Conventional Pituitary Irradiation Is Effective in Lowering Serum Growth Hormone and Insulin-Like Growth Factor-I in Patients with Acromegaly

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Background: There has been recent controversy as to the effectiveness of conventional pituitary irradiation in reducing circulating GH levels to less than 2.5 ng/ml and/or normalization of serum IGF-I.

Objectives: Our objectives were to determine the effects of conventional pituitary irradiation on 1) lowering of serum GH and IGF-I levels, 2) the proportion of patients who achieve a GH level less than 2.5 ng/ml and a normal age-corrected IGF-I and the time taken to achieve this, and 3) the incidence of hypopituitarism and other adverse effects.

Design: We conducted retrospective data collection from 14 centers throughout the United Kingdom.

Patients: We studied 1840 patients with acromegaly, of whom 884 had received conventional pituitary irradiation.

Measurements: We assessed circulating GH and IGF-I levels and pituitary function at intervals after irradiation.

Results: Mean GH levels declined from 13.5 to 5.3 ng/ml at 2 yr after irradiation, to 2.0 ng/ml by 10 yr, and to 1.1 ng/ml at 20 yr. Twenty-two percent of patients achieved a level less than 2.5 ng/ml by 2 yr, 60% by 10 yr, and 77% by 20 yr. The interval to achieve this depended on the preirradiation GH level. IGF-I levels fell in parallel to those of GH with 63% of patients having a normal level by 10 yr. The proportions of patients with new pituitary hormone deficiencies 10 yr after irradiation were 18% for LH/FSH, 15% for ACTH, and 27% for TSH. No other side effects were noted.

Conclusions: In this, the largest series reported, conventional pituitary irradiation is shown to be an effective and safe means of reducing both serum GH and IGF-I concentrations in patients with acromegaly.

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2.5 ng/ml and a normal age-corrected IGF-I and the time taken to achieve this, and 3) the incidence of hypopituitarism and other adverse effects.

**Patients and Methods**

**Patients**

Patient data have been retrospectively and prospectively collected from 14 centers throughout the United Kingdom. A standard pro forma has been used to enter data from review of individual case records from 1970–2004. At the time of this analysis, the records of 1840 patients with acromegaly had been entered on the UK National Register, of whom 884 patients had received pituitary irradiation. One hundred sixty-three patients were excluded from the analysis because irradiation had occurred before pituitary surgery or because they had been treated with pituitary irradiation on more than one occasion. Of the remaining patients, 44 who had received stereotactic radiotherapy, 13 who had received yttrium implants, and eight who had received unspecified forms of radiotherapy were also excluded. Of the remaining 656 patients who had received conventional external megavoltage pituitary irradiation, 193 had received irradiation but not pituitary surgery and 463 had undergone pituitary surgery before irradiation.

**Pituitary irradiation**

Precise details on the administration of external beam radiotherapy could not be obtained in all cases. Irradiation was delivered via a three-field technique to 400 (84%) of the 479 patients where this information was available. Total radiation dosage was recorded for 544 (83%) patients, and the median administered dose was 45 Gy, this being the dose administered in 358 (66%) of the cases. In only 63 cases (12%) did the total dose fall outside the range 40–50 Gy, the range being 10–55 Gy. The most common schedule for external beam fractionation was 45 Gy in 25 fractions (1.8 Gy per fraction) spread over 30–45 d. Where details of dosing schedules were available (472 patients, 72%), fraction doses fell outside the range 40–50 Gy, the range being 10–55 Gy. The median administered dose was 45 Gy, this being the dose that could not be obtained in all cases. Irradiation was delivered via a three-field technique to 14 centers throughout the United Kingdom. A standard frontal). GH (mean value from five serum samples taken at intervals through a single day over a 10-h period) and fasting plasma IGF-I levels are measured by in-house RIAs (coefficient of variation, <10%). A total of 159 patients have received pituitary irradiation, of which 144 (22% of the overall number of patients) fulfill the criteria for analysis of either GH (n = 144) or IGF-I (n = 39).

