Treatment of Nonfunctional Pituitary Adenoma Postoperative Remnants: Adjuvant or Delayed Gamma Knife Radiosurgery?

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■ OBJECTIVE: **It is still not clear whether Gamma Knife radiosurgery (GKRS) for nonfunctional pituitary adenomas should be used as a standard adjuvant postoperative therapy or applied when there is documented progression of the remnant on follow-up magnetic resonance imaging.**

■ METHODS: **We performed a retrospective study of patients with nonfunctional pituitary adenomas who underwent primary surgery and GKRS between 2002 and 2015. Patients were divided into 2 groups on the basis of the GKRS indication: adjuvant treatment (GKRS ≤6 months postoperatively) or delayed treatment (GKRS if documented progression occurred on the follow-up magnetic resonance imaging).**

■ RESULTS: **Fifty patients were included and grouped based on adjuvant (n = 13) or delayed (n = 37) GKRS following primary surgery. The adjuvant and delayed groups had 10-year actuarial tumor control rates of 92% and 96% (P = 0.408), respectively. The 10-year actuarial endocrinologic control rate was 82% for the adjuvant group and 49% for the delayed group (P = 0.597). None of the patients developed any new neurologic deficit post-GKRS. GKRS-induced complications (intratumoral bleeding and tumoral tissue inflammation) occurred in 6% of the patients, of whom 4% were in the delayed group and 2% in the adjuvant group.**

■ CONCLUSION: **Adjuvant treatment with GKRS yields the same high long-term tumor control as delayed GKRS. Neither adjuvant nor delayed GKRS induced additional neurologic complications. There is a trend that adjuvant GKRS induces less additional endocrinologic deficits compared with delayed GKRS.**

INTRODUCTION

Pituitary adenomas are nonmalignant tumors that arise from the cells of the pituitary gland located in the sella turcica. In the western world the prevalence and incidence of nonfunctional pituitary adenomas (NFPAs) ranges from 13.82–42.32/100,000/year[1-4] and 1–4.8/100,000/year,[1,4,5] respectively.

The most common presenting symptoms of NFPAs are visual field defects and hypopituitarism due to mass effect. The golden standard treatment for NFPA today is surgical resection, usually through an endoscopic transsphenoidal approach, for size reduction and thus improvement of symptoms. These tumors can extend into the suprasellar region and/or extend into the cavernous sinus. Therefore it can be difficult to achieve total resection without damaging vital anatomic structures. According to a meta-analysis, total resection can be achieved in 40%–50% of the NFPAs.[6] A way to increase total resection is the use of intraoperative magnetic resonance imaging (iMRI). Additional resection can be achieved in 15%–67% of the cases by using iMRI <0.5 Tesla or in 36%–83% of the cases by using iMRI ≥0.5 Tesla.[7] Even if complete resection has been achieved on postoperative MRI, the recurrence risk is 10%–20% at 5 years and 30% at 10 years' follow-up (FU).[8-14] In case of postoperative remnant, regrowth occurs in 25%–40% at 5 years and >50% at 10 years' FU.[8-17] In either case, postoperative treatment may be indicated. It is established that these remnants can be treated safely and successfully with Gamma Knife Radiosurgery (GKRS) with overall tumor control ranging from 83%–100%.[18-27] However, GKRS treatment carries the risk of endocrinologic

Key words
- Gamma Knife Radiosurgery
- Macroadenoma
- Nonfunctional pituitary adenoma
- Pituitary surgery

Abbreviations and Acronyms
CN: Cranial nerve
FU: Follow-up
GKRS: Gamma Knife Radiosurgery
NFPA: Nonfunctional pituitary adenoma

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complications. Development of new hypopituitarism after GKRS is reported to occur in 0%–39% of the cases.[18-27] Currently, patients are treated directly postoperatively (adjuvant) or a wait and scan policy is adopted and treatment is given once there is documented progression of the remnant.

A recent publication shows a greater overall tumor control and higher percentage of freedom from new or worsened endocrinopathy in the group treated within 6 months after surgery in comparison with the late cohort (treated after 6 months of FU).[27]

In our study we compared the tumor control rate, new endocrinopathy, and cranial nerve deficits in patients with a postoperative NFPA remnant who were treated with GKRS without any documented growth of the residual tumor (the "adjuvant" group) with patients who were treated for progressive remnants on FU MRI (the "delayed" group).

METHODS

Clinical Trajectory of NFPA Patients

Three months after endoscopic transsphenoidal resection, patients visit the outpatient clinic for clinical and radiologic assessment. If there is no remnant visible on the postoperative MRI scan, subsequent FU by the neurosurgeon is performed yearly for the first 3 years. If there is no recurrence, this is extended to once in 2 or 3 years. Yearly MRI scans are made for the first 5 years if there is remnant visible on the postoperative MRI. If there is no documented growth on the FU MRIs after the fifth year of FU, this is extended to once in 2 or 3 years.

