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Radiotherapy and stereotactic radiosurgery for pituitary tumors

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Radiotherapy was introduced to the management of patients with pituitary adenomas early in the twentieth century, initially as Radium-226 intracavitary brachytherapy and subsequently with fractionated external beam radiotherapy [1]. In the middle of twentieth century, proton beam irradiation was added to the radiotherapy options in the management of patients with pituitary adenomas [2], and in the subsequent two decades, heavy particle radiotherapy was also added [3–5]. Generally, treatment outcomes with radiotherapy were good, with a relatively low incidence of treatment toxicity. In 1968, gamma knife stereotactic radiosurgery (GKSRS) and, since the 1980s, linear accelerator (LINAC)–based stereotactic radiosurgery (SRS) were introduced to the clinic, with treatment of pituitary adenomas being one of the most important early indications for these treatment modes [6–8]. In addition to frame-based stereotaxy, frameless stereotactic systems have been developed, which have added a new dimension to the treatment of patients with pituitary tumors [9,10]. The Cyberknife (Accuray, Inc., Sunnyvale, CA) has become the most important instrument in frameless stereotactic treatment programs [9,11,12]. The last two decades of the twentieth century were characterized by an unprecedented growth of computer technology and sophisticated imaging. These developments helped to optimize radiotherapy in terms of improvement of treatment results and lowering treatment toxicity [13].

Radiotherapy represented the best available management for pituitary adenomas until the 1970s, when major progress in surgery and neuroanesthesiology provided the impetus for the growth of neurosurgery [14]. At the present time, the treatment of choice in patients with a pituitary adenoma is transsphenoidal surgical resection, which, in most cases, results in long-term tumor control and a normalization of hormonal hyperfunction. In addition to its effectiveness, this procedure is safe, of low toxicity, and compatible with an excellent quality of life. Only a few patients are considered for conservative therapy, which basically represents some form of radiotherapy. As an example, at the University of Southern California (USC), between 1983 and 2001, only approximately 5% of patients were treated with external beam radiotherapy or SRS. The indications for radiotherapy included: (1) patients with residual tumor after surgery, with residual disease in the cavernous sinus representing the most common indication; (2) patients with postsurgical tumor recurrence; and (3) a few patients who had medical contraindications to surgery.

External beam radiotherapy

External beam radiotherapy has undergone major evolution in the past 50 years. This

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treatment is currently delivered with a great degree of precision, results in excellent treatment outcomes in both hormone-inactive and hormone-secreting tumors, and produces a low incidence of toxicity [15–22].

Although a direct comparison between treatment results obtained with external beam radiotherapy and transsphenoidal surgery is difficult because of the apparent differences in patient and tumor characteristics in the patient groups, some comparisons have been attempted [23,24]. The reported treatment results obtained with surgery were better than those reported with the use of radiotherapy alone. A study of 145 patients was reported from Tufts New England Medical Center (Boston, MA) [23]. Patients were divided into three treatment groups, including Group I (n = 60) (41%) treated with surgery alone, Group II (n = 54) (37%) receiving surgery followed by external beam radiotherapy, and Group III (n = 12) receiving radiotherapy alone. Tumor control with a mean follow-up of 6.4 years was obtained in 85% of Group I, 93% of Group II, and 50% of Group III patients. The authors recommended surgical treatment, with radiotherapy reserved for tumor recurrence after surgery. The low tumor control rate in patients treated with radiotherapy alone does not have a satisfactory explanation.

An interesting study in 411 patients with pituitary adenomas treated with external beam radiotherapy between 1962 and 1986 was reported from the Royal Marsden Hospital (Sutton, UK) [15]. Radiotherapy consisted of 45 to 50 Gy in 25 to 30 daily fractions. Of the 411 study patients, 252 (61%) had hormone-inactive tumors, 131 (32%) had hormone-secreting tumors, and hormonal status was unknown in 28 (7%). Surgical treatment was given to 338 (82%) patients, resulting in 11 (3%) patients having complete tumor excision, but all patients received postoperative radiotherapy. The 10- and 20-year actuarial progression-free survival (PFS) rates for all study patients were 94% and 88%, respectively. They were 97% and 92%, respectively, for the 252 nonsecreting tumors and 77% and 58%, respectively, for hormone-secreting tumors. The relative risk of death for the study patients compared with the matched general population was 1.76 ($P < 0.001$).

The evaluation of radiation toxicity in this study is of interest. A total of 1.5% of patients demonstrated various degrees of visual deterioration, which was assumed to be radiotherapy related. At the nineteenth year after radiotherapy, 50% of patients required hormone replacement therapy, and at 20 years after treatment, 1.9% of patients had a second brain tumor. These treatment results are excellent. It is, however, not clear why only 3% of patients had complete tumor excision. As an example, another report on 45 patients with hormone-inactive adenomas demonstrated an 84% incidence of complete resection and a 6% incidence of tumor recurrence at 5 years after surgery [20]. It is apparent from this study that postoperative radiotherapy should be applied to a carefully selected minority of surgically treated patients. Other reports based on 112 and 70 patients, however, demonstrated a greater (78% and 87%, respectively) proportion of surgical patients requiring postoperative radiotherapy [18,25]. In the first study, which was reported from the University of Pittsburgh (Pittsburgh, PA) [18], the 5-, 10-, 15-, and 20-year PFS rates were 97%, 89%, 87%, and 76%, respectively. There was a low incidence of treatment toxicity reported in this study with a less than 1% incidence of optic neuropathy, which occurred in 1 patient who received a total dose of 47 Gy. Similar excellent treatment results have been reported from many other medical centers [26–32].

An important study on treatment effectiveness in 210 patients with pituitary adenomas and a median follow-up of 13 years was reported from Washington University (St. Louis, MO) [33]. The actuarial 10-, 20-, and 30-year PFS rates for patients treated with radiotherapy alone were 80.5%, 73.5%, and 73.5%, respectively. Incidence rates of PFS for patients treated with surgery followed by planned immediate postoperative irradiation were 93%, 71%, and 44%, respectively. A detailed analysis of failure was performed, with radiotherapy only patients having the greatest probability of recurrence within the first 5 post-treatment years and decreasing to 0% at 20 years. The pattern of recurrence was different for those treated with surgery and postoperative irradiation, where the risk of recurrence was apparent up to 30 years after treatment. These findings reinforce the need for careful follow-up for an indefinite period. Detection of tumor recurrence is of importance, because patients may be considered for reirradiation of their recurrent adenoma. This treatment has been found to be safe and effective in controlling recurrent tumors [34,35].

Patients treated for hormone-secreting adenomas tend to have a somewhat lower probability of benefit from radiotherapy than those treated for hormone-inactive tumors [16,17,19,22,24,36–39]. The effectiveness of radiotherapy in hormone-

secreting tumors has been investigated in a number of studies. In one report from the University of Madrid (Madrid, Spain), a total of 30 patients who failed transsphenoidal surgery for Cushing's disease received radiotherapy consisting of a mean dose of 50 Gy [16]. Postradiation remission with a median follow-up of 42 months was observed in 25 (83%) patients, occurring between 6 and 60 months. None of the 25 study patients with remission relapsed during the period of observation. Radiotherapy was well tolerated. Growth hormone (GH) deficiency was reported in 17 (57%) patients, gonadotropins in 10 (33%), thyrotropin in 4 (13%), and corticotropin in 1 (3%). In another report on 138 patients treated with radiotherapy, 90% had clear benefit from this therapy [22]. This benefit included a 38% incidence of hormonal normalization and a 52% incidence of substantial reduction in hormone overproduction. The study investigators recommended a 45- to 48-Gy radiation dose as a safe and effective treatment in patients with hormone-secreting adenomas. Similar results with radiotherapy have been reported by others [36,37].

Treatment planning and preparation for external beam irradiation of pituitary tumors is a complex process. Critical parapituitary dose-limiting structures, such as the chiasm, optic nerves, and hypothalamus, need to be carefully identified, and their radiation sensitivity needs to be assessed in a context of the overall clinical picture in a given patient. The dose to the eyes and normal brain can easily be kept below their radiation tolerance levels with the use of conventional treatment techniques. These techniques involve the use of (1) two to four fixed photon beams with energy greater than 15 MV; (2) arc rotation; and (3) a headholder and thermoplastic head mask, such as the BrainLab (Kirchheim, Germany) for patient immobilization and an accurate treatment field repositioning.

More elaborate treatment techniques include greater number of arcs or fixed beams, with the resulting isodose distribution strictly conforming to the desired target volume and better optimization of protection of normal structures. These techniques include intensity-modulated radiation therapy (IMRT) and stereotactic radiotherapy (SRT) and SRS. High-precision immobilization and repositioning devices are used with these techniques.

