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Treatment of Pituitary Tumors

Radiation

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In this paper, the role of conventional radiotherapy and radiosurgery in the management of pituitary tumors is reviewed. After a short summary of the mechanism of action of irradiation therapy and the types of different irradiation techniques, the therapeutic effects and side effects are analyzed in patients with different types of pituitary tumors, including our own experience with conventional radiotherapy and radiosurgery in patients with acromegaly. Conventional fractionated radiotherapy has long been used to control growth and/or hormonal secretion of residual or recurrent pituitary tumors. However, patient selection for conventional radiotherapy still remains a controversial issue, because a number of potentially significant side effects, including hypopituitarism and other complications, have been described. Stereotactic radiotherapy/radiosurgery methods have several potential advantages over conventional radiotherapy, including their use in patients with residual or recurrent pituitary tumors who had previously been treated by conventional radiotherapy, but long-term follow-up data with these relatively new techniques are still limited.

Key Words: Pituitary tumor; conventional radiotherapy; stereotactic radiosurgery; gamma knife.

Introduction

Among the different modalities available for the treatment of pituitary tumors (transsphenoidal surgery, conventional radiotherapy, radiosurgery, and medical therapy), irradiation techniques have long played an important role. In general, radiation therapy has been reserved for cases not cured by other treatments, when further therapy is required to control the growth and/or secretion of pituitary tumors *(1)*.

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Pituitary tumors are broadly classified into two groups: secreting and non-secreting tumors. Patients with hormone-secreting tumors are characterized by specific symptoms and signs of hormonal oversecretion (prolactin, GH, ACTH, TSH, LH, and FSH). In addition to these symptoms, local compression of the surrounding structures caused by the tumor can lead to headache, bitemporal hemianopsy, and other neurological defects, as well as hypopituitarism. Non-secreting tumors, on the other hand, present with symptoms and signs of tumoral compression. A comprehensive strategy for treating patients with pituitary tumors should aim to relieve compression symptoms by controlling tumor growth, suppress oversecretion of hormones, and prevent consequences of hormonal excess in the case of hormone-secreting tumors, while maintaining normal pituitary function. Although these treatment goals can be achieved in several cases by standard neurosurgical methods and/or medical therapy, irradiation remains an important adjunctive therapy to surgery and/or drug treatment in patients with secreting and non-secreting pituitary tumors. Recent technical development seems to enhance the role of radiation therapy and, in a few selected cases, radiosurgery may be considered as an alternative to neurosurgical procedures *(2)*, although its use for primary treatment of pituitary tumors is still reserved to a few cases resistant to medical therapy and unwilling or unsuitable, for medical reasons, to undergo pituitary surgery.

Mechanism of Action of Radiation Therapy

The effect of radiotherapy is based on the ionizing effect of radiation, i.e., the ability to convey sufficient energy to dislodge one or more orbital electrons from the atom or molecule the beam is colliding against *(2)*. Two types of ionizing radiation, high-energy electromagnetic radiation (X-rays and gamma-rays) or charged particles (electron, proton, neutron, α- or β-particle, negative π-meson, or heavy ion beams) can be used for therapeutic purposes *(2,3)*. Ionization and excitation caused by these radiations result in the development of free radicals that carry an odd electron on their outer shell. This state is accompanied by extreme chemical reactivity, which leads to biological effects by

damaging critical molecules (DNA and, to a lesser extent, cell membrane molecules and enzymes) in cells *(2,4)*.

There are two different effects of ionizing radiation; an immediate, deterministic one, and a delayed, stochastic effect. In the case of the former one, the intensity of the effect is proportional to the dose, however, only above a specific threshold. This leads to cell death, which is considered as the most important therapeutic effect. Based on the study of the effect of ionizing radiation doses of 20–50 Gy on a somatomammotroph pituitary cell line GH3, Marekova et al. found that the basic mechanism of cell death induced by irradiation using gamma rays is programmed cell death (apoptosis) following cell cycle arrest in the G2/M phase *(5)*. The stochastic, sublethal effect occurs incidentally at a given dose, but it does not have a threshold. In this case, the probability of the damage occurring is proportional to the dose, and this effect is responsible for late side effects of radiation such as point mutations, chromosomal aberrations, or malignant transformation.

