Experience in management of 51 non-functioning pituitary adenomas: Indications for post-operative radiotherapy

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ABSTRACT. Object: The indications for additional radiotherapy (RT) after surgery for non-functioning pituitary adenoma are controversial. The goal of this retrospective study was to evaluate the outcome of surgically treated patients, with or without post-operative irradiation. Methods: Review of cases treated for non-functioning pituitary adenoma. Fifty-one patients were identified, with a mean post-operative follow-up of 6.4±3.5 yr. Twenty-nine patients showed residual tumor after surgery and 22 did not. Serial endocrine, visual and radiological evaluations were made after treatment to assess the efficacy and toxicity of surgery and RT. Twenty-seven patients with residual tumor after surgery received RT (22 of them during the post-operative period and 5 after an interval of several yr: 3 because of increased tumor size and 2 with stable residual lesion); tumors in 14 of these patients decreased in size, 11 appeared to be stable on imaging and one patient showed some increase in tumor size (one patient was not followed-up). The residual tumors of the 2 non-irradiated patients remained stable after 5 and 7 yr, respectively. Twenty-two patients without residual disease after surgery (11 with post-operative irradiation, 1 with RT 5 yr after transsphenoidal surgery because of tumor recurrence, and 10 without RT) have shown no evidence of tumor regrowth on serial images. Conclusions: Radiotherapy can be avoided in patients with complete macroscopic resection and absence of residual tumor in post-operative images; they must be carefully followed using imaging techniques and, in the case of recurrence, they should be re-operated and/or irradiated.


INTRODUCTION

Non-functioning pituitary adenomas represent 18-40% of all pituitary tumors (1, 2). The diagnosis is usually based on the absence of clinical evidence of pituitary hormone hypersecretion and normal pituitary hormone levels. Mild hyperprolactinemia is possible, attributed to the impairment of dopamine transport due to stalk compression by the tumor. Most patients present with symptoms related to mass effect that impairs visual function and causes headaches. Partial or complete hypopituitarism is frequent secondary to compression of the normal functionary pituitary gland. The initial management of these tumors is surgical resection, to improve visual defects and to remove as much of the tumor as possible. The follow-up after surgery is more difficult than that of hormone-secreting adenomas because of the lack of markers of hormonal activity. Residual tumor can be detected only by neuroradiology. Thus, the indications for and timing of radiotherapy (RT) as adjuvant treatment are controversial. Some authors (3, 4) advocate RT during the early post-operative phase. Others prefer to document the presence of residual tumor before deciding on a complementary treatment (2, 5, 6).

Here we compare the results of transsphenoidal surgery (TSS) with and without adjuvant RT in 51 patients with non-functioning pituitary adenomas.
MATERIALS AND METHODS

Patient population
The records of 51 patients with a diagnosis of non-functioning pituitary adenoma who underwent surgery, with or without adjuvant RT, in our hospital between 1976 and 1995 were reviewed retrospectively. After 1995, the number of patients irradiated decreased and new irradiation techniques were used. All the patients included in the study had pre- and post-treatment morphological and endocrine assessment. Non-functioning pituitary adenoma was defined as histologically proven adenoma without clinical or biochemical evidence of hormone overproduction. Data are expressed as means±SD of the means. Twenty-one patients were males and 30 females. The mean age at diagnosis was 46.4±12.5 yr. All patients had a follow-up of 1 yr or more, with a mean follow-up of 6.4±3.5 yr; 46 patients were followed for more than 2 yr.

Clinical evaluation
Pre-operatively, we evaluated the primary complaint leading to medical referral and the presence of symptoms of endocrine, neurological or visual dysfunction.