Conventional treatment techniques

In the past, parallel opposed lateral photon beams were commonly employed. Bitemporal field size was typically approximately 5 cm × 5 cm. The resulting dose distribution using 20-MV photon beams is shown in Fig. 1. Although the eyes are completely outside the radiation fields, the normal brain surrounding the target receives the same dose as the target. The irradiated volume of the normal brain is even larger if lower energy beams are used, such as Cobalt units or 4- to 6-MV X-ray beams. At the present time, the use of opposed lateral fields with low-energy photon beams is not recommended.

The treatment setup with lateral opposed wedged fields and an anterior-vertex field is shown in Fig. 2A. The need for a wedge on the vertex field depends on the curvature of the patient's skull. The radiation fields are shaped with the multileaf collimator as shown on digitally reconstructed radiographs (see Fig. 2B, C). The resulting dose distributions in the transverse and sagittal planes are presented in Fig. 2D and 2E. This technique has been widely used and described in detail elsewhere [13,40,41]. An appropriate choice of the relative weights used with the three-field technique limits the dose to the normal brain to approximately 55% of the target dose. A further decrease of the dose to the normal brain can be achieved by adding a posterior-vertex field to the three-field setup (Fig. 3A) or by using bilateral arcs augmented with a sagittal arc (Fig. 4A). The corresponding dose distributions in the transverse and sagittal planes are also shown in Fig. 3B and 3C and Fig. 4B and 4C. The extent of the arcs and gantry angles of the fixed beams are determined by the position of the eyes; the beams must avoid

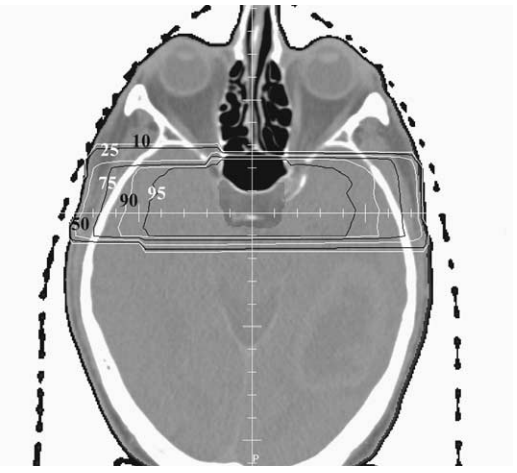

Fig. 1. Dose distribution of lateral opposed 20-MV photon beams is shown in the transverse plane.

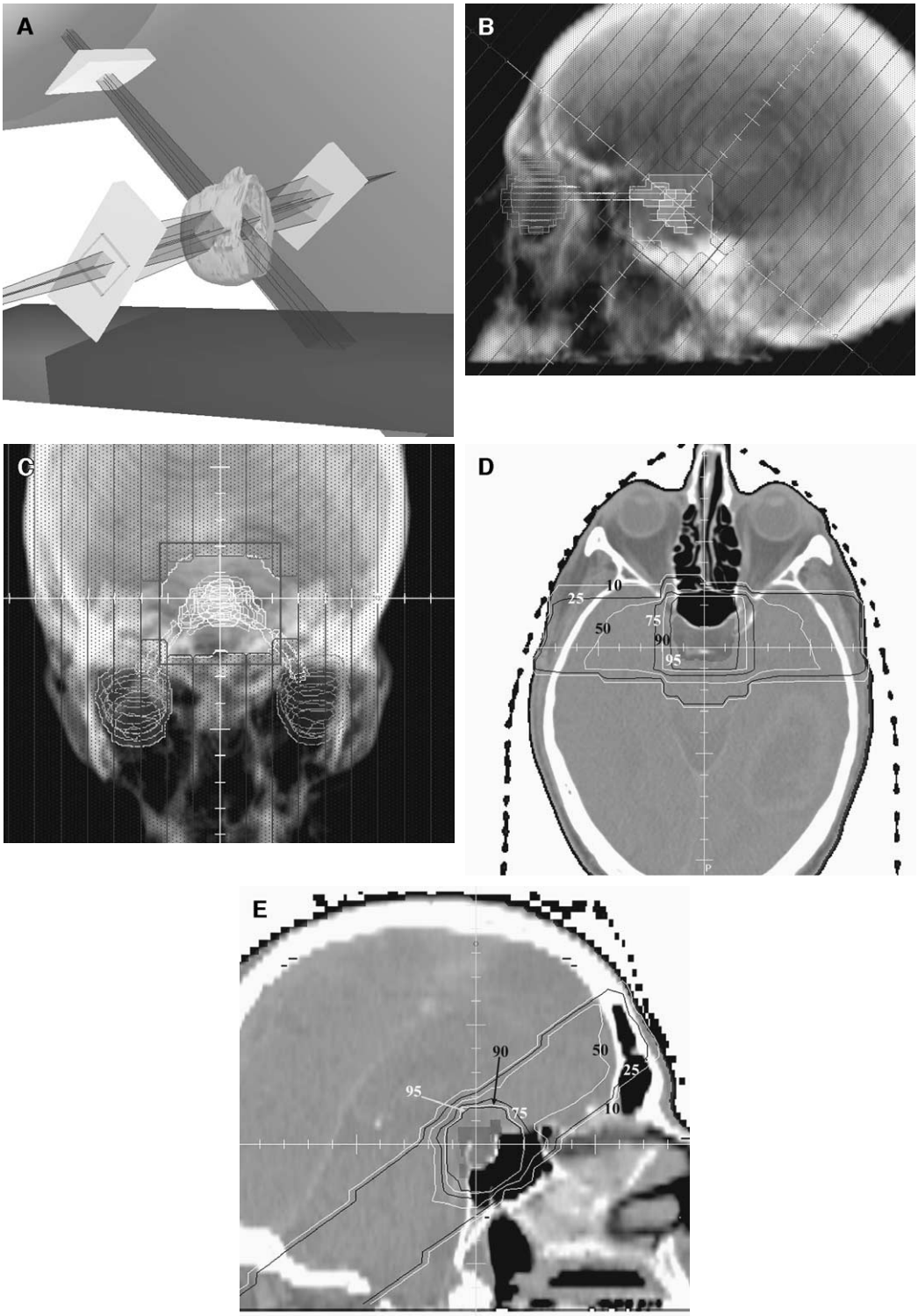

Fig. 2. Three-field technique with the use of lateral opposed and anterior-vertex portals. Beam energy was 20 MV. (*A*) Schematic representation of the setup. (*B*) Digitally reconstructed ''beam's eye view'' radiograph of the lateral fields. (*C*) Digitally reconstructed beam's eye view radiograph of the anterior-vertex field. (*D*) Dose distribution in the transverse plane. (*E*) Dose distribution in the sagittal plane.

