Effect of surgery and radiotherapy on visual and endocrine function in nonfunctioning pituitary adenomas


*Dipartimenti di Endocrinologia ed Oncologia Molecolare e Clinica, **Neurochirurgia, ***Radiologia, Università Federico II, Napoli, Italy

ABSTRACT. The effect of surgery alone or followed by radiotherapy in recovering visual abnormalities, debulking tumor mass and restoring hormone impairments was evaluated in 84 patients with clinically nonfunctioning pituitary adenomas (NFPA) subjected to 1-10 yr follow-up. All patients underwent surgery via transsphenoidal (in 69) or transcranio-pterional approach (in 15). Radiotherapy was performed after surgery in 59 of 72 patients with incomplete tumor removal. The assessment of pituitary function was performed in all patients before and every 1-2 yr after surgery and/or radiotherapy. Radiological and ophthalmologic assessment was performed before and 3, 6 and 12 months after surgery, then yearly. At diagnosis, headache and visual disturbances occurred in 63 and 58 patients, respectively, while deficiency of GH, TSH, ACTH, FSH, LH and ADH was documented in 55, 7, 19, 47 and 6 patients, respectively. After surgery, gonadal function recovered in 12 women, visual disturbances improved in 43 patients (15 regained normal vision), pituitary function improved in 8 of 62 patients, worsened in 34 patients. At MRI, complete tumor removal was documented in 12 of 84 patients. After surgery alone, tumor regrowth was observed in 7 patients between 3-7 yr. After radiotherapy, vision improved in 9, remained unchanged in 49 and worsened in 1 of 59 patients. After radiotherapy, tumor regrowth was documented in 9 patients between 2-12 yr and the prevalence of hypopituitarism raised from 28.8% to 92% after 1 and 10 yr. In conclusion, surgery alone is effective only in a minority of patients (14.3%) and radiotherapy causes hypopituitarism in rather the totality of patients after 10 yr. The prevalence of tumor regrowth was similar in irradiated ones (15%) and non irradiated patients (28%; \( \chi^2, p=0.4 \)). Therefore, a careful radiological follow-up is suggested after surgery so that radiotherapy can be performed promptly on the basis of clinical data, tumor regrowth and/or invasiveness documented at histology. (J. Endocrinol. Invest. 21: 284-290, 1998) ©1998, Editrice Kurtis

INTRODUCTION

Approximately 25-30% of pituitary adenomas lack of hormone hypersecretion and are classified as clinically nonfunctioning pituitary adenomas (NFPA) (1). Lack of clinical evidence often delays the time of diagnosis, that is overall based on the presence of compressive symptoms as ophthalmologic abnormalities, headache and hypopituitarism. First line treatment of NFPA is surgery, in most cases via a transsphenoidal approach (2). However, though transsphenoidal surgery causes a rapid decompression of the optic nerves with improvement of visual field, complete excision is often difficult because of extrasellar extension, and remnants exist in 30-50% of cases (3). To reduce the risk of tumor regrowth, radiotherapy is required in case of known, or even suspected, incomplete tumor resection at the time of surgery (2, 4-6). However, radiotherapy needs 5-10 yr to complete its effects, causes adverse reactions and may deteriorate pituitary function. This study reports the effects of surgery and surgery followed by radiotherapy in recovering visual field defects, debulking tumor mass and restoring hormone impairments in patients with NFPA subjected to a careful follow-up lasting 1-10 yr, taking into account that a few data are currently available and
concern short-term follow-ups (2, 6-8) and that the long-term prevalence of tumor regrowth after surgery alone or associated to radiotherapy is yet rather difficult to establish.