Endocrine evaluation
Evaluation of pituitary function included pre-operative and post-operative determinations of serum TSH, LH, FSH, PRL, cortisol and free T₄ (FT₄) in all patients, as well as free testosterone in men and estradiol in women. Pre-operative studies also included urinary free cortisol, GH and IGF-1. Dynamic testing of the pituitary-gonadal, adrenal and thyroid axes with TRH (Tregamin®, 400 μg), GnRH (Luforan®, 100 μg) and insulin-induced hypoglycemia (soluble insulin 0.1-0.15 IU/kg) was carried out in 20 patients pre-operatively and in 17 post-operatively, to study GH deficiency. Pre-operative GH levels were <10 mU/l and IGF-1 <2 μU/l in all patients. GH deficiency was diagnosed if plasma GH concentrations failed to reach a value of at least 10 mU/l following stimulation by hypoglycemia. The normal increment of cortisol following hypoglycemia was >220 nmol/l, with an upper value of >550 nmol/l. Lower values were diagnostic of ACTH deficiency. Very low plasma cortisol levels (under 130 nmol/l) were also considered to indicate ACTH deficiency. TSH deficiency was diagnosed when low FT₄ concentrations were associated with low or normal TSH levels. The response to TRH was assumed to be normal when the maximum response occurred at 20 min and showed an increment >5 mU/l. Hyperprolactinemia was considered to be present if plasma PRL level was >20 μg/l. Hypogonadotrophic hypogonadism was diagnosed when low levels of sex steroids were associated with low or normal gonadotrophin concentrations in men or post-menopausal women or with amenorrhea in pre-menopausal women. A maximum net increase after GnRH to >300% over the basal LH value indicated normal gonadotrophin reserve.

Radiological evaluation
Computed tomographic (CT) scan (33 patients) or magnetic resonance imaging (MRI) (18 patients) were performed for the diagnosis and evaluation of recurrence in all cases, the first one after surgery at 6 months. Serial images for each patient were compared by a neuroradiologist and an endocrinologist. Images were examined for enlargement of the sellar contents or parapituitary structures compared with the previous scan.

Visual evaluation
Visual fields were assessed pre- and post-operatively according to Goldmann perimetry.

Radiotherapy
Radiation was delivered by an 18 MV linear accelerator in 27 patients and a cobalt-60 source in 12. A parallel-opposed, two-field technique was used. The treated volume consisted of individualized portals designed to encompass the tumor with a 1.5 to 2 cm margin. Total doses delivered were 4986±151 cGy (180-200 cGy a day, five days a week).

RESULTS

Clinical evaluation
The presenting complaints were: loss of vision in 62% of cases, endocrine disturbances in 18%, headache in 8% and pituitary apoplexy in 6%. Endocrine symptoms were present in 57% of the patients after a meticulous interview.

Endocrine studies
Only 15% of the patients presented normal hypothalamic-pituitary function (GH included). GH deficiency was the most frequent. The mean PRL level was 56.4 μg/l (range 20-100 μg/l). Simultaneous involvement of 3 axes (panhypopituitarism) was diagnosed in 18% (Table 1).

Radiological findings
All the tumors were macroadenomas (>1 cm in size). Only 3 patients (6%) had intrasellar adenomas. Suprasellar extension was present in 82% of patients, lateral extension in 23% and infrasellar extension in 25%. Haemorrhage was found in 10% of cases.

Surgery
Forty-nine patients underwent transsphenoidal surgery (TSS), associated with craniotomy in one case. In the remaining two, access to the tumor was achieved by means of craniotomy. All surgical procedures were performed by a single neurosurgeon (J. G.-U). Twenty-two patients had complete surgical excision, as judged by the surgeon and indicated by the absence of residual tumor in post-operative

Table 1 - Endocrine function before and after surgery.

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<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
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<tbody>
<tr>
<td>GH deficiency</td>
<td>80%</td>
<td>88%</td>
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<tr>
<td>Gonadotrophin deficiency</td>
<td>62%</td>
<td>57%</td>
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<tr>
<td>TSH deficiency</td>
<td>21%</td>
<td>27%</td>
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<tr>
<td>ACTH deficiency</td>
<td>19%</td>
<td>19%</td>
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<tr>
<td>Panhypopituitarism</td>
<td>18%</td>
<td>13%</td>
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<tr>
<td>Normal function</td>
<td>15%</td>
<td>11%</td>
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<tr>
<td>Hyperprolactinemia</td>
<td>53%</td>
<td>0%</td>
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