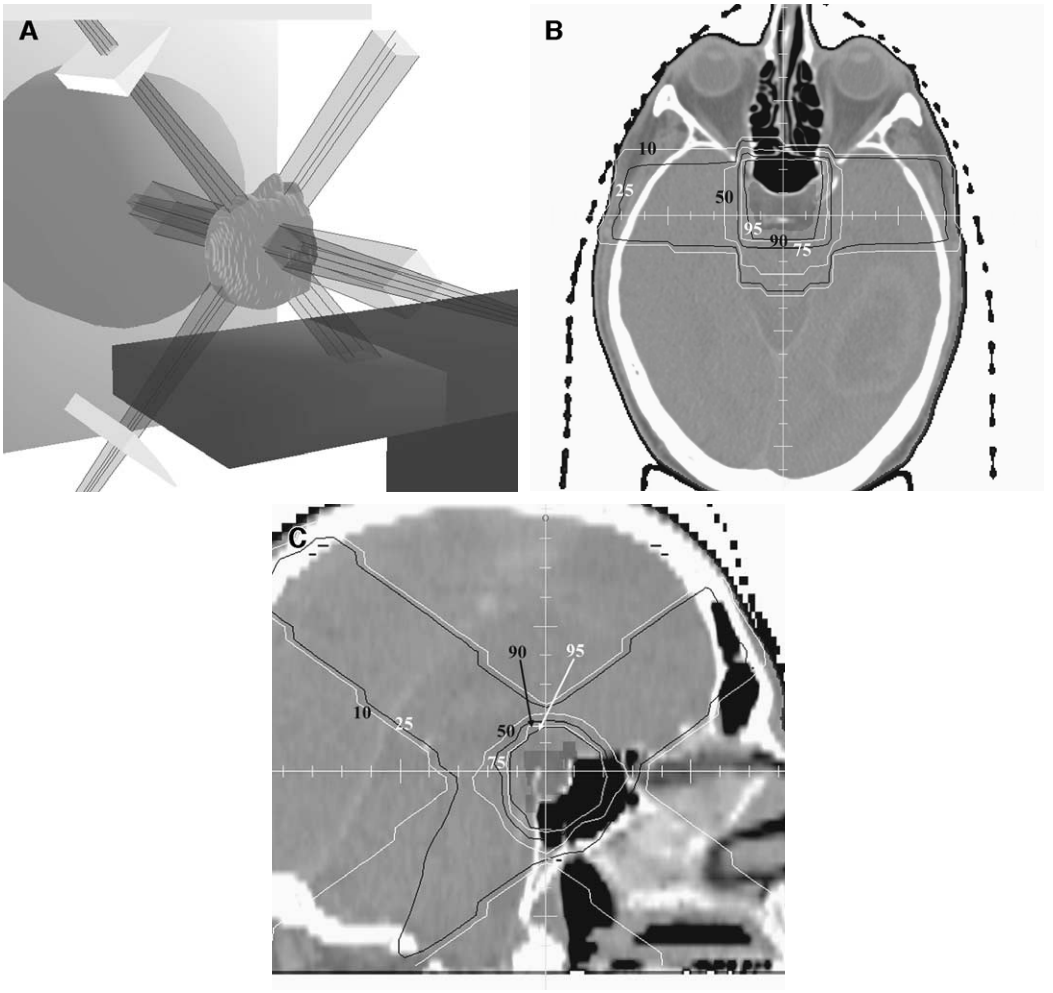

Fig. 3. Four-field technique with lateral opposed, anterior-vertex, and posterior-vertex fields. Beam energy is 20 MV. (*A*) Schematic representation of the setup. (*B*) Dose distribution in the transverse plane. (*C*) Dose distribution in the sagittal plane.

the lens by a comfortable margin to minimize the possibility of future cataract formation. As a coplanar technique, bilateral arcs only or two pairs of opposed lateral oblique fixed beams can be used. The limitations on gantry angles and arcs are the same as described previously.

Adding more non-coplanar arcs or fixed beams can further decrease the dose to the normal brain. There is, however, a problem in patients with larger pituitary tumors, which require larger fields. The radiation beams begin to overlap at some distance from the edge of the target, resulting in a less optimal dose gradient between the tumor and the normal structures. Therefore, the advantage of using more arcs or a greater number of fixed fields is of more importance in treating smaller lesions. The larger number of fields also allows for more conformal isodose distribution.

Conformal techniques

Conformal techniques require particularly accurate anatomic information. MRI typically provides better information for treatment planning in patients with pituitary tumors than that obtained with the use of CT. Although the CT images are geometrically more accurate, MRI scans might have some distortions [42]. As a result, the best choice is to use image fusion, which is available in most commercial treatment planning systems. The best treatment plans in terms of normal

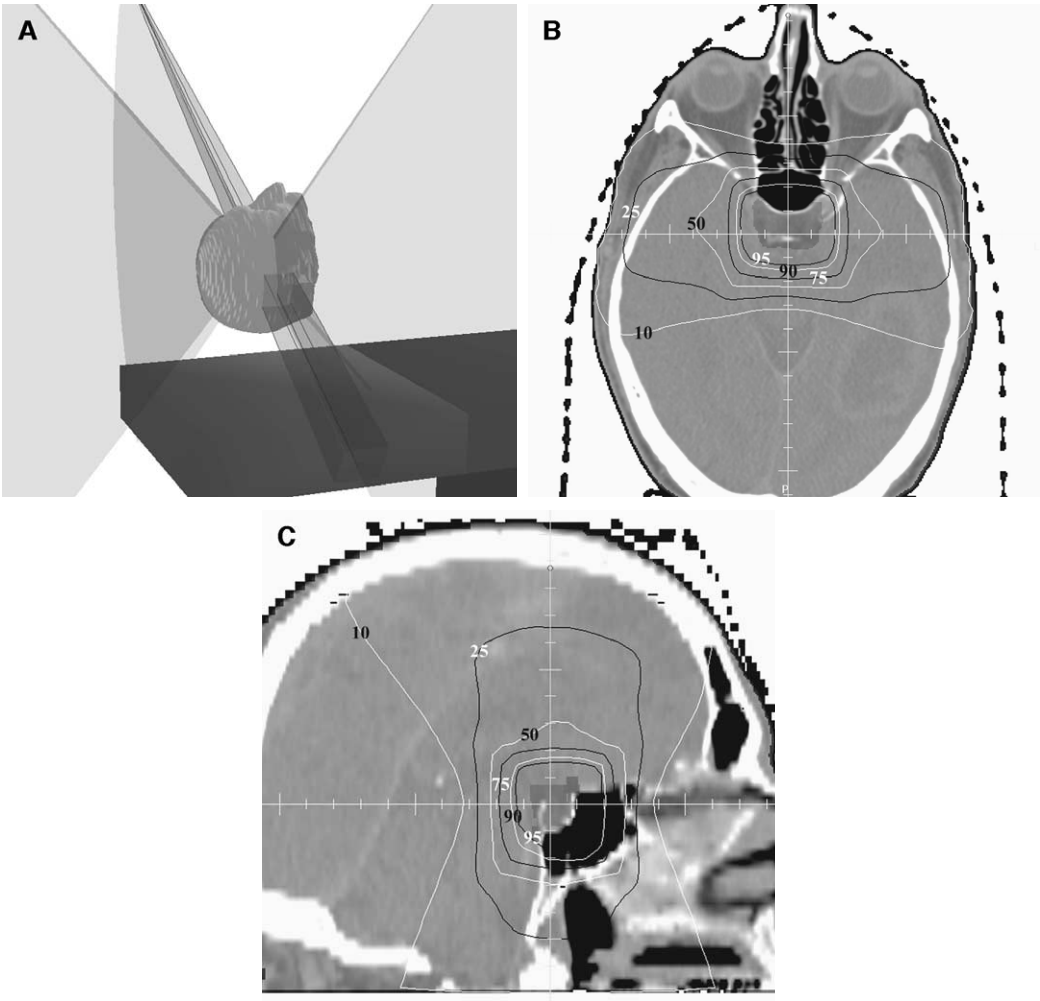

Fig. 4. Three-arc technique with bilateral and parasagittal arcs. Beam energy is 20 MV. (*A*) Schematic representation of the setup. (*B*) Dose distribution in the transverse plane. (*C*) Dose distribution in the sagittal plane.

brain tissue sparing and relative ease of setup with good reproducibility were reported in a study of eight patients [43]. The recommended stereotactically guided conformal treatment consisted of four to six widely spaced fixed fields. An increase in the field number did not improve the normal brain-sparing effect of the four- to six-field setups.

As discussed previously, consideration should be given to the possible inaccuracies of patient setup and repositioning. Most contemporary LINACs have better than or equal to ±1 mm accuracy on mechanical parameters when used according to their manufacturer specifications. Conventional head and neck masks have a repositioning inaccuracy of approximately ±2.5 to 3 mm, whereas more accurate relocatable head-holding systems with a rigid frame can help to obtain a better accuracy of less than 1.5 mm [44,45].

Invasive head frames (eg, Brown-Robert-Wells or Leksell systems) are attached to the skull, eliminating the repositioning inaccuracies. A major drawback with these head frames is a limitation to single-fraction radiosurgery. Repeated treatments with head frames left in position are difficult, if not impossible, because of the discomfort they cause to the patient.

If the chiasm is involved by a pituitary tumor, there is no possibility of protecting it without compromising the dose given to the part of the tumor adjacent to the chiasm. Even with only a small separation between the target and the chiasm, however, conformal techniques are able to keep the