The aim in tumor therapy is to destroy all tumor cells without causing any irreversible damage to normal cells. This can potentially be achieved because undifferentiated and fast dividing (e.g., tumor) cells are more sensitive to radiation than differentiated ones that are dividing at a slower rate. From remaining healthy stem cells, normal tissue is capable of regenerating itself *(3,4)*.

Conventional External Beam Radiation Therapy

By means of conventionally administered external beam radiation therapy, a uniform dose of radiation is given to the entire region affected by the tumor. When conventional external beam radiation is used, the total dose is given in small fractions. Fractionation is useful because normal healthy tissue is more likely to regenerate during the treatment intervals than tumoral tissue. Additionally, tumor cells being in G_0 or S phases and insensitive to radiation at one treatment can turn into more sensitive such as in M or G_2 phases for the next treatment *(4)*. Disadvantage of this technique is that the effect develops relatively slowly, and the maximal effect often requires many years to develop *(6)*.

Stereotactic Radiotherapy/Radiosurgery

In neurosurgery, stereotaxy refers to the geometric determination of the spatial position of intracranial target points by means of a three-dimensional coordinate system. Stereotactic radiosurgery allows the destruction of previously localized brain structures (based on CT or MRI scans) by precisely focused, single high-dose external radiation without opening the skull *(2)*. During stereotactic procedures, the head of the patient must be immobilized with skeletal fixation devices. The entire treatment planning, as well as the treatment itself, is aided by a computer.

There are three distinct radiation methods currently available to deliver stereotactic radiotherapy depending on the source of the radiation. The first uses fast charged particle beams (e.g., protons) that, while slowing down in matter, are losing energy more rapidly because of their interactions with constituent molecules. Therefore, this technique deposits its energy maximally at the end of the particular track (the Bragg peak) *(7)*. The breadth of the Bragg peak may be exactly predetermined by adjusting the energy of the particles, thus allowing the precise deposition of ionizing radiation over a finite track length. Mixing energies allows conformation of dose distribution to tumor volume *(8)*. Because particle acceleration requires a cyclotron, in spite of apparent advantages, its use is limited.

The second type, linear accelerator (LINAC)–based technology, utilizes the so-called arc principle. In this method a single radiation source (X-ray) is moved along an arc continuously emitting a sub-threshold beam and places the cumulative destroying dose to the pathological target in the center of the circle (isocenter), while the surrounding normal tissues receive only tolerable radiation dose.

The third technique, the gamma knife, was designed for fixed radiation sources and fixed targets to reduce mechanical mistakes originating from movement. The gamma knife operates with 201 hemispherically distributed radioactive cobalt-60 sources along an iron shell, focused very precisely into the center by means of primary and secondary collimators (of either 4, 8, 14, or 18 mm in diameter and all positioned radially from the isocenter) with an accuracy of less than 0.5 mm. Each of the 201 beams enters the skull at different points, and delivers a harmless dose on the normal brain tissue surrounding the target. However, in the focus (where the pathological structure is also placed), their energies sum up into a devastating dose *(2,8,9)*. In order to protect brain structures that are more sensitive to radiation (such as the optic nerve or chiasm), collimators of beams that would pass through these structures can be blocked by tungsten (wolfram) plugs. The gamma knife is ideal for sophisticated treatment of small intracranial lesions (<3 cm in diameter) at critical locations.

To determine the radiation dose for radiosurgery, two basic principles must be taken into account: the entire therapeutic dose must reach the target, while steep radiation gradient fall-off is desired toward the surrounding normal tissue. In order to cover irregularly shaped structures, multiple isocenters can be used to establish a conformal shape adapted to the target. The prescribed dose is based on the volume and position of the target tissue, the selected isodose line, and previous conventional radiotherapy *(2)*.

Radiosurgery is usually considered as an adjunctive therapy in the treatment of residual or recurrent pituitary tumors or for tumors extending into the cavernous sinus that are inaccessible for surgical resection *(10)*. It can be used in patients who have already received the maximum conventional radiotherapeutic regime. It has been proposed that maximal tumor reduction and remission of hormone secretion develop earlier following radiosurgery compared to that reported after conventional fractionated radiotherapy

(11,12), although a recent literature review found no clear evidence of a faster decline of elevated hormone levels after radiosurgery *(13)*.

