, or densely attached to the brainstem. These small remnants may then be treated effectively with postoperative irradiation. Even with apparent gross resections of meningiomas in the base of the skull, there is a higher incidence of recurrence; thus, immediate postoperative irradiation is indicated or close monitoring should be undertaken, with radiation therapy offered to the patient at the earliest indication of recurrence, before the patient becomes symptomatic. Patients with atypical and malignant meningiomas are generally referred for radiation treatment.

**Schwannomas**

Intracranial schwannomas are uncommon. Vestibular schwannomas, arising from CN VIII, are the most common of these tumors, yet they comprise only 8% of intracranial tumors even though they account for 80% of cerebellopontine angle masses. Other forms of intracranial schwannomas, such as lesions of the trigeminal nerve, the jugular foramen, and the facial nerve, are even less common. These tumors arise from the margin of the CN where central, glial myelin merges with peripheral, Schwann-cell myelin (the Obersteiner–Redlich zone). The vast majority of these tumors are benign and relatively slow growing, and thus many tumors have achieved a fairly large size by the time of diagnosis.

The major factors dictating treatment for intracranial schwannomas are patient age, general medical condition, degree of symptoms, and the size and location of the mass. Another factor is patient choice. In this age of widespread Internet medical information, patients are more informed than ever and play a major role in treatment selection.

In tumors that compress the brainstem, there is a risk of increased pressure both from brainstem edema and from tumor swelling during radiation therapy. For tumors involving brainstem compression (generally > 2.5 cm in diameter), surgical decompression or complete excision is the preferred treatment method. These tumors respond well to radiation, however, and this information is key in choosing the treatment strategy for individual patients and should be presented to the patient as a factor in selecting treatment. Patients > 70 years of age, patients < 70 years of age but with additional medical concerns, or patients with tumors < 2.5 cm in diameter are ideal candidates for radiation therapy, which has been shown to be effective in both SRS and fractionated radiotherapy. Additionally, radiation therapy has been shown to be useful for adjunctive postsurgical therapy for recurrence or residual tumor. This finding has some importance for determining the extent of surgery when faced with a large tumor densely attached to the accompanying CN. Leaving a small tumor remnant on the CN, yet preserving critical neurological function, followed by radiation therapy is a choice that may have significant benefit. Additionally, irradiation of tumors located within the cavernous sinus or the jugular foramen has a reduced risk of cranial neuropathy when compared with excision. If the patient has significant symptoms that can be reversed drastically by surgery, then that should be the treatment of choice, as long as the patient is medically stable for surgery. Postoperative radiation therapy can be employed if a significant residuum exists. If patients’ symptoms are minimal and they risk a higher likelihood of morbidity with surgery, then they are candidates for definitive radiation therapy. Available choices include SRS, SRT, and fractionated radiation therapy, any of which can be accomplished using photons or protons.

Over the past 2 decades, the standard dose of radiation in SRS given for intracranial schwannomas has been reduced substantially. This reduction has been mainly driven by cranial neuropathies caused by higher radiation doses, specifically, CN V, VII, and VIII dysfunction. Lower radiation doses have been shown to control tumor recurrence while resulting in a lower incidence of cranial neuropathy.

The use of fractionated radiation therapy has traditionally been associated with the sparing of dysfunction in CNs V, VII, and VIII. Excellent control of acoustic neuromas has been achieved with both fractionated radiotherapy, and more recently, with radiosurgery. Maire and colleagues reported a 10-year tumor control rate of 88% using a fractionated mean radiation dose of 51 Gy. Sakamoto and associates reported a 5-year actuarial tumor control rate of 92% using a fractionated radiation dose range of 36–50 Gy.

Photon radiosurgery for schwannomas has also yielded excellent results. Kondziolka and associates reported a tumor control rate of 98% at 10 years’ follow-up after GKS. Facial and trigeminal nerve function were preserved in 79 and 73% of patients, respectively. In patients with serviceable hearing (Gardner–Roberson Class I or II) prior to treatment, useful hearing was preserved in 47%. Recently, Friedman et al. reported the results of LINAC-based radiosurgery with 1- and 2-year control rates of 98% and a 5-year control rate of 90% with minimal complications. Similar results have been confirmed in other patient series.

Sheehan and colleagues have reported excellent results using GKS in 26 patients with trigeminal schwannomas, and Hasegawa and associates found similar results in 37 patients. Kida et al. reported a 100% tumor control rate of facial neuromas after a mean follow-up of 31 months with GKS. Litter et al. reported that 10 of 11 patients with facial schwannomas were stable after this same treatment. This group suggests that, given the advantages noted in the results of their study, these results should lead to the consideration of GKS as a primary treatment option for small- to medium-sized facial schwannomas. Recently, Martin et al. published a report on a series of 34 patients with jugular foramen schwannomas treated with GKS. They concluded that the procedure was a safe and effective treatment and that CN function remained stable or improved along with long-term tumor control.