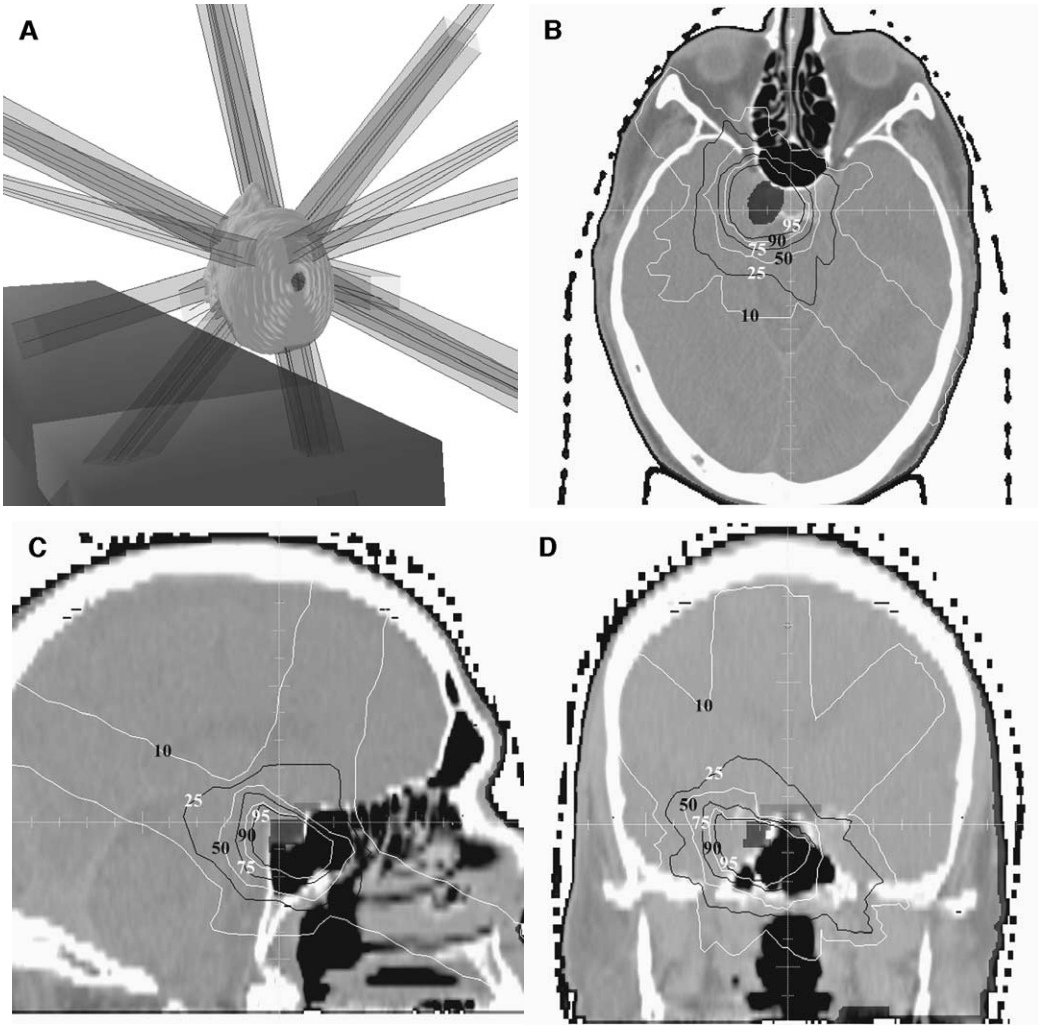

Fig. 5. Conformal therapy with nine fixed beams. (*A*) Schematic representation of the setup. (*B*) Dose distribution in the transverse plane. (*C*) Dose distribution in the sagittal plane. (*D*) Dose distribution in the coronal plane.

dose to the chiasm below its tolerance level. Fig. 5 demonstrates a setup of nine fixed beams, which illustrates the previous point. From six of the nine beam directions, it was possible to completely protect the chiasm; therefore, the dose delivered to it is only approximately one third of the target dose. The high-dose region surrounds the tumor with a comfortable margin of 1 cm, where it is not adjacent to the chiasm. The availability of multileaf collimator beam blocking and "beam's eye view" reconstruction of the anatomy is a requirement for conformal treatment planning and delivery.

The treatment planning process can be automated with IMRT. Each beam consists of several subbeams, blocking parts of each beam for different amounts of time. The beam directions and their blocking pattern can be optimized to achieve a desired dose distribution. The beam can remain on or be turned off while the blocks are moved into position, creating dynamic and "step and shoot" techniques. Fig. 6 shows a dose distribution created by this step and shoot method. The region receiving the tumor dose (180-cGy line) has a "dent" where the dose is only 140 cGy, providing the desired protection of the chiasm.

Stereotactic radiosurgery

In the past 10 years, SRS has emerged as an important treatment modality in the management

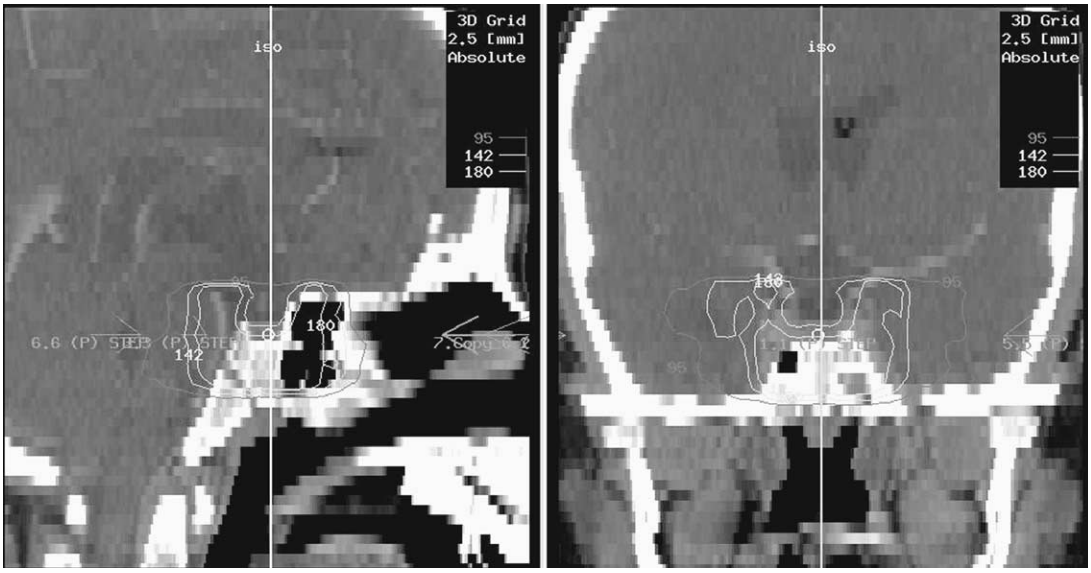

Fig. 6. Intensity-modulated radiation therapy dose distributions. (*Courtesy of* Art Olch, PhD, University of Southern California Childrens' Hospital, Radiation Oncology Division.)

of patients with pituitary adenomas. There has been an unprecedented growth of all forms of SRS, helping to redefine management of patients with many malignant and benign intracranial lesions [1,46–48]. Frameless stereotaxy with the Cyberknife has been developed and is currently being used in the clinic [9,11,12]. It provides new and expanded SRS applications inside and outside the cranial cavity. One of the major benefits of frameless stereotaxy is the ability to use multifraction SRS, which is difficult if not impossible with frame-based SRS systems.

Proton beam radiosurgery

Based on the unique physical characteristics of charged particle beams, their therapeutic use was initially proposed by Wilson [49] more than 50 years ago. The Bragg peak of a monoenergetic proton beam is sharply defined, with the dose in the peak region being much higher than that in the plateau (Fig. 7). This unique characteristic allows for successful treatment of tumors adjacent to a critical structure, such as the chiasm, without causing radiation injury. Because of virtually zero exit doses for proton beams, normal brain tissue surrounding the lesion can be successfully protected. SRS usually requires the use of multiple proton beams, which are applied at different angles either in a coplanar or non-coplanar fashion. SRS permits the achievement of a well-localized and conformal dose distribution. Each beam can be collimated by a metallic aperture to conform to the cross-sectional size and shape of the lesion in a projection along the path of the beam. Three-dimensional conformal dose distributions can be obtained by (1) adjusting the range, (2) spreading the Bragg peak, (3) introducing tissue-equivalent compensators, or (4) using an appropriately shaped aperture for each beam [4,50,51]. In 1954, the first patient was treated at the University of

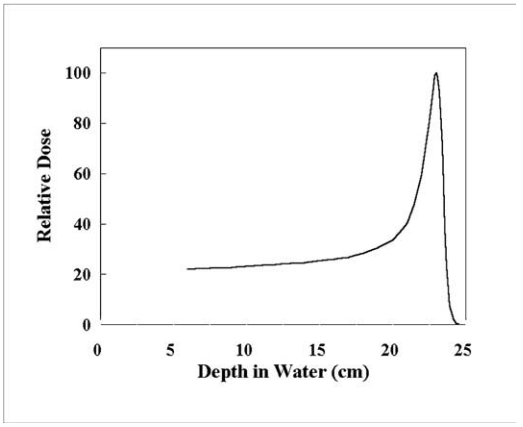

Fig. 7. A typical depth-dose distribution for the proton beam with the Bragg peak at a depth of approximately 23 cm.

California at Berkeley–Lawrence Laboratory with a proton beam to suppress pituitary hormone production [5]. During the past 40 years, proton beam radiosurgery has been used extensively for lesions in the pituitary region with the following indications [2,3]: (1) primary treatment for pituitary adenomas, (2) adjuvant therapy for postoperative residual tumors, and (3) in patients with recurrent tumors after surgery. A major disadvantage of proton and heavy particle beam therapy is its high cost, limiting the use of this important modality to a few centers in the country. Some of the best treatment results in patients with pituitary adenomas have been obtained with proton or heavy particle beams [2,3,5].

