Radiation Therapy Alone for Growth Hormone-Producing Pituitary Adenomas

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We present our experience in the treatment of growth hormone (GH)-producing pituitary adenomas using irradiation alone. Between 1983 and 1991, 21 patients suffering from GH-secreting pituitary adenomas were treated with radiotherapy alone. Two bilateral opposing coaxial fields were used in 10 patients and in the remaining 11 a third frontovertex field was added. Treatment was given in 1.8–2 Gy daily fractions and total dose ranged between 45 and 54 Gy. Treatment was given using a cobalt unit. Four patients treated with somatostatin prior to and 14 patients treated after the end of radiotherapy experienced symptom relief for 6–28 weeks. The 5-year actuarial rate of disease control was 72%. Five out of six failed patients had macroadenomas. Hypopituitarism was observed in 5/21 (24%) patients. Whereas RT alone is effective in the treatment of microadenomas, this is not true for large infiltrative macroadenomas.

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Therapy for pituitary adenomas includes surgery, irradiation, somatostatin analogs and dopamine agonists, either as single or combined treatments (1–10). Radiation therapy (RT) is used in the following cases: (a) after surgical resection (combined treatment modality) as recurrence rates are high especially for macroinvasive adenomas (3–7, 11), (b) recurrence after surgery or irradiation, and (c) as a sole treatment for older or medically inoperable patients or for patients refusing surgery. The dose for optimal tumor control probability is in the range of 45–55 Gy, whereas some authors recommend lower doses for postoperative RT (12). Radiation-induced cerebral necrosis is a very rare complication within this dose range (4–7).

In this study we present our experience on the treatment of growth hormone (GH)-producing pituitary adenomas with irradiation alone, between 1983 and 1991.

MATERIAL AND METHODS

Between March 1983 and March 1991, 21 patients (12 males, 9 females) aged 20–68 years (median 50 years) suffering from GH-secreting pituitary adenomas were referred for radiation therapy alone at the University of Athens, Department of Radiology. Patients received radiotherapy alone for one of the following reasons: (a) inoperable for medical reasons (6 patients). Two of these patients suffered from chronic pulmonary obstructive disease as a result of heavy smoking and 4 patients suffered from hypertension, probably secondary to acromegaly; (b) refused surgery (4 patients); and (c) surgery was reserved (by the referring endocrinologist) for recurrent tumors (11 patients). Apart from a clinical examination, diagnosis was based on the value of basal state serum growth hormone. Values in excess of 10 ng/ml (15 patients) were considered as diagnostic. In the case of normal or borderline values, a non-suppressibility with hyperglycemia test (6 patients) was used to establish diagnosis. The endocrine profile of all the patients was obtained by a complete hormonal evaluation, and size and extent of the tumor were studied in all patients prior to any treatment using CT scanning. In 15 patients, the tumors were less than 1 cm in diameter (15 microadenomas); they had a normal sella and none of them had a visual field deficit. In 3 patients an enlarged sella and in another 3 patients an extra-sellar extension were noted (6 macroadenomas). In 3 out of 6 patients with macroadenomas, visual field deficits were diagnosed.

Treatment

All patients were treated with radiotherapy alone by the same doctors, technicians and radiographers during this time interval. The same treatment unit (cobalt-60) was also used. Two bilateral opposing coaxial fields were used in 10 patients and in the remaining 11 a third frontovertex field was added. The radiation field size was usually 5×5 cm^2 in microadenomas or it was designed with a 1 cm margin in case of extrasellar extension. To ensure reproducibility

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of treatment, three localizing light beams were used and field verification films were taken periodically. Treatment was given in 1.8–2 Gy daily fractions and total dose ranged between 45 and 54 Gy. Two patients with macroadenomas with extrasellar extension were given the total dose of 54 Gy.

Somatostatin was given in 4 patients prior to and in 14 patients after the end of radiotherapy to relieve symptoms, especially headache and soft-tissue swelling, for 6–28 weeks.

Follow-up and response to treatment

Patients were all formally evaluated by general and neurological examination, visual field and visual acuity assessments, CT and/or MRI scans and endocrinological studies. No psychometric tests were performed. Follow-up data were obtained from radiotherapy records, hospital charts and referring endocrinologists. Follow-up time ranged from 5 to 13 years (median 7 years), while 6 patients (28.5%) were observed for more than 10 years. Response to treatment was defined by one or more of the following criteria: (a) normalization of GH levels (< 10 ng/ml), (b) remission of clinical signs and symptoms and/or (c) lack of radiographic evidence of tumor progression. A stable picture in CT/MRI was considered as a response if normalization of hormonal levels was evident. Inversely, patients were considered to have tumor recurrence in the case of: (a) rising hormone levels, (b) deterioration of clinical signs and/or symptoms, and/or (c) increase in tumor size revealed by CT/MRI examinations.