Efficacy of Radiation Therapy in Hormone-Secreting and Non-Secreting Pituitary Tumors

Although several reports have indicated that surgery alone results in a durably maintained remission of most pituitary tumors *(14)*, there is a risk of tumor recurrence of up to 20% at 5 yr and up to 40% at 10 yr after pituitary surgery in non-irradiated patients *(7)*. In an effort to reduce the risk of tumor recurrence, radiotherapy is frequently employed, but its routine use after surgery is still controversial. It has been assumed that signs of aggressiveness on presurgery MRI scan and proliferation activity and/or expression of oncogenes or tumor suppressors in tumoral tissues determined by immunohistochemical or other methods may help the decision whether or not postoperative radiotherapy should be employed *(7,8)*. At present, however, there are no prospective clinical, radiological, pathological, immunohistochemical, or molecular parameters that predict the likelihood of tumor recurrence *(15)*.

According to one proposal, postoperative radiotherapy is recommended in all patients presenting with large tumors or features of aggressiveness *(8)*. Others recommend radiotherapy if a significant tumor remnant is present in postoperative MRI scan performed 4–6 mo after surgery *(14–16)* or, in case of hormone-secreting pituitary tumors, increased hormone concentrations persist after surgery. Because progressing pituitary tumors can be readily diagnosed by repeat magnetic resonance scanning, small intrasellar tumor remnants in the absence of hormonal oversecretion do not necessarily require radiotherapy *(15)*.

In case of secreting adenomas, the shrinkage of tumors and the decrease in hormone oversecretion after radiotherapy is not necessarily simultaneous. Sasaki et al. found that during a median follow-up period of 3 yr, conventional radiotherapy improved symptoms related to compression of surrounding structures in 79% of patients with secreting pituitary tumors who had such symptoms. Also, they noted that the effects of radiotherapy on tumor size and hormonal oversecretion may be mismatched in some secreting tumors *(17)*. In the study of Milker-Zabel et al., fractionated, stereotactically guided radiotherapy resulted in a complete remission of tumor volume and hormonal oversecretion in 26% and 19% of patients with secreting pituitary tumors, respectively, after a mean follow-up of 34 mo *(18)*, suggesting again a dissociation of the effects on tumor control and hormone secretion.

It has been proposed that pituitary hormone–suppressing medications used in the treatment of pituitary tumors exert a radioprotective effect and, therefore, drugs such as somatostatin analogs and dopamine agonists should be discontinued prior to radiosurgical treatment *(19,20)*. However, the data supporting this proposal are still limited.

Prolactinoma

In patients with macroprolactinomas, radiation therapy may be an additional option when medical therapy and surgery fail as well as when the patients are unsuitable for transsphenoidal surgery *(17,21)*. Using conventional radiotherapy, reduction of plasma prolactin levels can be achieved in 44–79% of patients, but irradiation will not always lead to normalization of serum prolactin levels *(22)*. Sasaki et al. found that 10 yr after conventional radiotherapy the local control rate was 83% *(17)*. A recent analysis including 330 patients with prolactinomas from 16 studies with a median follow-up of 6–45 mo after gamma knife radiosurgery indicated that plasma prolactin levels were normalized in 26% of patients and decreased in 62% of patients *(13)*.

Acromegaly

In patients with acromegaly, primary conventional radiotherapy decreases serum GH and IGF-1 concentrations in 70–90% of patients, with a decrease rate of 10–30% per year *(22)*. The probability of normalization is related to pretreatment serum GH levels; irradiation appears to be the most effective in patients with relatively low serum GH levels *(22–24)*. Similar results were obtained in patients who underwent postoperative conventional radiotherapy; in these patients the local control rate was 76–82% 10 yr after therapy *(17,22)*. However, Freda et al. noted that in contrast to a reduction of serum GH levels in most patients, only 5–42% of patients achieve normalization of serum IGF-1 levels after radiotherapy. This finding, together with the long lag time to therapeutic effect and the high incidence of postirradiation hypopituitarism, led to the proposal to reserve conventional radiotherapy for large or invasive macroadenomas that could not be completely removed surgically or for patients resistant to medical therapy *(1)*. According to the study of Shin et al., radiosurgery produced hormonal normalization in more than 65% of patients with acromegaly during a follow-up of 3 yr; the hormonal control rates seemed to be slightly better in patients with acromegaly compared with those with ACTH-producing pituitary tumors *(25)*. Ikeda et al. reported normalization of serum IGF-1 levels in 82% of patients 2 yr after postoperative radiosurgery; they also showed that serum IGF-1 levels become stable 4 yr after therapy *(26)*. By contrast, several other studies reported lower remission rates following radiosurgery *(18,27–29)*. In fact, a recent analysis of 361 patients from 19 published series indicated that only 38% of acromegalic patients had normalization of serum GH levels at a corrected median follow-up of 29 mo after gamma knife radiosurgery *(13)*.

