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Gamma Knife Radiosurgery for Pituitary Adenomas

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Although surgical extirpation by transsphenoidal microsurgery is a major remedy for pituitary adenomas, adjuvant therapy also plays an important role in achieving tumor growth control and endocrine normalization in hormone-secreting tumors. Historically, the treatment options for pituitary adenomas included microsurgery, medical management, and fractionated radiotherapy, but radiosurgery has recently emerged as a practical treatment option. In this paper, we will describe the indications, radiosurgical procedure, results, histological change, and complications of gamma knife radiosurgery (GKS) for pituitary adenomas based on our experience since 1991 and a review of the literature.

Key Words: Gamma knife radiosurgery; pituitary adenoma.

Introduction

The treatment goals for pituitary adenomas are tumor growth control and endocrine normalization in hormone-secreting tumors. Surgical extirpation by transsphenoidal microsurgery is a major remedy for pituitary adenomas. Despite progress in surgical techniques, instruments, and neuroimaging studies, it is occasionally difficult to accomplish the goals by surgical removal alone, especially in cases with cavernous sinus invasion. Even if the total removal of the tumor is achieved, recurrence-free survival at 5 and 10 yr are only 82% and 56%, respectively *(1)*. The efficacy of fractionated radiotherapy for residual or recurrent tumor following surgical removal has been established *(2–5)*. However, it also has the disadvantage of a high rate of radiation-induced complications such as hypopituitarism and optic nerve neuropathy. Another issue related to fractionated radiotherapy for hormone-secreting pituitary adenoma is that the mean time to attain endocrine normalization is more than 5 yr *(2)*.

Gamma knife radiosurgery (GKS), originally designed by Leksell in 1968 *(6)*, has spread since the 1990s as an alternative treatment modality for pituitary adenomas. The principle of GKS is that a target, which is set into the center of the collimator helmet, receives 201 gamma rays converging from each cobalt-60 source which is placed on a hemispherical surface. GKS is characterized by high precision and a sharp dosage fall-off at the edge of the target, together with an excellent target coverage and dosage conformity.

We will present the indications, radiosurgical procedure, results, histological change, and complications of GKS for pituitary adenomas based on our experience since 1991 and a review of the literature.

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Indications

In non-functioning pituitary adenomas, they are usually of large volume when they are found because the initial symptom is the result of compression of the surrounding structures. Hormone-secreting pituitary adenomas are not always large when the symptoms are noted, but, in either case, volume reduction by surgical removal is needed. As a therapeutic option, GKS must be considered for patients with a residual or recurrent pituitary adenoma after surgical removal. GKS is used as the primary treatment only for those patients who have a high surgical risk. In our experience of 137 pituitary adenoma cases that have been treated by GKS, there are only 14 cases that underwent GKS as the initial treatment.

The volume of the tumor is generally a dose-limiting factor in GKS. As the target volume of the tumor is larger, the dosage that is given to the tumor must decrease to avoid radiation-induced complications *(7)*. However, in GKS for pituitary adenomas, the limiting factor is usually not tumor volume, but rather the proximity of the tumor to the optic nerve and the chiasm that is the most radiosensitive tissue among neighboring structures. It is recommended that the dose given to the visual pathways be constrained to remain less than 10 Gy to prevent radiation-induced optic neuropathy *(8)*. The radiation dose required for the tumor growth control is thought to be a minimum of 10–12 Gy *(9,10)*. For endocrine control, a higher dosage is required to be administered to the tumor *(11)*. Thus, the distance between the tumor margin and the optic apparatus needs to be at least a few millimeters in order to deliver the optimal dose to the tumor without exceeding the maximum permissible dose to the optic pathways.

Radiosurgical Procedures

First of all, a Leksell frame is fixed to a patient's head under local anesthesia. We utilize T1-weighted enhanced magnetic resonance (MR) images, T2-weighted MR images, and computed tomography (CT) for dose planning. Both MR and CT images, which are obtained stereotacticly with a thickness of 1 mm, are exported to the Leksell GammaPlan software (Elekta Instruments AB, Stockholm, Sweden). The MR images are used to determine the location of the adenoma and the position of the optic nerves and the optic chiasm. The CT images are mainly used as a control for possible minor distortions on the MR images. The dose plan is designed to make a prescribed isodose curve, according to which 50% or greater isodose is adopted, to conform to the tumor volume using multiple small radiation isocenters. It is also necessary to ensure that the dosage delivered to both the optic pathways and normal pituitary gland is minimized. In particular, the radiation dosage given to the optic pathways must be planned so as to be than 8–10 Gy. In our series, the prescription dose to the tumor margin was 13–35 Gy (mean 23.1 Gy) and the number of isocenters was 1–17 (mean 4.4). After the accomplishment of dose planning, irradiation is performed in accordance with the dose plan. The treatment finishes with the removal of the Leksell frame from the patient's head.