Bush et al. reported their experience with fractionated proton-beam radiation therapy of acoustic neuromas in 2002 (Fig. 3). A total of 31 acoustic neuromas were treated in 30 patients. Patients were divided into 2 treatment
groups based on pretreatment hearing assessment. Patients with Gardner–Robertson Class I or II hearing received a conformal fractionated radiation dose of 54 CGE over 30 treatments, whereas those without useful hearing received a conformal radiation dose of 60 CGE fractionated over 33 fractions. Twenty-nine patients were available for follow-up at a mean of 34 months, with no patients showing tumor progression and 11 showing tumor regression. Of the patients with useful hearing prior to treatment, only 31% retained useful hearing. No damage to CNs V or VII was detected.

**Pituitary Tumors**

Pituitary adenomas are primarily benign neoplasms arising from cells of the anterior hypophysis. These cells produce a variety of hormonal substrates that, with the development of the tumor, cause hypersecretion of that particular hormone with resultant physiological consequences. Nonsecreting tumors cause more symptoms that are related to bulk effect due to compression of the optic chiasm or cavernous sinus contents. In the past several decades these tumors have been preferentially treated using transsphenoidal microsurgical techniques and, more recently, with endoscopic resections. Transcranial resections have primarily been reserved for large or recurrent tumors with extracranial extensions.

Radiation therapy has been used in the treatment of pituitary tumors since the time of Harvey Cushing. In 1939, Henderson reviewed the records of 338 pituitary patients who had undergone operations by Cushing and found that of the recurrent tumors, 56% had not received radiation, whereas only 13% of irradiated tumors recurred. This trend has been confirmed in all but 2 published series.

Radiation therapy can be used to treat pituitary adenomas of the secreting and nonsecreting types. In the case of the latter, however, even with modern radiographic technology, the differential clinical diagnosis is rather extensive and the probability of obtaining a correct diagnosis in the absence of histological confirmation is low. Definitive irradiation (that is, treatment undertaken without such a diagnosis) is therefore usually not indicated.

The significant risk associated with pituitary tumor irradiation is damage to the optic apparatus, temporal lobes, normal pituitary gland, and hypothalamus. Precisely targetted radiosurgery or radiotherapy reduces this risk, but the overall dosage is limited by these structures to the tolerance dose of these structures. In a review, the rate of visual loss following pituitary irradiation was only 1.5% in 471 patients; this rate was reduced by using SRS. Additionally, there is a risk of panhypopituitarism following radiation therapy, even when fractionated to fairly low total doses. There is evidence, however, that SRS produces more rapid correction of endocrinopathies when compared with fractionated photon radiotherapy. Complications of radiosurgery are relatively low.

Compiled data from >1300 patients by Shrieve and colleagues demonstrated that 0.3% developed subsequent blindness, 0.7% developed visual field defects, and 0.9% developed oculomotor deficits after radiosurgery for pituitary tumors. Evidence has been presented that suggests radiotherapy for pituitary tumors does not reduce the quality of life or cognitive function in these patients. Several LINAC-based trials report similar results.

Recent experience with GKS has been reported in the treatment of Cushing disease, acromegaly, and Nelson syndrome. Jagannathan and colleagues reported a 54% endocrine remission rate and 96% tumor control rate in 107 patients with Cushing disease. Pollock and associates demonstrated actuarial rates of biochemical remission at 2 and 5 years to be 11 and 60%, respectively, in 46 patients with acromegaly. Additionally, these investigators commented on the benefits of discontinuing pituitary suppressive medications at least 1 month prior to radiation therapy, because it significantly improved endocrine outcome.

Radiation therapy has been used in the treatment of pituitary adenomas since the time of Harvey Cushing. In 1939, Henderson reviewed the records of 338 pituitary patients who had undergone operations by Cushing and found that of the recurrent tumors, 56% had not received radiation, whereas only 13% of irradiated tumors recurred. This trend has been confirmed in all but 2 published series.

Radiation therapy can be used to treat pituitary adenomas of the secreting and nonsecreting types. In the case of the latter, however, even with modern radiographic technology, the differential clinical diagnosis is rather extensive and the probability of obtaining a correct diagnosis in the absence of histological confirmation is low. Definitive irradiation (that is, treatment undertaken without such a diagnosis) is therefore usually not indicated.