Cushing's Disease

Primary conventional radiation therapy reduces hypercortisolism in 50–75% of adults and in 80% of children with Cushing's disease *(17,22,30)*. The time until remission is generally less than 9 mo, which is considerably shorter com-

pared with that found in patients with acromegaly *(22)*. Postoperative radiation therapy for patients with residual ACTH-secreting pituitary tumor results in remission rates of up to 83% within 6–60 mo after irradiation *(22)*. Nevertheless, conventional radiotherapy should be considered only in patients not cured by repeat transsphenoidal surgery *(1)*. Using radiosurgical techniques, single fraction proton beam therapy produced better results than linear accelerator radiosurgery with multiple isocenters in patients with Cushing's disease, as hormonal normalization was achieved within 5 yr in 80% and 50% of patients, respectively *(22)*. When the data from 19 studies including 208 patients with Cushing's disease undergoing gamma knife radiosurgery were analyzed, 58% of patients had normalization of hormone levels at a corrected median follow-up of 55 mo *(13)*.

Glycoprotein-Hormone Secreting Pituitary Tumors

In patients with glycoprotein hormone (TSH, LH, FSH)–secreting tumors, conventional radiotherapy is recommended as routine adjunctive therapy when surgery has not been curative *(1,31,32)*; nevertheless, only approximately two-thirds of tumors will be under control biochemically *(1,33)*. TSH-secreting tumors, especially when invading the parasellar region, are considered suitable for radiosurgery, but until now this method has been used only in a few patients with such tumors *(31,34,35)*.

Non-secreting Pituitary Tumors

At the time of diagnosis, non-secreting pituitary tumors often present as large lesions with supra- and parasellar extension that cannot be always resected completely by standard neurosurgical techniques *(1,36)*. Postoperative conventional radiotherapy is an option for treatment of residual tumor, especially in the presence of tumor progression *(1)*. Data from eight studies reviewed by Becker et al. indicated that the local control rate after conventional fractionated radiotherapy alone was comparable to surgery alone with recurrence rates from 7% to 50% (median 25.5%) and that the 5- and 10-yr progression-free survival rates were both 84% *(22)*. Surgery followed by postoperative conventional radiotherapy reduced the recurrence rate to 11%, and the 5-, 10-, and 20-yr progression-free survival rates of patients increased to 92%, 89%, and 79%, respectively *(22)*. Breen et al. found that after conventional radiotherapy for non-secreting pituitary tumors, the tumor control rates were 88%, 78%, and 65%, at 10, 20, and 30 yr, respectively, and that tumor progression occurred in 12.5% of patients within 25 yr *(37)*. In the series of Losa et al., surgical debulking followed by gamma knife radiosurgery of non-secreting pituitary tumors resulted in recurrence-free interval of 88% at 5 yr, with 20% or greater reduction of tumor volume in 42% of patients *(38)*. Sheehan et al. demonstrated that after gamma knife radiosurgery adjuvant to surgical resection or conventional radiotherapy, tumor control was achieved in 100% of patients with residual or recurrent non-secreting pituitary microadenomas and 97% of patients with such macroadenomas. Gamma knife radiosurgery proved to be also effective in controlling pituitary tumors with cavernous sinus invasion and/or suprasellar extension *(39)*.

Side Effects of Radiation Therapy

Hypopituitarism

After 10 yr, up to 56% of patients receiving conventional radiotherapy develop hypopituitarism *(22)*, and the incidence increases annually thereafter. The time lag until onset is related to the total and fractionated dose of radiotherapy and the incidence increases with time after the exposure. The overall incidence of postirradiation hypopituitarism is increased in patients who had disturbed pituitary function prior to radiotherapy *(8)*. Rarely, irradiation therapy may provoke pituitary apoplexy.

Postirradiation hypopituitarism may reflect not only a direct damage to the pituitary but also a secondary defect in hypothalamic hormone secretion, because exogenous hypothalamic releasing hormones may effectively stimulate pituitary hormone secretion *(15)*. The sensitivity to radiation damage may follow a typical order (GH and gonadotrop hormone deficiency, followed by ACTH and TSH deficiency); diabetes insipidus occurs very rarely, while plasma prolactin levels may rise. In children, puberty is occasionally accelerated. After radiation treatment, monitoring for the development of new hormone deficits is, therefore, a very important part of the management *(1,23)*.