**Statistics**

All data are expressed as mean ± 95% unless otherwise stated. Changes in proportion of patients achieving target GH levels against time were assessed by χ² test for trend. Significance was taken as a P value of <0.05.

**Results**

**Patients**

The mean age at time of irradiation was 48 ± 12 yr (range, 14–80 yr). The median interval between surgery and irradiation was 198 d (range, 1 d to 22 yr; 5–95th percentile, 20 d to 7 yr), and the median duration of follow-up since irradiation was 7 yr (interquartile range, 3–13 yr), with 35% of patients being followed up for up to 5 yr, 26% up to 10 yr, 20% up to 15 yr, 10% up to 20 yr, and 9% for more than 20 yr.

**GH**

Among all patients, the mean serum GH level fell from a baseline value of 13.5 to 5.8 ng/ml at 2 yr (56.0% decrease), 3.3 ng/ml at 5 yr (74.4% decrease), 2.0 ng/ml at 10 yr (82.5% decrease), 1.4 ng/ml at 15 yr (88.2% decrease), and 1.1 ng/ml at 20 yr (92.7% decrease) (Fig. 1). Among all patients, 22% achieved a level of less than 2.5 ng/ml at 2 yr, 36% at 5 yr, 60% by 10 yr, 74% by 15 yr, and 77% by 20 yr (Fig. 2). A similar, but exaggerated fall also occurred in the 60 patients with a baseline GH level of more than 30 ng/ml; the mean level of 64.5 ng/ml decreased to 16.5 ng/ml at 2 yr (74.3% decrease), 6.2 ng/ml at 5 yr (90.4% decrease), 4.4 ng/ml at 10 yr (93.2% decrease), 2.3 ng/ml at 15 yr (96.4% decrease), and 0.9 ng/ml at 20 yr (98.5% decrease) (P < 0.0001 for trend).

The proportion of patients who achieved a safe GH level and the time to do so depended on the baseline GH level (Fig. 2). Thus, for patients with a preirradiation GH level of less than 10 ng/ml, 35, 49, 73, 88, and 100% achieved GH of less than 2.5 ng/ml by 2, 5, 10, 15, and 20 + years post irradiation respectively, compared with 11, 27, 51, 69, and 79% of patients with a preirradiation GH level of 10–30 ng/ml at the same time points and 10, 16, 48, 67, and 67%, respectively, of patients with a preirradiation GH level of more than 30 ng/ml (P < 0.0001) for all comparisons between groups. There was no influence of age or sex on GH decline.

Similar results were obtained from independent analysis of the largest single series of patients from one center, St. Bartholomew’s Hospital. The overall mean GH level was 12.5 ng/ml preirradiation and 5.6, 3.4, 2.1, and 1.8 ng/ml at 2, 5, 10, and 15 yr post irradiation, respectively, with levels less than 2.5 ng/ml occurring in 27, 33, 51, and 72% of patients at 2, 5, 10, and 15 yr post irradiation (P < 0.0001 for all comparisons between groups).

**IGF-I**

IGF-I levels fell in parallel with those of serum GH; the proportion of patients achieving an IGF-I level within the normal range increased steadily with time: 38% at 2 yr, 50%
at 5 yr, 63% at 10 yr, 56% at 15 yr, and 55% at 20+ yr (Fig. 3) \( (P < 0.0001 \text{ for trend}) \). Similar results were seen in the patients from St. Bartholomew’s Hospital, with 46% having a normal IGF-I level at 5 yr and 59% at 10 yr after irradiation. Again, the proportion of patients with normal IGF-I levels at increasing time points after irradiation was influenced by basal GH levels; in those with basal GH levels less than 10 ng/ml, IGF-I levels were normal in 40, 50, 70, 67, and 100% of patients at 2, 5, 10, 15, and 20+ yr, respectively, post irradiation. In those with basal GH levels between 10 and 30 ng/ml, the respective figures were 25, 43, 41, 36, and 71%, and in those with basal GH levels more than 30 ng/ml, they were 0, 30, 50, 17, and 38% \( (P < 0.0001 \text{ for all comparisons between groups}) \).