The significant risk associated with pituitary tumor irradiation is damage to the optic apparatus, temporal lobes, normal pituitary gland, and hypothalamus. Precisely targetted radiosurgery or radiotherapy reduces this risk, but the overall dosage is limited by these structures to the tolerance dose of these structures. In a review, the rate of visual loss following pituitary irradiation was only 1.5% in 471 patients; this rate was reduced by using SRS. Additionally, there is a risk of panhypopituitarism following radiation therapy, even when fractionated to fairly low total doses. There is evidence, however, that SRS produces more rapid correction of endocrinopathies when compared with fractionated photon radiotherapy. Complications of radiosurgery are relatively low. Compiled data from >1300 patients by Shrieve and colleagues demonstrated that 0.3% developed subsequent blindness, 0.7% developed visual field defects, and 0.9% developed oculomotor deficits after radiosurgery for pituitary tumors. Evidence has been presented that suggests radiotherapy for pituitary tumors does not reduce the quality of life or cognitive function in these patients. Several LINAC-based trials report similar results.

Recent experience with GKS has been reported in the treatment of Cushing disease, acromegaly, and Nelson syndrome. Jagannathan and colleagues reported a 54% endocrine remission rate and 96% tumor control rate in 107 patients with Cushing disease. Pollock and associates demonstrated actuarial rates of biochemical remission at 2 and 5 years to be 11 and 60%, respectively, in 46 patients with acromegaly. Additionally, these investigators commented on the benefits of discontinuing pituitary suppressive medications at least 1 month prior to radiation therapy, because it significantly improved endocrine outcome. Mauermann et al. reported no change or a reduction in tumor size in 20 of 22 patients following treatment for adenocorticotropic hormone–producing adenomas in patients with adrenalecomies; there were variable adenocorticotropic hormone results. Sheehan et al. reported that GKS was effective in patients with Cushing disease following failed transephenoidal surgery.

As noted earlier, one of the first applications of the proton beam was for the treatment of pituitary adenomas, an application that was feasible in the era before CT because of the location of these tumors. In 1991, Levy et al. reported on 840 patients who were treated at the Lawrence Livermore Laboratory using heavy-charged-particle radiosurgery of the pituitary gland. Indications for treatment included pituitary tumors and pituitary suppression. The first 30 patients were treated with proton-beam irradiation, and the remaining patients were treated with helium-ion irradiation. Complications included temporal lobe necrosis, transient visual problems, and pituitary dysfunction. These investigators concluded that the Bragg peak radiation therapy was an effective means of suppressing pituitary function or controlling tumor growth while preserving a rim of functional pituitary gland.

Ronson and colleagues from the Loma Linda University Proton Center described 47 patients with pituitary adenomas treated with fractionated proton SRT. Forty-two patients underwent prior surgical resection, and 5 were treated with primary irradiation. Approximately half the tumors were functional. The median radiation dose was 54 CGE. Tumor stabilization occurred in all 41 patients available for follow-up imaging; 10 patients had no residual tumor, and 3 had a >50% reduction in tumor size. Seventeen patients with functional adenomas had normalized
or decreased hormone levels, and tumor progression occurred in 3 patients. Six patients died, and 2 of these deaths were attributed to functional tumor progression. Complications included temporal lobe necrosis in 1 patient, new significant visual deficits in 3 patients, and incident hypopituitarism in 11 patients. The authors concluded that fractionated conformal proton-beam irradiation achieved effective radiological, endocrinological, and symptomatic control, and significant morbidity was uncommon, with the exception of postirradiation hypopituitarism, which they attributed in part to concomitant risk factors for hypopituitarism present in their patient population.

Conclusions

Although excision remains the overall definitive treatment of benign intracranial tumors because it enables rapid reduction in the intracranial mass effect and establishes a precise histological diagnosis, recent advances in a range of focused-beam radiation modalities as well as improved radiographic imaging capabilities have permitted alternative treatment strategies to emerge. It is now possible, based on imaging characteristics, to treat specific benign tumors definitively using fractionated radiation therapy, SRT, or SRS. The availability of highly conformal modalities makes fractionated SRT or fractionated radiation therapy increasingly attractive as a treatment modality that combines the high-dose conformation associated with SRS with the traditional benefits of dose fractionation. Candidates for SRS or SRT would typically be those patients with smaller tumors and imaging characteristics of a benign tumor. There is also the ability to use SRS or SRT to treat small tumor residua following surgery that are purposefully left attached to critical structures by the surgeon to preserve critical neurological function.

References


W. D. Johnson, L. N. Loredo, and J. D. Slater
Surgery and radiotherapy for benign intracranial tumors


Address correspondence to: Walter D. Johnson, M.D., F.A.C.S., Department of Neurosurgery, 11234 Anderson Street, Room 2562B, Loma Linda, California 92354. email: wjohnson@llu.edu.