Linear accelerator-based radiosurgery

LINAC-based SRS was originally developed in the early 1980s as a modification of the standard LINAC with the addition of tertiary collimation and a stereotactic frame system. Various dedicated SRS systems are currently commercially available, such as the X-knife (Radionics, Burlington, MA), Brain-Lab (Heimstetien, Germany), and Peacock system (Nomos Corporation, Sewickley, PA).

Most of the accelerator-based SRS techniques use circular collimators usually ranging from 5 to 40 mm in diameter. Each collimator is attached to the head of the LINAC, which is set to its primary rectangular collimators or jaws to a field size of 5 cm × 5 cm at the isocenter. In SRS for pituitary adenomas, conforming dose distributions for an elongated target can be achieved by shaping the dose through the use of (1) different sized circular collimators, (2) increasing the number of isocenters used in the treatment, (3) modifying the extent of beam rotation, and (4) varying doses for each arc [52,53]. Larger and irregularly shaped targets can be treated by placing different isocenters with appropriate collimator sizes for each isocenter. The protection of the optic nerves and chiasm can be achieved by (1) selecting appropriate arcs, (2) modifying the extent of arcs, and (3) varying collimator diameter. Fig. 8 shows a modified 4-MV LINAC-based SRS system used in the treatment of a patient with a pituitary adenoma at USC.

Unlike most of the LINAC-based SRS techniques, which involve rotations of the gantry (Fig. 9) and the treatment couch, the Cyberknife (Fig. 10), also known as frameless SRS, uses the image-guided robotic technique [9,11,12]. The system provides excellent flexibility in targeting and dose delivery. Advanced image guidance technology is designed to track patient and target position during treatment, ensuring accuracy without the use of an invasive head frame. The Cyberknife allows for delivery of precisely localized irradiation to focal lesions within the central nervous system (CNS) or elsewhere in the body. In this image-guided robotic system, treatment planning, real-time

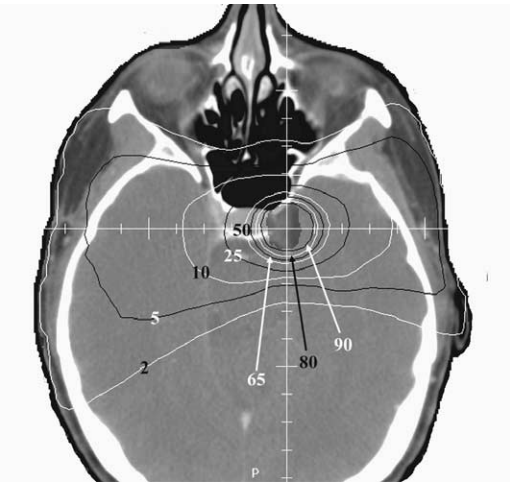

Fig. 8. Transverse CT image with superimposed isodose lines of 2%, 5%, 10%, 25%, 50%, 65%, 80%, and 90% for the treatment of a residual pituitary adenoma in the left cavernous sinus. The irregularly shaped lesion had a volume of 2.3 cm^3, with dimensions of 13.0 mm (X) × 17 mm (Y) × 22 mm (Z). The treatment plan was developed with seven evenly spaced arcs. The lesion was fully covered with the 90% isodose line.

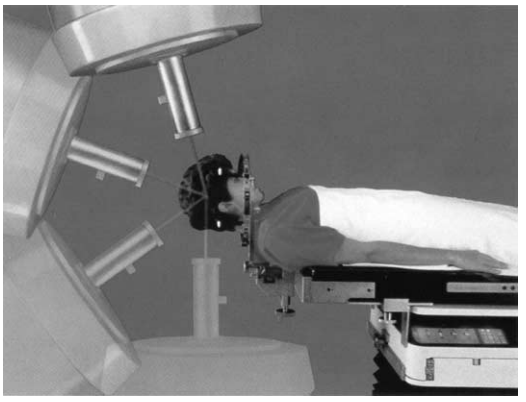

Fig. 9. Linear accelerator–based multiple arc technique. Each arc is achieved by rotating the gantry in the vertical plane about the isocenter while keeping the treatment couch stationary. (*Courtesy of* Radionics, Burlington, MA.)

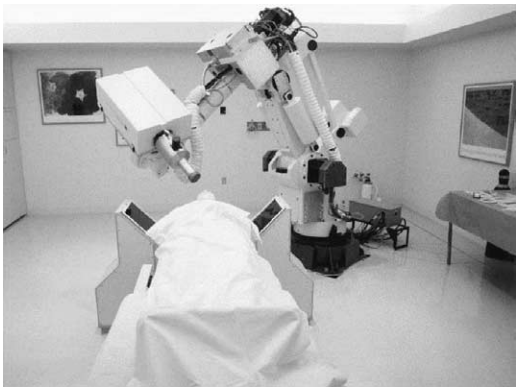

Fig. 10. A picture of the CyberKnife, showing the linear accelerator, the robotic arm, the treatment couch, and the amorphous silicon image detectors. (*Courtesy of* the Cleveland Clinic Foundation, Cleveland, OH.)

imaging, and treatment delivery components are all integrated by a powerful computer workstation. Another form of frameless stereotactic system for fractionated radiotherapy was reported from the University of Florida (Gainesville, FL) [10].

Over the past 20 years, a relatively large number of pituitary adenoma patients have been treated with SRS with good outcomes. In one review of 1070 patients treated with SRS, more than 75% responded well to SRS [8]. The evaluation of SRS treatment efficacy, however, presents a problem, because there has been (1) wide variation in treatment indications for SRS; (2) differences in reported study end points; (3) wide variations in radiation doses, with a range from 30 to 150 Gy; and (4) wide variation in duration of follow-up [8]. For the same reasons, a direct comparison with external beam radiotherapy presents a difficult problem. As an example, patients selected for SRS at USC would have smaller (<3.5 cm) tumors located not closer than 3 mm to the chiasm or optic nerves, whereas those treated with external beam radiotherapy would typically have larger (>3.5 cm) tumors frequently involving those critical structures.

It is of interest to review a study of 48 patients reported from Harvard University, which attempted a comparison of SRS with SRT [48]. As expected, the 18 (37%) SRS-treated patients had a smaller median tumor volume than the 30 (63%) patients treated with SRT (median: 1.9 cm^3 versus 5.73 cm^3). SRS radiation doses to the tumor periphery ranged from 10 to 18 Gy defined to the 70% to 90% isodose line using a single isocenter for all but 2 patients. The SRT dose was 45 Gy at a rate of 1.8 Gy daily to the 90% or 95% isodose line. The median follow-up for all patients was 36 months (47 months for SRS and 34 months for SRT). The overall 3-year survival rates were 93% for SRS patients and 100% for SRT patients. The overall local tumor control at 3 years after treatment was 91%, including 100% for SRS and 85% for SRT. Hormonal response was noted in 50% of the 18 SRS patients and in 62% of the 30 SRT patients. The treatment was well tolerated by patients in both groups. Three of the 18 SRS patients developed ring enhancement in the adjacent temporal lobe on MRI, with 1 patient symptom-free and 2 patients with temporal lobe epilepsy. The presence of this ring enhancement in 3 (17%) patients treated with SRS is difficult to explain. It is likely related to a higher than expected radiation dose to the affected sites. Freedom from late CNS toxicity at 3 years was 90%, with a 72% incidence for SRS patients and a 100% incidence for SRT patients. Freedom from hormone replacement therapy at 3 years after treatment was 78%, with no significant difference for patients in either treatment group. There was no cranial nerve injury reported in this study. Based on their experience, the study investigators recommended SRT rather than SRS for patients with pituitary adenomas.

Similar treatment outcomes with a lower incidence of toxicity were noted in a study of 24 patients [54]. The study authors demonstrated a more rapid clinical and hormonal response in SRS-treated patients when compared with a similar patient population treated with conventional external beam radiotherapy. Fractionated SRT in 63 patients was compared with SRS in 5 patients at the University of Heidelberg (Heidelberg, Germany) [55]. The mean radiation dose for the SRT group was 52.2 Gy given at a rate of 1.8 to 2.0 Gy daily, and it was 15 Gy for SRS patients. The mean follow-up was 39 months. The overall incidence of tumor control was excellent at 93%. Somewhat disappointing was the 6% incidence of decreased visual acuity. The study investigators, however, viewed fractionated SRT and SRS as safe and effective therapy in the management of patients with pituitary adenomas. Similar conclusions were reported in a small study using fractionated SRT from Thomas Jefferson University (Philadelphia, PA) [56].