FU by the endocrinologist is performed directly after initial surgery and at 6 weeks, 3 months, 6 months, and yearly to assess whether there are any new hormonal deficits that need supplementation.

Before GKRS, all patients are seen in a multidisciplinary clinic by neurosurgeons, endocrinologists, and radiation oncologists. A detailed assessment of signs and symptoms is performed, and the decision to treat patient with GKRS is made by the multidisciplinary team.

Definitions

We divided the population into an "adjuvant group" and a "delayed group". Adjuvant was defined as GKRS within 6 months after initial surgery without any documented growth on the FU MRI. Delayed was defined as GKRS of the remnant after documented growth on the FU MRI. Outcome measures were tumor control after GKRS, GKRS-induced cranial nerve (CN) deficit, and GKRS-induced endocrinologic deficit. Tumor control was defined as freedom from radiologic progression from the date of GKRS. The FU MRIs were compared with the planning MRI at the time of GKRS. These FU MRIs were assessed by a team of experts that included a neurosurgeon, radiation oncologist, and neuroradiologist, who indicated whether there was progression, stabilization, or regression. GKRS-induced CN deficit and endocrinologic deficit were defined as new or worsening of neurologic symptoms or new hormonal deficiency, respectively.

Case Selection

We performed a retrospective analysis of prospectively collected data of all patients who underwent GKRS for pituitary adenoma at the Gamma Knife Center Tilburg between 1 January 2002 and 31 March 2015. The study was approved by the medical ethical committee. Hospital records including clinical notes, doctor's letters, radiology reports, and demographic data were reviewed, and data were extracted for analysis. Pre- and post-GKRS clinical characteristics were reviewed. We included all patients with histologically confirmed NFPAs, a minimal FU time of 1 year, available preoperative and postoperative MRIs, and no prior radiation therapy for pituitary adenoma (Figure 1). Of the 263 patients who underwent primary surgery, we yielded 50 NFPA patients fulfilling the selection criteria (see Figure 1). Figure 1 shows the different treatment modalities for this kind of tumor after primary surgery. Our protocol dictates a wait and scan policy if there is a postoperative remnant detected after surgery. In case of regrowth of the remnant, we have the option of using 2 types of radiation therapy dependent on the radiologic features of the remnant. For instance, fractionated radiotherapy is proposed for large remnants with ill-defined tumors, parasellar involvement, and in proximity of the optic chiasm. For GKRS, the remnant is small with good target definition and not in proximity of the optic chiasm.

Baseline Characteristics

The median age at time of GKRS was 57 years (range 34–75). All patients had undergone at least 1 operation before GKRS and had histologically confirmed NFPA. Twenty-four percent of the patients had undergone more than 1 operation in the past. These patients underwent reresection due to a symptomatic large remnant. Pretreatment patient characteristics are summarized in Table 1.

Gamma Knife Radiosurgical Procedure

All GKRS procedures were performed at the Gamma Knife Center Tilburg. The procedures were performed using the Leksell Gamma Knife 4C before 2009 and Leksell Gamma Knife Perfexion thereafter. GammaPlan Software (Elekta) was used for treatment planning. The application of the Leksell G-Frame with fixation posts and screws at 4 points was performed at the patient's room using a local anaesthetic solution (9 mL of lidocaine 2% + epinephrine 0.125% combined with 1 mL of $NaHCO_3$ 84 g/1000 mL). Following frame placement, high-resolution stereotactic MRI was performed for treatment planning. Precontrast and postcontrast (Dotarem 15 mL) T1-weighted axial and coronal plane images through the sella were obtained with a slice thickness of 1.5 mm for the axial and 0.8 mm for the coronal. Fat-saturated stereotactic imaging was also performed if appropriate. Stereotactic radiosurgery and dose planning were then performed in consultation with a neurosurgeon, radiation oncologist, and medical physicist. The median tumor volume was 3.4 cm^3 (range 0.22–11.1 cm^3). A median dose of 15 Gy (range 10–25 Gy) was prescribed to the isodoseline covering 89%–100% tumor volume. The minimal and maximal doses varied from 6.9–33.3 Gy (median 14.0 Gy) and 23.3–50 Gy (median 30.4 Gy), respectively. The reason for 6.9 Gy in 1 patient was because the tumor was touching the optic chiasm and we defined 9 Gy as the tolerance dose for the optic chiasm. The radiation dose to the optic nerve was kept below 8 Gy in all other cases. After the procedure, all patients could leave the hospital the same day of radiosurgery.