Using proton and heavy ion beam irradiation, hypopituitarism was observed in up to 50% of patients *(22)*. By contrast, the function of the normal pituitary was less affected in patients treated by modern gamma knife radiosurgery *(40,41)*; a literature review by Becker et al. showed that this single-dose radiosurgery method resulted in a decreased pituitary function in only 0–15% of patients during a follow-up time between 6 and 60 mo *(22)*. Milker-Zabel et al. found that partial hypopituitarism developed in 4.4% of patients after fractionated stereotactically guided radiotherapy or radiosurgery during a follow-up time of 39 mo *(18)*. In a study of Losa et al., new cases of hypogonadism, hypothyroidism, and hypoadrenalism at 41 mo following postoperative gamma knife radiosurgery occurred in 12%, 9%, and 2%, respectively *(38),* whereas in some other radiosurgery series new endocrinological deficiencies were absent during a follow-up time between 6 and 36 mo *(39,42, 43)*. It has been assumed that the low incidence of hypopituitarism following radiosurgery may reflect a high selectivity of the single high-dose irradiation to neoplastic tissue *(44)*, and a minimal dose to normal pituitary gland, stalk, or hypothalamic regions *(45)*.

It has been noted that in addition to the inconvenience of taking life-long hormone replacement therapy, postirradiation hypopituitarism may have other unfavorable impacts *(15)*. As shown in several studies, patients with hypopitu-

itarism have a significantly increased mortality, possibly related to uncorrected GH deficiency, although the doses of other hormones used in replacement therapy may also play a role.

Radiation Damage to the Optic Chiasm

Although pretreatment visual defects may improve in 50–67% of the patients following radiotherapy of pituitary tumors *(22)*, blindness due to irradiation-induced chiasmal damage with a latency of between 2 mo and 4 yr has also been documented. The risk of chiasmal damage is strongly correlated with single doses greater than 2.0 Gy and/or a total dose exceeding 50 Gy *(22)*. When single radiation doses of less than 2.0 Gy and total fractionated doses of 45–50 Gy were used in patients with an intact optic chiasm, the risk of deterioration of vision was less than 1% *(22,37,46)*. However, the optic chiasm compressed by the tumor for a long period of time appeared to be more vulnerable *(8,22)*. With modern stereotactic radiation techniques, special care must be taken to avoid damage to the visual pathways; limiting the dose to the optic chiasm below 8–9 Gy by selective beam blocking and shifting seemed to be safe *(11,12,38,45)*. In radiosurgery series Landolt et al. found no cases of optic neuropathy *(42)*, whereas Sheehan et al. reported that deterioration of visual fields occurred in 2.4% of patients *(39)*. Using the linear accelerator technology, visual field disturbances developed in 2% of patients *(22)*.

Cerebrovascular Lesion and Brain Necrosis

The risk of cerebrovascular accident depends on the dose of radiotherapy; the relative risk is 1.0 for doses less than 45 Gy, 1.7 for doses between 45 and 49 Gy, and 2.8 for doses over 49 Gy *(22)*. The vascular (and neuronal) structures running in the cavernous sinus are not very radiosensitive, allowing an ablative dose to be administered by gamma knife to tumors showing lateral invasion and impinging on cranial nerves III, IV, V, and VI *(12)*.

In the series of Sasaki et al., one patient who received a 60-Gy dose of conventional irradiation developed temporal lobe necrosis, and another patient treated with the same method and dose suffered a hearing loss *(17)*. With modern irradiation techniques, the long-term overall risk of brain necrosis was estimated as 0.2% *(22)*. Milker-Zabel et al. found no cases of brain necrosis after fractionated stereotactically guided radiotherapy and radiosurgery *(18)*.