Gamma knife radiosurgery

The Leksell Gamma Unit was originally developed at the Karolinska Institute (Stockholm,

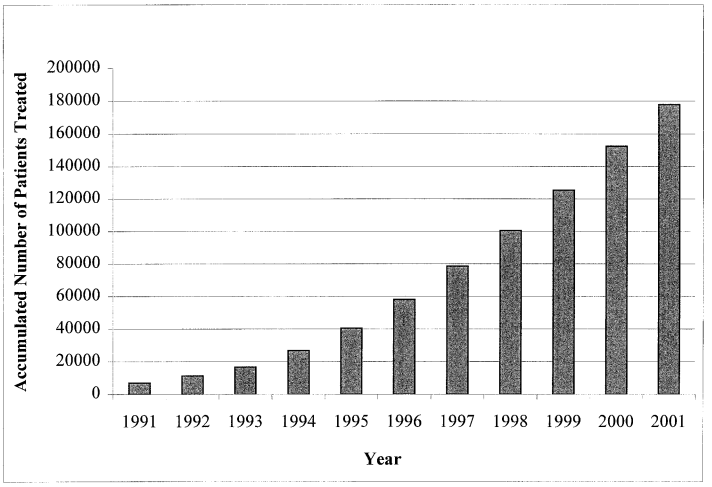

Fig. 11. Cumulative number of patients treated worldwide between 1991 and 2001. Note that there is a steep increase in the number of patients treated annually. (*Courtesy of* Gamma Knife Society, Norcross, GA.)

Sweden) in 1968 [6,7]. In recent years, there has been an exponential growth of GKSRS. As of April 2001, a total of 151 gamma knife facilities were treating patients worldwide, including 66 (43%) facilities in the United States (courtesy of Gamma Knife Society). A total of 177,846 patients received GKSRS worldwide, with the United States contributing 27% of patients (Figs. 11 and 12). This number included 14,752 (0.8%) patients with pituitary adenomas, with 1943 patients with this diagnosis treated in the United States (Fig. 13). It has been estimated that in the United States, approximately 800 new patients with pituitary adenomas per year are good candidates for GKSRS (courtesy of Gamma Knife Society).

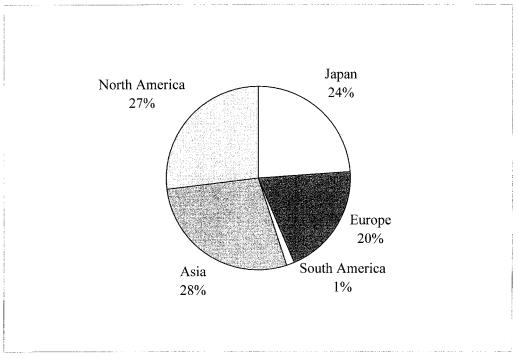

Fig. 12. Geographic distribution of patients treated with the gamma knife between 1991 and 2001. (*Courtesy of* Gamma Knife Society, Norcross, GA.)

The currently available gamma knife models include the B, U, and C models. Each model contains 201 cobalt-60 sources located in a hemisphere around a common focal point. The arrangement of cobalt-60 sources and the angle of the collimation helmet in the U model are different from those in the B and C models. The newly introduced model C (Fig. 14) is equipped with an automatic positioning system (APS), which allows for robotic setting of X, Y, Z coordinates for each isocenter used in a given treatment. The APS makes it practical to use as many isocenters as clinically required to obtain optimal treatment conformity. Digital integration of the system from a CT or MRI scanner to the treatment unit ensures accuracy, safety, and speed of the procedure.

The gamma unit is designed with four different sizes of collimators, including 4, 8, 14, and 18 mm. Radiation dose distribution for each isocenter can be altered by replacing some of the collimators with solid tungsten plugs. This allows for the optimization of protection of critical structures, such as the optic nerve or chiasm. Fig. 15 demonstrates the use of GKSRS for a patient with a pituitary adenoma treated with the C model at USC. Unlike treatment with the U model, where most beams come from the vertex, there was no need to use any special plugs with the C model to optimize the radiation dose distribution. The use of plugs would be required in the U model to reduce the dose to the optic nerves and chiasm. Selected beam channels were blocked in our patient to reduce radiation exposure to the anterior part of the eye.

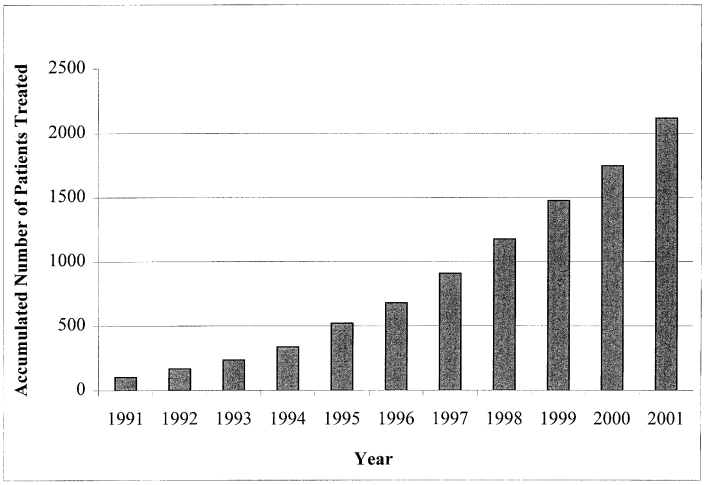

Fig. 13. Number of patients with pituitary adenomas treated annually in the United States between 1991 and 2001. (*Courtesy of* Gamma Knife Society, Norcross, GA.)

Patients presenting with symptomatic macroadenomas need surgical treatment, which is curative in most instances [47]. In a small subset of patients, elective GKSRS is required if an incomplete resection was performed [47]. Planned postoperative GKSRS for minimal disease is preferred to the treatment of larger recurrent lesions. Most frequently, residual adenoma is found in the cavernous sinus, and GKRSR is the treatment of choice for this tumor manifestation at the present time.

A study in 73 pituitary patients treated with GKSRS was reported from the University of Graz (Graz, Austria) [57]. Hormone-secreting adenomas were diagnosed in 42 (58%) patients, whereas 31 (42%) had hormone-inactive tumors. The mean target volume and mean radiation dose were 6.7 cm^3 and 14.2 Gy, respectively, for prolactinomas; 2.9 cm^3 and 16 Gy, respectively, for GH adenomas; and 3.6 cm^3 and 17 Gy, respectively, for corticotropin adenomas. The mean target volume and radiation dose in hormone-inactive patients were 4.4 cm^3 and 13.8 Gy, respectively. The reason for the higher radiation doses given to patients with hormone-secreting adenomas than to those with hormone-inactive tumors was the perceived lower response rates to radiation in this patient group. Mean follow-up was 29 months. Mean radiation doses to the chiasm ranged from 7.4 to 9.2 Gy. MRI assessment of tumor response was available in 58 (79%) study patients. No change in tumor volume or tumor volume reduction was noted in 98% of patients. During the period of observation, only 1 patient showed an increase in tumor

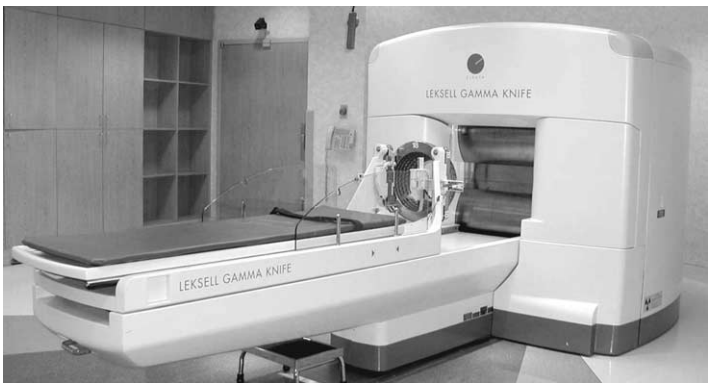

Fig. 14. The model C Leksell Gamma Unit with the 18-mm collimator helmet in position before treatment.

