Long-Term Effects of Radiotherapy for Acromegaly

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Radiotherapy is a largely safe procedure and if carefully carried out, has few side effects. It is most frequently indicated after unsuccessful or incompletely successful surgery. Often in these circumstances, growth hormone levels are significantly reduced by surgery, although not to normal. Radiotherapy can work more quickly if growth hormone levels have been reduced to less than 50 mU/L. The beneficial effects of radiotherapy on growth hormone secretion continue for more than 10 years after its administration.

HISTORICAL INTRODUCTION

PATIENTS WITH acromegaly were first treated by external irradiation in France and Italy in 1909. Symptoms improved and the method quickly became popular.[1] In 1961, Sheline et al described the benefits of pituitary irradiation in their series, with clinical improvement in 70%.[2] However, these results were described before the advent of growth hormone assays. With these, it became apparent that treatment had been less successful[3] and radiotherapy fell into temporary disrepute. However, with continued follow-up evaluation and careful monitoring of the clinical and biochemical progression of the disease, it has been appreciated that this is in time usually a highly successful form of treatment. The time factor is important; although growth hormone levels decrease more significantly after treatment, they continue to do so for more than 10 years after irradiation has been given. This means that radiotherapy is usually given as a secondary form of treatment for the condition.

ADMINISTRATION OF CONVENTIONAL MEGAVOLTAGE IRRADIATION

Conventional megavoltage radiotherapy is the use of photon irradiation. The use of a three-field technique (bilateral, temporal, and single frontal) is the preferred method of administering pituitary irradiation in the 1990s and has been widely adopted. There is now considerable evidence that a tumor dose of 4,500 to 5,000 cGy is optimum and, in earlier work, Sheline has described the control rate of tumors given different amounts of radiotherapy. Fractionation is also important and no more than 180 to 200 cGy should be delivered daily as complications ensue above this. Thus, a total tumor dose of 4,500 cGy given in 26 daily treatments over a period of 5 weeks is a well-established and commonly prescribed radiation dose.

The first important step in the administration of conventional megavoltage radiotherapy is to adequately delineate the tumor in all planes. This is now easy with the advent of modern imaging techniques for the pituitary. During planning, a mask is made individually for each patient to ensure accurate administration and immobilization during therapy. It is advisable to use a linear accelerator because of the beam characteristics. After careful planning, the dose is administered in 26 fractions, 5 days a week for just over 5 weeks, and during this time it is important to keep an eye on visual fields and visual acuity.

EFFECTS ON GROWTH HORMONE SECRETION

Effects of conventional megavoltage radiotherapy on growth hormone levels in 80 patients, followed at St Bartholomews Hospital, London for 2 to 15 years after radiotherapy, have shown that the largest decrease in serum growth hormone occurs during the first 2 years. Levels of growth hormone continue to decrease for many years thereafter. At 5 years, growth hormone levels are less than 10 mU/L in 40% and by 7 years less than 10 mU/L in 86%. These figures are comparable with other series. The likely success of treatment is influenced by pretreatment growth hormone levels. In the 80 patients described here, 70% who achieved growth hormone levels of less than 10 mU/L had pretreatment levels of less than 50 mU/L, whereas only 37 achieved less than 10 mU/mL if the pretreatment growth hormone level was greater than 50 mU/L. We have also shown a significant decrease in growth hormone levels between 10 and 15 years after radiotherapy.[4] In recent years, others have achieved similar results.[5,6]

SIDE EFFECTS OF RADIOTHERAPY

Side effects of radiotherapy remain controversial, but there is no doubt that they can be minimized by attention to detail and by using the now conventional ex-irradiation prescription described earlier. Conventional megavoltage irradiation has minimal acute morbidity and no early mortality. A minor side effect is skin epilation over the irradiated portals during and after radiotherapy. This hair regrows—probably more quickly in young patients. An important long-term side effect is the development of hypopituitarism. This occurs gradually. It is important therefore to assess patients regularly after radiotherapy. It has recently become clear that hypopituitarism can develop many years after the administration of pituitary radiotherapy. In our series, followed up for 12 years, hypopituitarism developed in 25% overall who required replacement therapy 5 years after treatment. The incidence of thyroid, adrenal, and gonadal deficiencies increased to 19%, 38%,

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and 55%, respectively, 10 years after treatment, but not all required replacement therapy for gonadal deficiency.

Hypopituitarism appears an unavoidable side effect with current dose regimens. One important consideration is the possibility of malignant transformation, either in the pituitary itself or in the region near the pituitary. Sarcomatous degeneration has occurred in pituitaries of patients treated previously, although this complication is rare. At St Bartholomew's Hospital in the period 1961 to 1982, 332 patients with pituitary adenoma received megavoltage irradiation by linear accelerator. The series was reviewed after periods of 7 to 27 years (median, 11 years) postirradiation. One case of glioma was consonant with radiation induction, but was paralleled by a contemporaneous case in a nonirradiated patient with Cushing's disease. One case of malignant nasoethmoidal neuroblastoma and two of myelogenous leukemia were considered, on the grounds of spatial dosimetry, as unlikely to have been radiation-induced.[7] However, Brada has suggested that there is an excess of brain tumors in patients treated and followed up for up to 20 years. The figures are small and, as the St Bartholomew's Hospital series shows, not present in all series. Optic tract damage can occur, but again this is extremely uncommon if currently accepted isodoses are adhered to.[8]

INDICATIONS FOR RADIOTHERAPY IN THE TREATMENT OF ACROMEGALY

The most important indication for radiotherapy is postoperative. There is good evidence that growth hormone levels that remain greater than 5 mU/L postoperatively are associated with a higher mortality rate. If, after surgery, growth hormone levels are not reduced to this level, and especially if there is resistance to treatment with either octreotide or bromocriptine, radiotherapy should be considered.

CONTRAINDICATIONS

It is not current practice to irradiate tumors with suprasellar extensions touching the chiasm, for fear of edema developing during the radiotherapy and causing chiasmal pressure and later ischemic damage. Second, it is not now common practice to irradiate patients with acromegaly who have a partial or empty sellar syndrome, for fear of chiasmal damage if the tip of the diaphragm is drawn into the chiasm.

REFERENCES

1. Beclere: The radiotherapeutic treatment of tumours of the hypophysis, gigantism and acromegaly. Arch Roentgen Ray 3:114, 1909

2. Sheline GE, Goldburg MB, Feldman R: Pituitary irradiation for acromegaly. Radiology 76:70-75, 1976

3. Roth J, Gordon B, Brace K: Efficacy of conventional pituitary irradiation in acromegaly. N Engl J Med 282:1391, 1970

4. Wass JAH, Plowman PN, Jones AW, et al: The treatment of acromegaly by external pituitary irradiation and drugs, in International Symposium: Challenges in Hypersecretion: Human Growth Hormone. New York, NY, Raven 1985

5. Pistenma DA, Goffinet DR, Bagshaw MA, et al: Treatment of acromegaly with megavoltage radiation therapy. Int J Radiat Oncol Biol Phys 1:885-893, 1976

6. Feek CM, McLellan J, Seth J, et al: How effective is external pituitary irradiation for growth hormone secreting pituitary tumours? Clinical Endocrinol 20:401-408, 1994

7. Jones A: Radiation oncogenesis in relation to the treatment of pituitary tumours. Clin Endocrinol 35:379-397, 1991

8. Jones A: Complications of radiotherapy for acromegaly in treating acromegaly, in Wass JAH (ed): 1994, pp 115-125