Radiation-induced Secondary Tumors

There is still some uncertainty about the relative and actuarial risks of developing a second brain tumor in patients with pituitary tumors treated with surgery and irradiation. Most second tumors diagnosed were sarcomas, gliomas, and meningeomas, with a median period of time to detection of 7.0, 9.7, and 13.8 yr after irradiation therapy, respectively *(22)*. Breen et al. found one case of a glioblastoma multiforme and another case of a meningioma 7.5 and 8 yr after radiation doses of 50 Gy in 25 fractions and 50.4 Gy in 28 fractions, respectively *(37)*. When reviewing reported series, Becker et al. found that the cumulative risk of developing a secondary brain tumor was 1.3% at 10 yr and 1.9% at 20 yr after conventional radiotherapy *(22)*. A more recent report by Minniti et al. noted that during a longer follow-up following conventional radiotherapy the relative risk was unchanged, and that the actuarial incidence of 2.4% risk at 20 yr remained low. Therefore, the risk of developing a second brain tumor should not preclude the use of radiotherapy as an effective treatment option *(47,48)*. In addition, there is a debate about the incidence of second brain tumors in patients with pituitary tumors treated with surgery alone, as cases of brains tumors, especially meningiomas, have been reported in patients with pituitary tumors not receiving irradiation therapy *(47,49)*.

It has been assumed that the potential long-term risk of developing a second brain tumor is less likely to occur after gamma knife treatment *(12),* and that radiosurgery-induced malignancies may be extremely rare if high single doses are applied *(22)*. However, there is insufficient information regarding the long-term risk of radiosurgery-induced second brain tumors.

Neuropsychological Changes

According to a literature review by Becker et al., impairment of brain functions may occur in 0.7% of patients with pituitary tumors undergoing conventional radiotherapy *(22)*. Although impaired memory, depression, anxiety, personality changes, and social withdrawal have been well documented in patients with pituitary tumors who underwent conventional radiotherapy, it has been difficult to demonstrate that irradiation could be regarded as the only contributing factor. It has been proposed that the potential long-term risk of developing neuropsychiatric side-effects may be lower in patients treated with gamma knife compared with those undergoing conventional radiotherapy *(12)*.

Comparison of the Efficacy of Radiosurgery vs Conventional Radiotherapy in Patients with Acromegaly

Material and Methods

To analyze and compare the efficacy of different irradiation methods, hormonal and clinical follow-up data of 40 acromegalic patients who underwent conventional fractionated radiotherapy and of 26 patients who were treated with gamma knife stereotactic radiosurgery were reviewed. The clinical data obtained before irradiation are summarized in Table 1. In the conventional radiotherapy group, 2 patients (5%) had microadenomas, 30 (75%) had macroadenomas, while the tumor size in 8 patients (20%) who were referred to us after irradiation was unknown. Of the 30 macroadenomas, 20 showed extrasellar involvement. The mean of the largest diameter of the tumors was 17.4 mm (range, 8–25). In the gamma knife stereotactic radio-

Table 1
Clinical Data of Patients with Acromegaly Treated with Conventional Radiotherapy or Gamma Knife Stereotactic Radiosurgery

Parameter	Conventional radiotherapy	Gamma knife stereotactic radiosurgery
Age (yr)	Mean: 39, range 18–59	Mean: 50, range: 6–81
Gender	25 female, 15 male	20 female, 6 male
Size of the pituitary tumor	Microadenoma: 2 Macroadenoma: 30 Unknown: 8	Microadenoma: 8 Macroadenoma: 18
Primary therapy	8 (5 of 8 underwent surgery afterward)	6
Previous treatment	1 transsphenoidal resection: 25 1 transcranial resection: 1 1 resection from unknown approach: 3 2 operations: 3	1 transsphenoidal resection: 13 2 operations: 5 3 operations: 1 1 transsphenoidal resection + radiotherapy: 1

surgery group, 8 patients had microadenomas (35%) and 25 (65%) had macroadenomas. The mean of largest tumor diameter was 14.6 mm (range, 7–26). The types of treatment modalities used prior to conventional radiotherapy or gamma knife stereotactic radiosurgery and the number of patients who had undergone the different preirradiation treatments are summarized in Table 1.