RESULTS

All of the patients were alive at the time of the last follow-up. Hormonal tumor response was evident between 0.8 and 3.2 years (median 2.5 years) after the end of radiotherapy. At the time of the last follow-up the number of patients in response was 15/21 and the actuarial rate of patients without evidence of progressive disease was 72% (SE: 11.8%) at 5 years. Eight out of 15 responders were in the group receiving somatostatin to ameliorate mainly soft-tissue swelling, for 6–28 weeks.

Five out of six patients with active disease after RT had macroadenomas (Fisher's exact test, $p = 0.017$). Four of them were medically inoperable and were treated by somatostatin thereafter, while the remaining patient and the single non-responder with microadenoma underwent a transphenoidal ressection because of rapid clinical deterioration.. The last two patients were in group c (see Material and Methods).

Univariate analysis for prognostic significance of age, sex, visual symptoms and radiation dose failed to demonstrate that a statistically significant correlation may be due to the small number of patients in this series. A dose-response relationship could not be established owing to the narrow range of given radiation doses.

Toxicity

None of the patients experienced serious life-threatening side effects of radiotherapy. Transient side effects included mild skin reaction, temporal hair loss and serous otitis media. Permanent hypopituitarism requiring replacement with thyroxine, glycocorticoid and sex hormone was observed in 5/21 (24%) patients. In 3/5 of these patients a radiation dose of 50 Gy was given. In the other two patients doses of 46 and 48 Gy were given respectively. All of the patients had a visual field and visual acuity assessment and none experienced a deterioration of vision as a consequence of treatment.

Radiologic study

CT scans were available for all patients. Radiologic follow-up time ranged between 5 and 13 years (median, 7 years). In 4 patients a diffuse cerebral and cerebellar atrophy was noted, but it was not specifically related to RT fields. Two patients suffered from cerebrovascular accident and had an ischemic change on CT scans, located in the frontal lobe. One of them was treated with a three-field technique and the ischemic lesion was marginally included in the irradiated (through the frontal field) volume.

DISCUSSION

This small series of patients represents the total number of acromegalic patients treated by radiation therapy alone at our department within the above-mentioned time interval. It has been reported that the greatest number of recurrences occurs between 4 and 8 years after treatment (1, 13). Although follow-up time (median 7 years, range 5–13 years) of our patients was not long enough for this kind of tumor, we conclude that RT alone with the applied technique and within this dose range is of limited effectiveness for macroadenomas, since 5/6 patients failed to control the disease. Surgery with postoperative RT remains the mainstay of treatment for GH-secreting pituitary macroadenomas.

For microadenomas, we report a 5-year control rate of 72%. This is in accordance with control rates reported in the literature for surgically treated microadenomas.

However, there is a relative paucity of clinical data in the literature addressing the role of RT alone in improvement of endocrinopathy by current treatment standards. Grigsby et al. (7) reported a 10-year NED survival of 69% for GH pituitary adenomas treated by radiation therapy alone.

In the present study symptomatic treatment-related hypopituitarism was 24% into the follow-up interval, which is consistent with previous reports (14). In 1/2 patients who had a cerebrovascular accident, the ischemic lesion was marginally included in the irradiated (through the frontal field) volume.

Long-term visual sequelae were not recorded in the present study. In a study by Grigsby et al. in which RT alone was used for the treatment of pituitary adenomas, 5/70 (7%) patients experienced detrimental effects of radiation. One patient suffered a CNS necrosis at 27 months after receiving 5 400 cGy with parallel opposed portals (7). Visual complications following RT to the pituitary region have been associated with a daily fraction greater than 250 cGy (15).

Four patients were given somatostatin prior to and 14 patients after the end of radiotherapy to relieve symptoms (headache and soft-tissue swelling) for 6–28 weeks. Several studies have demonstrated that long-acting somatostatin analogue SMS 201-995 results mainly in remission of symptoms and reduction of GH plasma levels (16). In a large multicenter randomized trial with 115 acromegalic patients, 70% of whom had persistent disease after surgery or radiotherapy, a substantial decrease in headache, amount of perspiration, joint pain and finger circumference occurred in two-thirds of the patients. The pituitary size was reduced in 19% and 37% (depending on dose) of patients receiving octreotide while GH concentration decreased in 53% of patients (17).

Because some patients present with severe symptoms caused by GH hypersecretion and, on the other hand, because RT may take years to produce an effect, patients received somatostatin analog for a few weeks, a policy that has also been applied by other authors (18). The dose was in the range of 0.05–0.1 mg $\times$ 1–3 times daily. We note that none of our patients received somatostatin at the time of last follow-up. The only side effect recorded was a transient diarrhea in 3/18 patients treated.

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