Results

Tumor Growth Control

Tumor growth control signifies that the tumor volume did not increase during the observation period. The control rates reported in the literature are 93–100% *(9,12–20)*. Losa et al. found that the recurrence-free survival at 5 yr after GKS was 88.2% *(21)*. In our experience of patients with 64 nonfunctional pituitary adenomas that were followed for 12–145 mo (mean 61 mo), we found a control rate of 97%. An illustrative case successfully treated in our center is presented in Fig. 1. Two patients were required to undergo surgical removal owing to a recurrence of the tumor at 84 and 120 mo after GKS. It is important to keep in mind that the decision that a patient can be considered free of the threat of tumor recurrence should be made only after a sufficiently long follow-up period.

Endocrine Normalization

In the literature, the rates of achieving endocrine cure after GKS for growth hormone (GH)–producing pituitary adenomas are wideranging (20–100%) *(9,12–18,22–27)*. However, it is difficult to compare them because the criteria for defining "endocrine cure" vary considerably in each study. The strictest criterion adopted in these studies is that endocrine cure is defined as both normalization of insulin-like growth factor-I (IGF-I) and a nadir GH level less than 2 ng/mL after the oral glucose tolerance test. According to this criterion, Ikeda et al. reported that 14 in 17 patients (82%) with GH-producing pituitary adenoma, who underwent GKS in our center after transsphenoidal microsurgery, achieved endocrine cure *(28)*. The mean time to endocrine normalization after GKS was 1.4 yr, while it was 7.1 yr after fractionated radiotherapy *(3)*.

With regard to the outcome of GKS for Cushing's disease, many studies have been carried out *(9,13–18,24–26, 29)*. The summarized results in the literature showed that endocrine cure could be achieved in 58% of the patients *(30)*. However, studies that analyzed the number of cases with a sufficiently long follow-up period are limited. The results from the patients with Cushing's disease who were followed for more than 2.5 yr (mean 5.3 yr) after GKS indicate that serum adrenocorticotrophic hormone (ACTH) and cortisol levels were normalized in 35%, decreased significantly in 60%, and decreased in 85% of cases *(31)*. A study that analyzed the outcomes of the patients with Cushing's disease who were followed up for 12 to 22 yr after GKS shows that the effect of GKS on the hypersecretion of ACTH is long-standing *(32)*. A fall in urinary cortisol level could be found even after more than 10 yr, although it began to decrease within the first 3 mo after GKS *(32)*.

The role of GKS for the treatment of prolactinomas is relatively minor because dopamine agonists offer an affective alternative. The results of GKS for prolactinomas in the literature, in which rates of endocrine normalization were 0–56% *(9,14–18,23,24,26,33)*, are less favorable as compared with those for acromegaly or Cushing's disease. Interestingly, the endocrine cure rate was significantly affected by the use of dopamine agonists at the time of the GKS *(33,34)*.

Histology after GKS on a Pituitary Adenoma

Despite the widespread use of radiosurgery, relatively little is known about the cellular mechanisms underlying the induction of necrosis and radiation injury in pituitary adenomas. The histologic, immunohistochemical, and ultrastructural features of adenoma tissues obtained in surgery after GKS are various because they depend on the dosage level irradiated and/or the length of time since irradiation. Some adenoma cells are swollen and vacuolated, with an irregular shape and irregular nucleus, suggesting cell membrane damage, dilatation of membraneous organelles, and cellular injury. Cellular degeneration or nuclear fragmentations were also mentioned in acoustic tumors after GKS *(35,36)*. In contrast some adenoma cells seem to be normal and show immunopositivities against their original secreting hormones. Therefore, those areas with intact-looking tumor cells were only slightly affected by radiation compared to those areas with cellular degeneration. It has been widely accepted that ionizing radiation damages tissues in which the cells are forming DNA to prepare for mitotic division *(37)*. Therefore, radiosurgery can cause acute necrosis of malignant tumor cells, whereas in slowly growing tumors such as pituitary adenomas, the cytotoxic effects of radiation