Conventional fractionated radiotherapy was applied by linear accelerator; the doses were determined on the basis of tumor volume and surgical history. The average total irradiation dose was 50 Gy (range, 29.5–60). Stereotactic radiosurgical treatment procedures were carried out and the data were kindly provided by Dr. L. Dade Lunsford and Dr. Douglas Kondziolka, Center for Image Guided Neurosurgery, Presbyterian University Hospital, Pittsburgh, PA, USA *(45)*. Radiosurgery was performed using the Leksell Gamma Knife (Elekta Instruments, Atlanta, GA). Radiosurgical image-integrated dose planning was based on CT (before 1991) or MR scans (after 1991). Multiple irradiation isocenters were used to construct a conformal plan that fit irregular tumor margins *(50)*. Doses were selected on the basis of tumor volume, surgical history, and previous history of radiotherapy *(51)*. The 50% isodose line was used to cover the tumor margin in 24 cases. One tumor was irradiated using 60% isodose, and one using 70% isodose coverage. When necessary, individual collimators were plugged to limit the dose load to the optic apparatus to less than 8 Gy *(52)*. The mean radiation dose to the tumor margin was 21 Gy (range 10–25). After irradiation, serial imaging studies (MRI or CT) were performed every 6 or 12 mo for 2 or 4 yr, and every 24 mo thereafter. Repeat hormonal testing was also carried out in both groups, which included measurements of serum GH, IGF-1, prolactin, cortisol, thyroxin, LH, FSH, and, in men, testosterone levels. All patients underwent regular neuroophthalmological examinations. Serum GH levels <1 ng/mL were considered indicative of an endocrine cure.

In the conventional radiotherapy group, follow-up data were available in all patients over a period of 3–34 yr (mean, 13 yr). In the gamma knife stereotactic radiosurgery group, imaging follow-up was available in 23 of the 26 patients over a period of 8–124 mo (mean, 4 yr), while endocrine evaluation was available 2 yr after radiosurgery in 21, and 3 yr after radiosurgery in 12 patients.

Results and Discussion

In the conventional radiotherapy group, tumor growth control during follow-up was achieved in all 40 patients; the tumor totally resolved in 16 patients (40.0%), the volume decreased in 15 patients (37.5%), and remained unchanged in 9 patients (22.5%). Of the 30 macroadenomas treated with conventional radiotherapy, total tumor resolution was observed in 12 cases, reduction of tumor volume in 12 cases, and the tumor volume remained unchanged in 6 cases.

In the radiosurgery group, tumor growth control during follow-up was detected in all 23 evaluable patients (100%). The tumor totally resolved in 6 patients (26%), the volume decreased in 12 patients (52%), and was unchanged in 5 patients (22%). Of the six patients whose tumors totally resolved after radiosurgery, four were macroadenomas and two microadenomas; all these six patients had undergone transsphenoidal tumor resection before radiosurgery. Of the tumors that decreased in size, eight were macroadenomas and four microadenomas.

As shown in Table 2, serum GH levels were decreased below 5 ng/mL in 17 patients (42.5%) in the conventional radiotherapy group and in 13 patients (62%) in the gamma knife steraotactic radiosurgery group at 24 mo during follow-up. This moderate difference in serum GH levels between the two groups of patients was also detectable 3 yr after radiation therapy, as serum GH levels of 5 ng/mL or less were found in 50% and 92% of patients who received conventional radiotherapy and gamma knife stereotactic radiosurgery, respectively (Table 2). Long-term follow-up

Table 2
Endocrine Follow-up After Conventional Radiotherapy (n = 40) or Gamma Knife Stereotactic Radiosurgery (n = 21)

	Conventional radiotherapy		Gamma knife stereotactic radiosurgery	
Serum GH (ng/mL)	Number of patients	Percentage of total (%)	Number of patients	Percentage of total (%)
24 mo post	Total: 40		Total: 21	
<5	17	42.5	13	62
5–10	9	22.5	4	19
>10	14	35	4	19
36 mo post	Total: 40		Total: 12	
<1	4	10	3	25
1–5	16	40	8	67
>5	20	50	1	8
Long term follow up	Total: 40		Total: 21	
<1	19	47.5	8	38
Time to reach this level	Average: 7.9 yr (median: 6 yr)		Average: 4.5 yr (median: 57 mo)	

Follow-up time was 3–34 yr (mean, 13 yr) in patients receiving conventional radiotherapy and 8–124 mo (mean 4 yr) in patients treated with gamma knife radiosurgery.

lasting between 3 and 34 yr (mean, 13 yr) after conventional radiotherapy revealed that in 19 of the 40 patients serum GH levels decreased below 1 ng/mL at a median of 72 mo. Interestingly, long-term follow-up data during a period of 8–124 mo (mean, 48 mo) indicated a similar median period of time (57 mo) to reach serum GH levels less than 1 ng/mL in 8 of the 21 patients who were treated with gamma knife stereotactic radiosurgery. These findings indicate that gamma knife stereostactic radiosurgery in our patients resulted in a more rapid improvement of serum GH levels, but the difference between the hormonal effects of the two radiotherapy methods failed to persist during a long-term follow-up period.

