Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas

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Object. The authors studied the efficacy of gamma knife radiosurgery (GKS) in the prevention of regrowth of nonfunctioning pituitary adenomas (NPA).

Methods. One hundred nineteen patients were included in this study and were divided into two groups. All patients had undergone surgery in our department and recurrent or residual adenoma was demonstrated on postoperative MR imaging. Group A consisted of 68 patients who were followed without additional treatment. Group B was composed of 51 patients who received GKS within 1 year after microsurgery. There was no significant demographic difference between the two groups. In Group B the mean margin dose was 16.5 ± 0.3 Gy (range 13–21 Gy). Fifty one and one tenth percent of patients in Group A were recurrence free at 5 years and 89.8% in Group B (p < 0.001). In Group B patients, tumor volume decreased from a baseline value of 2.4 ± 0.2 cm³ to 1.6 ± 0.2 cm³ at last follow up (p < 0.001).

Conclusions. The results of this study suggest that GKS is effective in controlling growth of residual NPA for at least 5 years following initial maximal surgical debulking compared with no radiation therapy. Thus, GKS is recommended after microsurgery when visible tumor can be detected on imaging studies.

Key Words • nonfunctioning pituitary adenoma • gamma knife surgery • pituitary
Clinical Material and Methods

Patient Population

All patients included in this study harbored residual NPA, which was demonstrated on postoperative MR imaging, after maximal surgical debulking. All surgical procedures were performed by two of us (P.M. and M.G.). No patient had clinical or biochemical evidence of hormone hypersecretion.

The presence of residual tumor tissue was assessed on the first postoperative MR image, usually performed 3 to 6 months after surgery. Patients were then grouped according to whether they were followed up with serial MR imaging (Group A) or whether GKS was performed on the residual NPA (Group B).

Group A included 68 patients, 42 men and 26 women, aged 54.5 ± 1.8 years. The patients included in this group did not undergo adjunctive radiation therapy either because they refused (55 patients) or because a more conservative approach was advised, especially in elderly patients with small residual tumors (13 patients).

Group B included 51 patients, 24 men and 27 women, aged 51.2 ± 1.5 years. All patients in Group B underwent GKS within 1 year after surgery as part of a combined treatment strategy aimed at preventing tumor regrowth following incomplete removal. From this group we excluded the patients in whom there was a follow-up period after GKS of less than 1 year and those who were treated only after tumor recurrence.

Gamma knife surgery was performed as previously described. The 50% isodose line was used to cover the target volume. Conformal multiple isocenter GKS was performed with small collimator sizes (4 and 8 mm) and frequent source blocking (plug) to keep the the dose away from the optic pathways. The mean margin dose was 16.5 ± 0.3 Gy (range 13–21 Gy). The maximum dose to the optic pathways was kept below 8 Gy in 37 patients (72.5%) but doses of more than 10 Gy were delivered in nine patients (17.6%) to allow complete coverage of the tumor. All patients were discharged the day after GKS.

Follow Up and Assessment of Tumor Regrowth

After the initial postoperative examination, additional MR imaging sessions were planned at yearly intervals in Group A patients. Group B patients underwent repeated MR imaging 6, 12, 24, 36, and 48 months after GKS and then at 2-year intervals or when clinically indicated. Recurrence of NPA during follow up was defined as evi-

TABLE 1

Clinical characteristics of 119 patients with residual NPA after maximal surgical debulking according to whether they received GKS after the first postoperative MR image or were followed-up by serial MR imaging

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No GKS (68 patients)</th>
<th>GKS (51 patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>54.5 ± 1.8</td>
<td>51.5 ± 1.8</td>
<td>0.21</td>
</tr>
<tr>
<td>male sex</td>
<td>42 (61.8%)</td>
<td>24 (47.1%)</td>
<td>0.16</td>
</tr>
<tr>
<td>no. of previous ops</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>0.55</td>
</tr>
<tr>
<td>Max tumor diameter preop (mm)</td>
<td>32.7 ± 1.3</td>
<td>32.6 ± 0.9</td>
<td>0.95</td>
</tr>
<tr>
<td>gonadotropinoma*</td>
<td>23 (41.2%)§</td>
<td>18 (37.5%)§</td>
<td>0.86</td>
</tr>
<tr>
<td>mean follow up (mos)</td>
<td>41.6 ± 3.2</td>
<td>40.6 ± 3.4</td>
<td>0.83</td>
</tr>
</tbody>
</table>

* NPA was classified as gonadotropinoma when at least 5% of tumor cells stained positive for either luteinizing hormone or follicle-stimulating hormone.