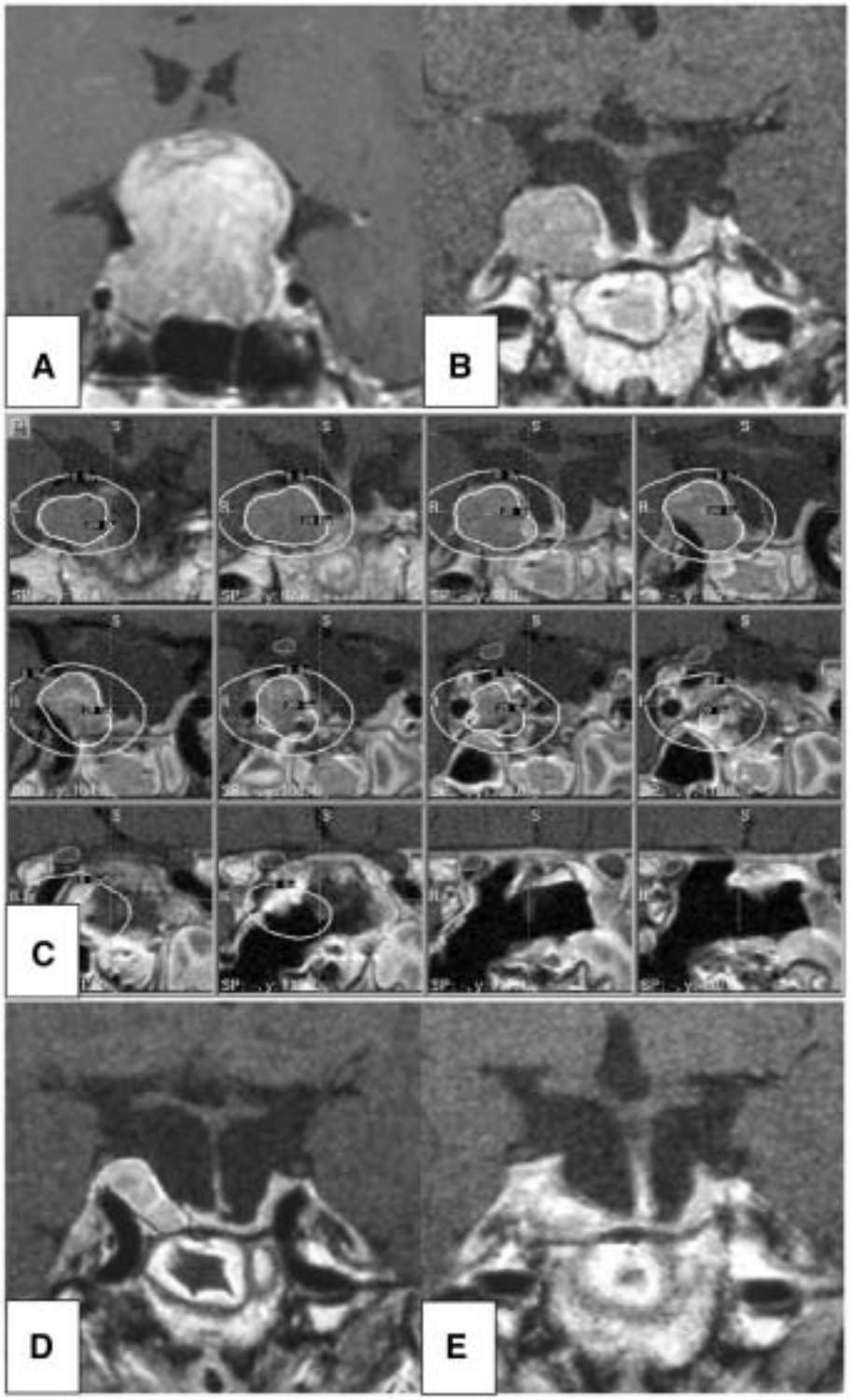

Fig. 1. Serial gadolinium-enhanced coronal MR images obtained in a 49-yr-old woman with non-functioning pituitary adenoma who suffered from bitemporal hemianopsia. (**A,B**) Preoperative (**A**) and postoperative (**B**) MR images revealing that the decompression of the optic nerves was well achieved. Her visual field defect recovered completely, but the tumor still remained in the right cavernous sinus after the surgical removal. (**C**) The dose plan for GKS displayed on Leksell GammaPlan. The residual tumor was given a prescription dose of 20 Gy defined by the inner circle. An outer circle indicates an area that was to received a dose of 8 Gy. Note the right optic nerve (arrows) wholly located outside the 8 Gy-line. (**D,E**) MR images obtained 6 mo (**D**) and 12 mo (**E**) after GKS showed progressive shrinkage.