There is still some controversy whether acromegalic patients undergoing radiosurgery develop a faster and more substantial decline of serum GH levels and/or serum IGF-1 levels compared with those patients receiving conventional radiotherapy. Landolt et al. found that the mean time for normalization of hormone values was 7.1 yr in acromegalic patients treated with fractionated radiation therapy, but only 1.4 yr in those treated with stereotactic radiosurgery *(42)*. Holdaway reported a 10-yr remission rate of 47% after fractionated external beam radiotherapy and a 3-yr remission remission rate of 40% following stereotactic radiotherapy and gamma knife radiosurgery *(53)*. Powell et al. showed also different remission rates after different forms of radiotherapy *(54)*. In a study using stereotactic multiple arc radiation therapy, normalization of GH and IGF-1 levels was reached in 58% of the patients within a median follow-up time of 20.1 mo (3–36 mo) after therapy *(55)*. These differences between the different studies may be related to several variables, including differences in patient selection for each type of radiotherapy, technical differences in the methods used, different follow-up periods, as well as variations in the cut-off of serum GH and IGF-1 values used for the definition of cure *(1,17,25,26,42,53–55)*. Thus, clearly, further studies with long follow-up are needed to elucidate the potential advantages of radiosurgery over conventional radiotherapy in acromegalic patients for achieving hormonal control.

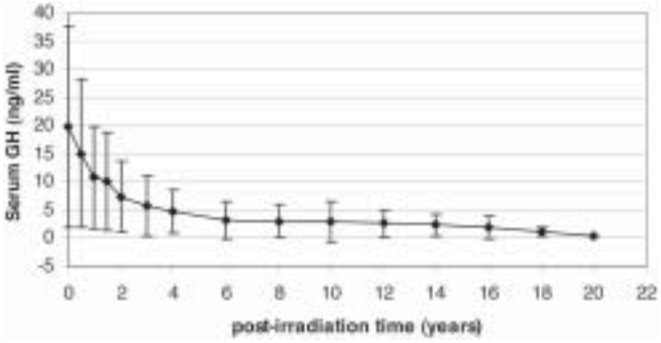

Fig. 1. Mean serum GH levels after conventional fractionated radiotherapy in 40 patients with aromegaly. Each point represents the mean, and the vertical lines refer to the standard error.

In our study 26 of the 40 patients (65%) developed pituitary hypofunction after conventional radiotherapy over the follow-up period (thyroid hormone, glucocorticoid hormone, and sexual steroid supplementation were given in 21, 16, and 12 patients, respectively, while 2 patients required treatment for diabetes insipidus). However, 11 of 26 patients had some decrease of pituitary function prior to radiotherapy due to tumoral compression or as a result of the neurosurgical procedure. Interestingly, serum GH levels in patients who had undergone conventional radiotherapy continued to decrease throughout the long-term follow-up period (Fig. 1). However, it is not known whether GH deficiency could

develop during the long-term follow-up, because this possibility was not tested in our patients. Several years after conventional radiotherapy, three patients showed memory impairment, three patients developed psychiatric disorder, one patient had internal hydrocephalus, and one patient had a brainstem vascular lesion.

In the radiosurgery group pituitary hypofunction was absent before and during follow-up. One patient developed diplopia following radiosurgery (which was later attributed to ocular myasthenia) but other complications were absent. These findings are in agreement with earlier observations showing a more favorable spectrum of side effects in patients undergoing radiosurgery compared to those receiving conventional radiotherapy. However, a shorter follow-up time of patients treated with radiosurgery remains a limitation of these earlier series and ours.

Conclusions

Treatment of patients with pituitary tumors should aim to relieve compression symptoms by controlling tumor growth, suppress oversecretion of hormones, and prevent consequences of hormonal excess in case of hormone-secreting tumors, while maintaining normal pituitary function. Although these treatment goals can be achieved in several cases by standard neurosurgical methods and/or medical therapy, irradiation remains an important adjunctive therapy to surgery and/or drug treatment in patients with secreting and non-secreting pituitary tumors. However, patient selection for conventional radiotherapy still remains a controversial issue, because a number of potentially significant side effects, including hypopituitarism and other complications, have been described. Recent technical development may enhance the role of radiation therapy, although long-term follow-up data with these relatively new techniques are still needed to define their optimal use in patients with pituitary tumors.

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