§ Immunohistochemical analysis was available for 56 patients in the no GKS group and 48 patients in the GKS group.

Fig. 1. Series of MR studies. A: T1-weighted Gd-enhanced image obtained in a 64-year-old woman with residual NPA after transsphenoidal surgery. A: The first postoperative MR image obtained 4 months after surgery. A small residual tumor rest, located near the right cavernous sinus is evident (arrowhead). The patient opted for further follow up. B: Follow-up image obtained 24 months after surgery. There is a slight increase in tumor size, especially toward the left side of the sella turcica (arrowhead). C: An MR image obtained 30 months after surgery, confirming further expansion of the tumor. The patient was then treated by GKS.
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![Graph showing a Kaplan–Meier analysis of time to recurrence of NPA in 68 patients with residual tumor demonstrated on the first postoperative MR image who did not receive any radiation treatment (Group A, closed circles) and in 51 patients who were treated with GKS (Group B, open circles). All patients were followed up for at least 1 year. The recurrence-free survival at 5 years was 51.1% (95% confidence interval 37.5–64.8%) in Group A and 89.8% (95% confidence interval 76.2–100%) in Group B.](image)

**Results**

The main features of the two groups of patients are summarized in Table 1. Groups A and B did not significantly differ in age, sex, number of previous surgical procedures, maximum tumor diameter before surgery, number of tumors positive for luteinizing hormone and/or follicle-stimulating hormone on immunohistochemistry, and mean available follow up.

The mean follow up after surgery in Group A patients was 41.6 ± 3.2 months (range 12–108 months). Regrowth of residual tumor tissue during follow up was demonstrated in 32 patients (47.1%; Fig. 1). Kaplan–Meier analysis showed that the recurrence-free interval at 5 years was 51.1% (95% confidence interval 37.5–64.8%) (Fig. 2). Further treatments after demonstration of tumor regrowth consisted of the following: eight patients underwent operation via the transsphenoidal approach and then received GKS (one patient) or fractionated radiotherapy (seven patients); six received fractionated radiotherapy, five patients underwent operation via the transcavernous approach and then received GKS (two patients), fractionated radiotherapy (two patients), or transsphenoidal surgery (one patient), and four patients underwent GKS. The remaining nine patients preferred no further treatment.

The mean follow up after surgery in Group B patients was 40.6 ± 3.4 months (range 29–94 months). Regrowth of residual tumor tissue during follow up was seen in two patients (3.9%). The recurrence-free interval at 5 years was 89.8% (95% confidence interval 76.2–100%) (Fig. 2). One patient received another GKS treatment, whereas the other patient underwent further surgery via the transsphenoidal route and then received fractionated radiotherapy. The risk of tumor regrowth was significantly higher in Group A than in Group B patients (p < 0.001). In Group B patients, tumor volume decreased from a baseline value of 2.4 ± 0.2 cm³ to 1.6 ± 0.2 cm³ at the most recent follow up (p < 0.001).

**Discussion**

The effectiveness of GKS in the prevention of recurrence of NPA has already been described in recent reports. The main advantage of GKS over fractionated radiotherapy seems to be a lower risk of side effects such as hypopituitarism, at least in the short- and mid-term. None of the published GKS series, however, contained control groups, that is, patients with residual tumor after surgery who did not receive any radiation therapy. Even though clinical recurrence of NPA is clearly higher in patients with residual tumor than in patients without such evidence, the natural history and the growth rate of incompletely resected NPA, using the more sensitive criterion of comparing serial MR studies, are less well defined. The purpose of our study was to provide an analysis compared with a relevant control group.

The results were quite convincing. At 5 years, the estimated recurrence-free survival in patients who underwent GKS was significantly higher than in the group that received no postoperative treatment. Moreover, the two patients with tumor recurrence following GKS had growth of adenoma tissue outside the GKS radiation field, which was not visible at the time of GKS.

The main and inevitable limitation of our study is its nonrandomized and retrospective design; however, the two groups were well balanced with respect to their demographic characteristics, including tumor size prior to surgery, all of which may affect the risk of tumor recurrence. Moreover, the duration of neuroradiological follow up in the two groups was very similar, thus eliminating another potential bias.

**Conclusions**

This study indicates that after midterm follow up, GKS is
effective in controlling the regrowth of residual NPA, following initial maximal surgical debulking, when compared with no radiation treatment. Gamma knife surgery is recommended for incompletely removed NPAs, in particular when a safe dosing plane for the optic pathway is feasible. Further studies and longer follow up are needed to assess the long-term efficacy of GKS in the management of these tumors.

References


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