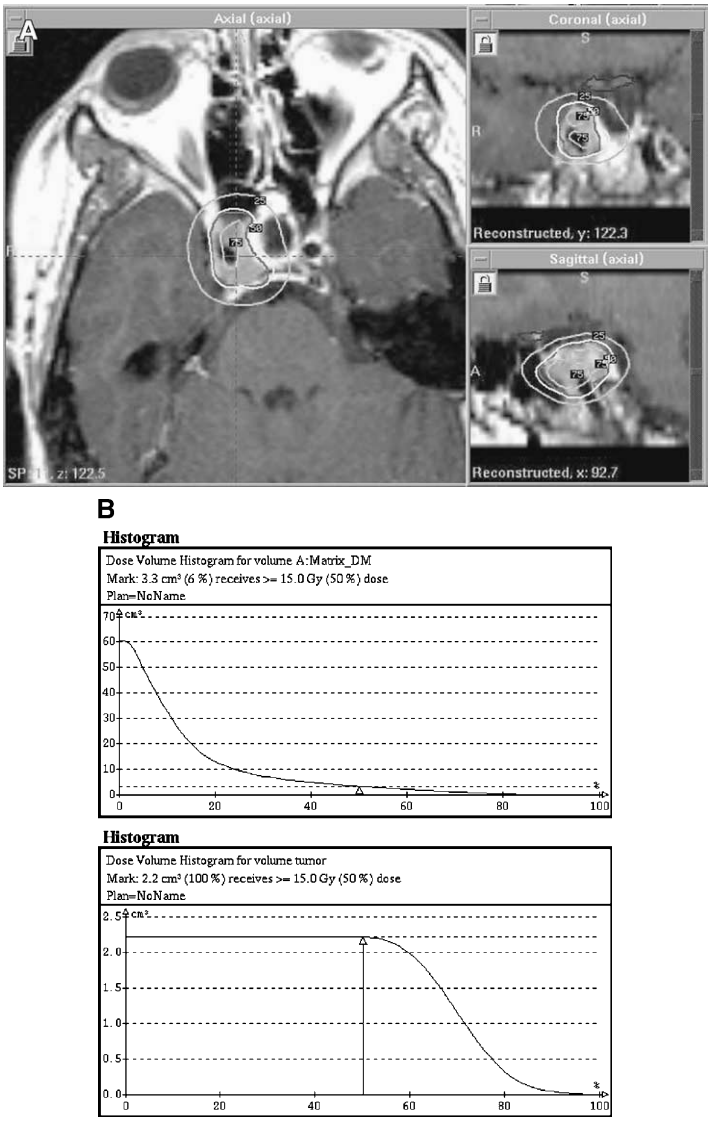

Fig. 15. (*A*) Transverse MRI with superimposed isodose lines of 25%, 50%, and 75% for treatment of a pituitary adenoma in the right cavernous sinus. The coronal and sagittal images reconstructed from the axial images are also shown on the right side of the picture. The irregularly shaped lesion was 2.2 cm^3, with dimensions of 15.0 mm (X) × 22.5 mm (Y) × 16.5 mm (Z). The outline of the lesion is indicated by the darker line appearing immediately inside the 50% isodose line. The treatment plan was developed with eight 8-mm collimator helmets. The lesion was fully covered with the 50% isodose line (ie, 15 Gy) relative to the dose maximum of 30 Gy. The maximum doses to the optic nerves and optic chiasm were 5.2 Gy and 2.7 Gy, respectively. (*B*) Dose-volume histogram shows tumor volume of 2.2 cm^3 and total treated volume of 3.3 cm^3.

size. Patients with hormone-secreting adenomas demonstrated a 57% incidence of normalization of pituitary function. A total of 19% of patients had decreased pituitary function, with no patient experiencing cranial nerve dysfunction or visual abnormalities. Of concern in this study is a higher than generally recommended radiation dose to the chiasm. This may result in late visual toxicity becoming apparent with longer follow-up. Similar treatment outcomes were reported in a study of 73 patients from the Shanghai Gamma Knife Hospital in Shanghai, China [58,59].

Multiple published reports consistently have demonstrated from an 80% to greater than 90% probability of tumor volume reduction or no change in tumor size in patients with hormone-inactive tumors [1,60–64]. The response rate in patients with hormone-secreting tumors was lower, with a range from 50% to greater than 75% [1,39,61–67].

Between 1994 and 2001, a total of 72 consecutive patients with pituitary adenomas underwent 76 GKSRSs at USC (unpublished data). Patients selected for this therapy met the following criteria: (1) recurrent adenoma after transsphenoidal surgery; (2) planned therapy for postsurgical residual disease, usually present in the cavernous sinus; (3) patient diagnosed with an adenoma based on hormonal and imaging studies and not a surgical candidate (uncommon indication); (4) patient with hormone-secreting tumor; and (5) presence of tumor greater than 3 mm from a critical structure, such as the chiasm. Those with chiasm involvement were considered for three-dimensional conformal external beam radiotherapy (see the preceding section for relevant details).

There were 42 (58%) male and 30 (42%) female patients. Four patients had extensive bilateral cavernous sinus disease requiring two gamma knife treatments. Nearly 90% of patients were treated for recurrent or residual involvement after one or more surgical procedures. Tumor in the cavernous sinus was diagnosed in 62 (86%) patients, including one third who presented with extensive involvement of this structure, resulting in encasement of the internal carotid artery. A total of 20 (28%) patients had hormone-secreting adenomas. This group included 12 (17%) prolactin-, 5 (7%) GH-, and 3 (4%) corticotropin-secreting tumors. The median tumor volume was 2.4 cm^3, with a median treated volume of 4.3 cm^3. The median radiation dose to the tumor periphery was 15 Gy defined to the 50% isodose line. A median of five isocenters was used in the treatment of these patients (Table 1). The treatment objective was to obtain the best possible tumor volume coverage and careful protection of the adjacent normal structures, such as the chiasm. Because of a relative paucity of data on the late effects of SRS on normal perisellar structures, conservative radiation dose limitations were selected. These included a dose of 8 Gy or less to the chiasm and a dose of 9 Gy or less to the optic nerves. The actual median doses delivered were lower, including 5.2 Gy to the chiasm, 6.8 Gy to the optic nerve, and 9.1 Gy to the pons (see Table 1). Important treatment details on SRS of tumors involving the cavernous sinus are presented elsewhere [46].

Table 1
Treatment parameters in University of Southern California study of 72 patients

Parameters	Median	Mean	Minimum	Maximum	SD
Tumor volume (cm^3)	2.4	3.9	0.1	27.4	4.9
Treated volume (cm^3)	4.3	5.5	0.4	33.8	5.7
Radiation dose (Gy)	15.0	15	14	16	0.25
Isodose line (%)	50	51	49	75	4.0
Number of isocenters	5	5	1	10	2.0

Before GKSRS, in addition to a routine history and physical examination, all patients had detailed neurologic, endocrinologic, and comprehensive ophthalmologic examinations. The latter included Humphrey's visual field and visual acuity examinations. All patients were treated on an outpatient basis under systemic sedation. MRI of the brain as a part of treatment planning was available in all but one patient, who had contraindications to MRI and was imaged with CT. None of the patients was lost to follow-up. The follow-up schedule was as follows: the first visit at 3 months after treatment, where interval history was obtained, a short examination was performed, and MRI of the brain was reviewed; subsequent visits were at 6-month intervals for the first year and annually thereafter. At each visit, MRI of the brain was reviewed and the treatment progress was assessed with special attention to the patient's quality of life. Special efforts were made to recognize any possible treatment complications, such as decreased pituitary function. This was done to initiate, if necessary, appropriate therapy before the patient developed clinical signs or symptoms of disease. A similar follow-up schedule was maintained by ophthalmology and endocrinology services. The former obtained visual acuity and Humphrey's visual field examinations among others, whereas the latter assessed pituitary function with a possible need for hormone replacement therapy. Follow-up ranged from 6 to 72 months, with a median of 34 months.

Of the 10 patients presenting with cranial nerve dysfunction, all experienced complete recovery or major improvement in their signs and symptoms

within 12 months of therapy. Among the 20 patients presenting with hormone-secreting tumors, all 8 patients with corticotropin- or GH-secreting adenomas responded well to therapy, whereas 10 of 12 patients with prolactinoma had normalization of their hormone level. The remaining 2 patients with high pretreatment prolactin levels experienced an increase in these hormone levels after therapy. There were two patients with amenorrhea secondary to a high serum prolactin level. Both of these patients subsequently had three normal pregnancies and deliveries. The median time to treatment response in patients with hormone-producing adenomas was 7 months.

Tumor volume reduction was a slow process, with 30% of patients showing decreased tumor volume more than 3 years after GKSRS. Two thirds of the study patients demonstrated slight to moderate tumor volume reduction. None of the 72 patients showed tumor progression in the treated volume. All patients were alive except one, who died at 3 years of therapy as a result of disseminated carcinoma of the colon.

GKSRS was well tolerated with acute toxicity of no clinical significance, such as a short period of fatigue or nausea. Late toxicity consisting of sixth nerve palsy was noted in 2 (3%) patients. Patient 1 developed it at 3 months after treatment, and there was no resolution during the 3 years of observation. Patient 2 developed sixth nerve palsy at 25 months after treatment with a spontaneous resolution 10 months later.