therapy may be manifested over a longer period of time *(38)*. Increase of connective tissue or prominent vasculopathy was also reported after GKS *(39)*. Although the impact of radiotherapy upon tumor vascularity is not well understood, various studies have shown that tumor necrosis induced by GKS was preceded by distinct microvascular changes *(40,*

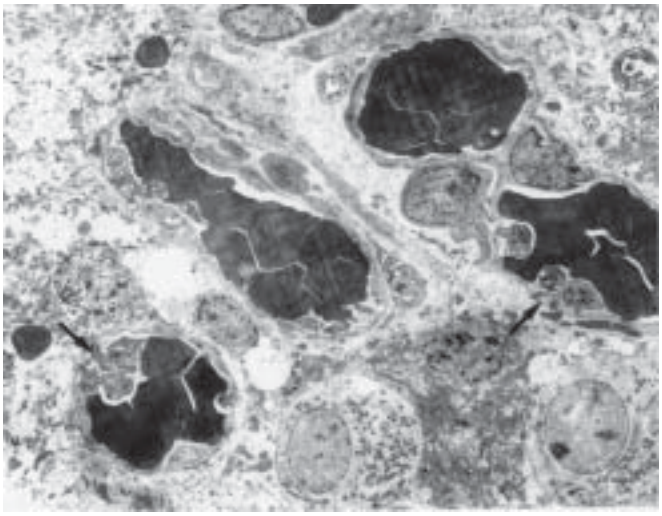

Fig. 2. Electron micrograph showing the marked injury of many adenoma cells and the aggregation of platelets covering the damaged endothelial lining in the capillaries filled with erythrocytes (arrows) in a gonadotroph cell adenoma after GKS. Note relatively intact tumor cells (arrow heads) (×2115).

41). Several animal studies using rats or cats confirmed that vasculopathy is the first morphological alteration and may serve as the initiating factor for subsequent changes *(40–42)*. Capillary endothelial cells are among the most radiation-vulnerable elements of mesenchymal tissues and damage to these cells may be a common pathway of delayed radiation injury *(37,43)* (Fig. 2). The ultrastructural features of vascular injury without significant damage in the tumor cells support the higher susceptibility of endothelial cells to irradiation, suggesting that vascular injury plays a crucial role in tumor shrinkage. In contrast, an increase of microvessel density has also been reported in areas more affected by radiation. Neovascularization possibly compensates for the loss of blood vessels induced by radiation. Since hypoxia generally induces angiogenesis, the existence of ischemic areas in the irradiated portions of the tumor could promote angiogenesis. The overexpression of vascular endothelial growth factor (VEGF) found in the injured areas of the tumor compared with those less affected might support this possibility *(39)*. It may well be that cell damage induced by vasculopathy depends on the balance between vascular injury and vascularization, and it appears that compensatory angiogenesis may prevent tumor cell degeneration due to vasculopathy produced by GKS.

Complications

Although the radiation dosage that the normal structures adjacent to the target tumor receive should be minimized, some radiation-induced complications after GKS for pituitary adenomas have been reported. A summary of those reported in the literature shows the possibility of some kinds of complications: visual disturbance, hypopituitarism, injury to cranial nerves located in the cavernous sinus, and radiation necrosis of the adjacent brain tissue *(30)*. The incidence of visual disturbance, hypopituitarism, and injury to cranial nerves (occulomotor and trigeminal nerves) was estimated at 2.3%, 3.4%, and 1.6%, respectively *(30)*. Although the incidence of optic neuropathy rises as the dose exposed to the optic pathway increases, no patients who received less than 10 Gy suffered optic neuropathy *(8)*. In our experience of 137 patients whose optic pathways received 8 Gy or less, there was no case of visual disturbance by GKS. At the time, the dose exposed to the optic pathway is strictly kept less than 8–10 Gy and this will likely reduce the incidence of this complication.

Conclusions

The tumor control rate after GKS for pituitary adenomas is equivalent to fractionated radiation therapy. The time required to achieve endocrine normalization after the GKS is also shorter than after fractionated radiation therapy, but with less risk of radiation-induced injury to the surrounding structures. In conclusion, GKS offers a safe and effective treatment option especially for those patients with recurrent or residual pituitary adenoma after surgical removal. To give full play to its ability, however, it is essential to deliver a sufficient dose to the target tumor with minimal exposure to the surrounding structures. Thus, in the surgical removal of pituitary tumors, the operator is expected to pay attention to ensure that the tumor detaches from the optic pathways as much as possible.

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