**Fig. 1.** Percentage of all patients achieving a serum GH level less than 2.5 ng/ml (bars) and the mean GH level (line) in the years after pituitary irradiation.

**Fig. 2.** The percentage of patients achieving a GH level of less than 2.5 ng/ml (bars) and the mean GH level (line) in the years after pituitary irradiation according to the baseline GH level.
Adverse effects

The proportion of patients with functioning pituitary axes declined with time (Fig. 4) \((P < 0.0001\) for trend for all axes), such that at 10 yr after irradiation, 58, 50, and 44% were deficient in LH/FSH, ACTH, and TSH, respectively. However, the proportion of patients with deficiencies before pituitary irradiation was 40, 35, and 17%, respectively. Among all patients, there were no cases of secondary intracranial tumor formation or visual impairment after irradiation.

Discussion

These data comprise the largest series of patients detailing the effects of pituitary irradiation in acromegaly. They confirm the efficacy of irradiation in lowering serum GH levels.

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Fig. 3. The percentage of patients achieving a normal IGF-I level in the years after pituitary irradiation, grouped according to the baseline GH level before irradiation. Note for some basal GH values, there was 0% with a normal IGF-I value and therefore no bar is visible.

Fig. 4. The proportion of patients with normally functioning pituitary axes after pituitary irradiation.
with a 50% decline in the first 2 yr, 75% by 5 yr, and a continuing fall thereafter. This evolving effect emphasizes the importance of long-term monitoring of these patients. It is interesting that a more rapid rate of decline in GH values occurred in those patients with the highest baseline GH secretion, an effect that might be related to the large size of the tumors. Although a number of previous studies have also demonstrated that pituitary irradiation reduces serum GH values, the majority have involved small numbers of patients, especially with regard to long-term follow-up (12, 16–24). There are also differences in long-term ascertainment; a low rate of follow-up may reflect a selection bias toward those patients with poor outcome, and thus ongoing symptoms, because of high biochemical activity.

Differences in the definition of cure also hinder direct comparisons between series. The majority of early studies used a target GH level of less than 5 ng/ml as representing a satisfactory outcome (12, 16, 18, 20, 22). It is now generally accepted that a mean level of less than 2.5 ng/ml should be the aim because such a level is associated with restoration of mortality rates toward those of the nonacromegalic population (5).

These limitations have been overcome in the present study by first, the large number of patients; second, the prolonged duration of follow-up, up to 25 yr post irradiation; and third, more stringent criteria with regard to efficacy. Using these criteria, among all patients, almost 25% achieved a safe GH level at 2 yr and 60% by 10 yr with the proportion continuing to increase with further follow-up, so that by 20 yr, more than 75% of patients had safe GH levels. The current data have also confirmed that the single most important factor governing the eventual success of irradiation is the initial baseline serum GH level. Of those patients with a preirradiation level of less than 10 ng/ml, 88% achieved a level of less than 2.5 ng/ml at 15 yr compared with 67% of those with a baseline level of more than 30 ng/ml. The proportion of patients who received primary radiotherapy in this series is higher than might be expected with current management strategies, and the resulting high basal GH levels will have reduced the rate of GH normalization.

These data also clarify the effects of pituitary irradiation on serum IGF-I levels, with more than 60% of patients achieving a level within the normal range by 10 yr. Reasons for the slight discrepancy between the decline in IGF-I levels and the more impressive results of GH decline might reflect the maintenance of GH pulsatile secretion after irradiation, which is able to stimulate hepatic IGF-I production, even with a mean GH level of less than 2.5 ng/ml (25). Another possible explanation might relate to the increased proportion of female patients becoming estrogen deficient in the years after irradiation and the consequent increased hepatic IGF-I sensitivity to circulating GH. However, regardless of the precise explanation, our reported effects on IGF-I are in line with other recent reports (21, 22, 25, 26), which report normalization in 60–70% of patients by 10 yr and up to 85% by 15 yr. The marginally lower normalization rate in the present data may reflect the large number of patients with very elevated GH levels before irradiation. The reasons for the increased proportion of patients with normal IGF-I levels at 10 yr compared with 15 or 20 yr are likely to reflect the cross-sectional analysis of the available data at these time points. Unlike the GH data, there are insufficient subjects with sequential IGF-I levels at all these time points to allow a cohort study. Regardless, these studies and the present data are in contrast to those of another study in which there was little apparent effect on serum IGF-I with levels remaining elevated in 95% of patients at 10 yr post irradiation (15). However, this report was limited by the small number of patients, both at baseline and especially for prolonged follow-up, and wide differences between patients in the irradiation modalities, techniques, and doses.