Based on our data, we believe that GKSRS is a safe and probably effective treatment for selected patients with pituitary adenomas. It is apparent that longer follow-up (>10 years) is required for a more complete assessment of late toxicity and ultimate treatment efficacy. At USC, we have a LINAC-based system as well as a gamma knife. For the treatment of pituitary tumors, we favor the gamma knife system over the LINAC-based system because of its greater potential for protection of normal critical structures, such as the chiasm or the second nerve.

Treatment toxicity

External beam radiotherapy

An overwhelming majority of patients treated with contemporary external beam radiotherapy tolerate the treatment well, experience no significant toxicity, and are able to lead a normal life after therapy. The incidence and severity of postradiation complications have to be compared with those of transsphenoidal surgery, which is a safe and effective therapy [68]. The most important but rare complication of radiotherapy is impairment of vision. In a carefully conducted study of 86 patients treated at the National Cancer Institute (Bethesda, MD) [69], the median radiation dose was 50 Gy (range: 45–59.4 Gy) and the median follow-up was 48 months. Of the 38 eyes with a long history of testing of visual acuity, 27 (71%) had no visual acuity problems and maintained this status after radiotherapy, 7 (18%) eyes had improved visual acuity, and 4 (11%) showed no change in their visual problems. One study patient developed vertical diplopia, 1 patient had a cerebrovascular accident 7 years after therapy, and 5 patients developed other neurovascular problems, such as migraine headaches, occurring from 1.5 to 3 years after therapy. It needs to be pointed out that all these patients had radiation doses greater than 50 Gy and none had radiation doses less than 50 Gy. Radiation doses greater than 50 Gy should be used infrequently in the treatment of patients with pituitary adenomas because they are likely to produce unacceptable complication rates [70,71]. The same caution applies to the use of a daily dose greater than 2 Gy, with the recommended daily dose being 1.8 Gy [71–73]. In a recently published study on 50 pituitary adenoma patients, 14 (28%) developed mild to moderate visual impairment after radiotherapy [38]. This incidence of toxicity is not acceptable in current practice. The incident of visual impairment after external beam radiotherapy should not exceed 1% to 2%. Most of the severe pituitary and parapituitary complications have been reported in patients receiving radiotherapy for the treatment of head and neck cancer or in those receiving irradiation for brain tumors [14,73,74].

The incidence of pituitary and hypothalamic dysfunction after external beam radiotherapy depends on a number of factors, including (1) patient age, (2) total radiation dose, (3) daily radiation dose, (4) prior surgery and its extent, and (5) the time of assessment of pituitary function [74,75]. In view of the fact that patients may develop hypothalamic-pituitary dysfunction many years after administration of radiotherapy, the need for long-term follow-up becomes apparent.

In the reported series, the incidence of decreased hypothalamic-pituitary function requiring replacement therapy varies widely. The incidence of decreased pituitary function after surgery is less than 20%, whereas that after radiotherapy,

particularly in patients who have had prior surgery, may exceed 40% [19,29,30,76,77]. In view of this problem, patients who have received pituitary irradiation should be carefully followed for an indefinite period so as to diagnose and treat pituitary dysfunction before the development of clinical signs and symptoms of disease.

Postradiation oncogenesis is an uncommon event after pituitary irradiation, and its true incidence is unknown [78], Patients develop secondary tumors in the vicinity of the irradiated region with great latency, which typically exceeds 10 years. Few studies have examined the incidence of secondary tumors [78–80]. A total of 29 patients with sellar and parasellar fibrosarcoma have been reported in the literature [78]. Most of these patients were treated in the premegavoltage era. The latent period from radiotherapy to a diagnosis of secondary malignancy in this group of 29 patients extended from 2 to 27 years, with a median period of 10 years. These patients were refractory to therapy and had a short length of survival not exceeding 2 years. The most common secondary tumor reported, however, was meningioma. Its true incidence in patients after pituitary irradiation is difficult to establish because of the relatively common occurrence of spontaneous meningioma in the region of the sella [78]. Radiation-induced meningiomas have been primarily reported in patients treated with radiotherapy in the head and neck region. The latency period may extend from 15 to 50 years.

Parasellar gliomas have been infrequently reported in patients who received radiotherapy during childhood [78]. Adult gliomas are uncommon secondary tumors after sellar irradiation, with a small number of patients reported in the literature [78–80]. An interesting study attempting to assess the risk of second brain tumors after surgery and radiotherapy for pituitary adenoma was reported from the Royal Marsden Hospital [79]. A total of 334 patients with pituitary adenomas received their treatment (median dose of 45 Gy) in that medical center and were followed for 3760 person-years. Second brain tumors were diagnosed in 5 (1.5%) patients and included two gliomas, two meningiomas, and one meningeal sarcoma. The cumulative probability of second brain tumors developing during the first 10 years after treatment was 1.3%, and over 20 years, it was 1.9%. No increase in the incidence of extracranial tumors was noted in this study. Similar conclusions were reached in a study of 367 patients treated with radiotherapy for pituitary adenoma at the Princess Margaret Hospital (Toronto, Ontario, Canada) [31]. Four (1%) gliomas was diagnosed, with all being in the previous radiation fields. The latency period extended from 8 to 15 years. The actuarial risk of second tumors at 10 years after treatment was 1.7%, and at 15 years, it was 2.7%.

The incidence of cerebrovascular accidents (CVAs) after pituitary irradiation is not known [76]. This incidence was studied in a group of 156 patients treated for pituitary adenomas at the University of Pittsburgh [81]. A total of 7 (4.5%) patients had strokes from 3 to 15 years after radiotherapy. In multivariate analysis, an increased risk of stroke correlated well with patient age but not with radiation dose ($P < 0.0001$). Based on this study, pituitary irradiation does not seem to be a predisposing factor for CVAs.

Stereotactic radiosurgery

All SRS treatment modes used in the management of patients with pituitary adenomas are well tolerated, and there is a low incidence of acute toxicity of clinical importance [46]. There is, however, a low probability of late treatment complications in patients in whom radiation tolerance of critical structures was clearly exceeded. Two studies analyzed risk factors for clinically important SRS toxicity [82,83]. A study of 133 consecutive SRS patients from the University of Cologne (Cologne, Germany) has shown the treatment volume and radiation dose to be important predictors of toxicity [83]. A study of 62 patients from Harvard University treated with SRS ($n = 29$ [47%]) and from the University of Pittsburgh treated with GKSRS ($n = 33$ [53%]) demonstrated posttreatment cranial nerve dysfunction in 12 (19%) patients [82]. This group of 12 patients included 4 with injury to the optic apparatus. No clear relation could be established between treated volume; radiation dose; and injury to third, fourth, and sixth nerves. There was, however, an important relation between radiation dose greater than 8 Gy in optic injury. None of the 35 patients receiving less than 8 Gy to the optic apparatus sustained an injury, whereas 4 of the 17 patients receiving greater than 8 Gy developed important visual complications ($P = 0.009$). Radiation doses less than 8 Gy to the optic apparatus seem to be safe, with optic neuropathy being an unlikely event [46,82–84]. Of concern, however, is a trend in some medical centers to use higher (up to 30 Gy) radiation doses to the tumor periphery, with higher doses to the chiasm and other critical

structures, which may produce significant toxicity apparent with longer follow-up [61,85–88].

A case of cerebral infarction caused by internal carotid artery occlusion occurring 4 years after GKSRS for a pituitary adenoma has been reported [89]. This complication occurred in a patient who received, in our opinion, an excessive dose of radiation (20 Gy). This complication has not been reported in patients receiving 15 Gy to the cavernous sinus.

It is apparent that an understanding of the important radiation dose limitations to the perisellar critical structures will make all forms of radiosurgery a safe, well-tolerated, and effective treatment.

Summary

Based on a review of the literature and our medical center experience, we believe that transsphenoidal surgery is the procedure of choice in most patients with pituitary adenomas. Conversely, SRS is a procedure of choice for those with cavernous sinus involvement. Patients with incomplete surgical excision should be considered either for a planned stereotactic treatment or for external beam radiotherapy. The same applies to patients with recurrent tumors. We favor stereotactic treatment in patients who have tumors that are less than 35 mm in diameter and at least 3 mm from the chiasm or optic nerves. Other patients should be considered for three-dimensional conformal radiotherapy. Radiotherapy provides a good treatment alternative in those patients who either refuse surgery or have contraindications to this therapy. Contemporary radiotherapy and SRS for pituitary adenomas is safe and effective treatment. This treatment should be undertaken in medical centers with appropriate expertise and instrumentation.

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