PATIENTS AND METHODS

Patients
Eighty-four patients with NFPA (48 women and 36 men, age range 18-75 yr) were hospitalized in our Department between January 1985 and October 1996. Computed tomography (CT) and/or magnetic resonance imaging (MRI) documented an intrasellar pituitary mass in 12 patients, suprasellar extension in 54 and extrasellar extension in 18 patients (10 of them with invasion of one or both cavernous sinuses). At immunostaining, 28 adenomas were negative, while monohormonal or plurihormonal positivity for FSH, LH, TSH, ACTH, PRL and GH was observed in 49, 56, 35, 7, 7 and 14 adenomas. All patients underwent surgery: 74 of them as first therapeutic option, whereas the remaining 10 patients were operated on after a 6-month treatment with octreotide, a long-acting somatostatin analog, without any change of tumor mass (9). Transsphenoidal surgery was the procedure of choice for all the patients but 15 who were operated on via a transcranio-pterional approach. The decision to perform a complementary treatment was made within 6-12 months after surgery on the basis of intraoperative findings together with radiological and clinical results. Seventy-two out of 84 patients had incomplete tumor removal and 27 of them had clinical recurrence (considering as clinical recurrence the evidence of tumor regrowth at CT scan or MRI and/or new visual disturbances). Radiotherapy was advised in all 72 patients but 13 refused the treatment.

Protocol of the endocrinological work-up and follow-up
Circulating total and free thyroid hormones, cortisol, PRL, gonadotropins, testosterone, and 17 β-estradiol were assayed in all the patients while IGF-I and α-subunit were assayed in 59 and 30 patients, respectively. TRH (200 μg iv bolus, Serono, Italy), GnRH (100 μg iv bolus, Serono, Italy) and insulin (0.12 U/kg, iv bolus) tolerance test (ITT) were performed in order to evaluate residual pituitary function. The diagnosis of TSH, ACTH or gonadotropin deficiency was made on the basis of low thyroid, adrenal or gonadal hormone levels together with low or absent pituitary hormone increase after stimulating tests. The diagnosis of GH deficiency was performed in keeping with a GH rise ≤3 μg/L after ITT (10). The diagnosis of central diabetes insipidus was made by dehydration test according to Thompson (11) and Baylis (12). Hypothyroidism and hypocorticism were treated with L-thyroxine (100-150 μg po daily) and cortisone acetate (25-37.5 mg a day). Men with hypogonadism were treated with testosterone depot (250 mg im monthly) and females in premenopausal age received estroprogestinic replacement treatment. Similarly, patients with diabetes insipidus were given endonasal desmopressin at the dose of 5-20 mg a day. The assessment of circulating hormone levels was repeated 1-3 months after surgery, quarterly during the first year of follow-up, then yearly, while TRH, GnRH and ITT were repeated every 1-2 yr. CT scan and/or MRI and ophthalmologic evaluation were carried out before and 3, 6 and 12 months after surgery, then yearly. The follow-up duration was 1 yr in 84 patients, 2-5 yr in 63 patients, 6-10 yr in 32 and more than 10 yr in 16 patients.

Radiotherapy
Radiotherapy was given at the rate of 1.8 Gy a day, 5 days a week over 5 weeks. A total dose of 45 Gy was delivered calculated on the 95% isodose line using two lateral wedged fields. For large invasive tumor the target volume took into considered larger margins of the known tumor volume.

Assays
Plasma ACTH and serum GH, PRL, TSH, total and free T₃ and T₄, FSH, LH, testosterone, 17 β-estradiol, progesterone and cortisol levels were assayed by RIA method using commercial kits. Plasma IGF-I levels were measured by IRMA method (DSL, Inc). Serum α-subunit levels were assayed by a RIA monoclonal antibody using commercial kits as elsewhere reported (9).

Radiological imaging
CT scan was performed by a III generation high-resolution scanner, before and after contrast enhancement. From 1985 to 1990 MRI was performed before and after gadolinium enhancement, by superconductive magnetic resonance (0.5 Tesla) and standard head-coil in axial, coronal (seven sections, thickness of 4 mm) and sagittal sections. The acquisitions were: 1) Spin-echo (SE) with 1000 ms repetition time (TR) and 40-120 ms echo time (TE); 2) partial saturation with TR of 500 ms and TE of 21 ms. From 1990 to 1996 MRI was carried out by superconductive magnetic resonance (1.0 Tesla) and standard head-coil in axial, coronal (seven sections, 3 mm of thickness) and sagittal sections. Acquisitions were performed as above.