The optimal objectives in the treatment of patients with acromegaly are now well established, comprising removal of the pituitary adenoma, restoration of normal GH secretion with preservation of remaining anterior pituitary function, and prevention of recurrence. Although transphenoidal surgery remains the first-line treatment for the majority of patients, its cure rate of between 40 and 80% according to the size of the tumor ensures that many patients will still require additional treatment. Furthermore, its success is also dependent on surgical expertise and should be performed only by experienced pituitary surgeons (27). The association between baseline GH levels and time to subsequent cure after irradiation demonstrates that even if not cured, the significant reduction in GH levels by surgery will improve the eventual efficacy of irradiation and decrease the interval to achieve a safe level. During this interval, persistent GH hypersecretion may require adjuvant medical therapy. Long-acting somatostatin analogs reduce serum GH levels to less than 2.5 ng/ml in approximately 50% of patients (11), but their drawbacks include cost, failure to treat the underlying disease, and long-term side effects, including an increased prevalence of gallstones (although these are usually asymptomatic). New therapies such as the GH receptor antagonist Pegvisomant may offer the hope of a more effective medical therapy, although their use has significant financial implications (28).

The reputed side effects of pituitary irradiation have long been regarded by some endocrinologists as arguing against its routine use. Such concerns include visual loss or deterioration, brain necrosis, secondary tumor formation, hypopituitarism, and neuropsychological damage. It is now clear that visual loss is extremely rare if the maximum daily radiation dosage is 2 cGy or less. There were no reported cases of visual deterioration after external beam radiotherapy in this series. A lack of visual disturbance was also reported in two other large series detailing the adverse effects of pituitary irradiation (29, 30). The incidence of secondary tumor formation after pituitary irradiation has been suggested to be 1–2% with prolonged follow-up (29). However, such studies are hampered by a lack of an adequate control population, and the discovery of incidental brain pathology in patients undergoing serial head imaging is a real possibility. Furthermore, those patients who do develop such tumors may have a predisposition to both a pituitary adenoma and intracranial tumor. Regardless of this, there were no cases of secondary intracranial tumor recorded among any patient in the present study. Although there is no doubt that irradiation does result in hypopituitarism, the varying sensitivities of the different hypothalamic-pituitary axes needs to be considered as does the prevalence of preexisting hypopituitar-
Radiotherapy and Acromegaly

Recent years single, high-dose, stereotactically delivered irradiation therapy has become available comprising either the γ-knife or multiple highly focused beams from a linear accelerator. By combining multiple, differently isocentered treatments, the dose distribution can be very accurately conformed to irregular targets. Although the use of these new techniques for pituitary tumors has their advocates, long-term efficacy data are lacking, and the published series have studied small numbers of patients. An early report on patients with acromegaly reported variable efficacy (35), although more recent data appear to suggest better results (36–40). However, additional long-term studies on large numbers of patients are necessary before firm conclusions can be drawn regarding the relative efficacy of stereotactic irradiation, the rate of decline of GH and IGF-I levels compared with conventional irradiation, and the side effects including hypopituitarism and its frequency and rate of onset.

In conclusion, this study has demonstrated that pituitary irradiation is an effective means of reducing not only serum GH but also IGF-I concentrations. It should be considered for patients with acromegaly who have persistent hypersecretion of GH after pituitary surgery, particularly in those not responsive to medical therapy. The preirradiation level will allow some prediction of the interval to achieve satisfactory post irradiation and thus the duration of medical therapy.

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