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Reevaluation of Conventional Pituitary Irradiation in the Therapy of Acromegaly

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Abstract. **External beam pituitary irradiation has been frequently used in the treatment of growth hormone (GH) secreting pituitary adenomas. Many studies have demonstrated that serum GH declines rapidly and reliably following treatment and early "cure" rates, based on a basal serum GH below 10 μg/L were as high as 80%. The definition of "cure" has become more stringent over time and retrospective studies have indicated that GH must be below 2.5 μg/L for acromegalics to achieve mortality rates comparable to a normal population. Only 20% of irradiated patients will achieve this goal by 10 yr. Even fewer will achieve a normal serum insulin-like growth factor I (IGF-I) levels. Although pituitary irradiation still has a role in the control of tumor size, its importance as a treatment for normalizing serum GH is being reevaluated.**

Keywords. **growth hormone, adenoma, anterior pituitary, insulin-like growth factor I, neoplasia**

Introduction

Acromegaly is a chronic disease that when inadequately treated results in significant morbidity and greatly increased mortality. Over the past 10–15 yr the treatment options for this disease have increased. Refinements in transphenoidal pituitary adenomectomy have occurred. However, despite advances in microsurgical techniques, surgery frequently does not result in cure. Long acting somatostatin analogs are available but are expensive and not uniformly effective. In the past, patients who were not cured by surgery underwent subsequent external beam irradiation of the pituitary with the expectation that tumor growth would be prevented, GH hypersecretion eliminated and the patient "cured". As will be discussed, this treatment is effective in decreasing GH. However, recent data suggest that pituitary irradiation in acromegaly infrequently results in a cure.

What Defines "Cure" in Acromegaly

A major difficulty in determining the efficacy of the various treatments for acromegaly has been the definition of "cure" for the disease. Clayton recently outlined criteria for the determination of an absolute biochemical cure [1]. These included (a) restoration of normal secretory dynamics; (b) abolition of paradoxical GH responses and (c) normalization of basal GH and IGF-I to age- and gender-specific ranges. Not all of these criteria have been equally addressed, and most studies on the efficacy of pituitary irradiation have been limited to normalization of basal serum GH concentration and to a lesser degree, abolition of paradoxical GH responses.

Over the past 15 yr there has been an evolution regarding the definition of what is a normal, basal serum GH concentration. For many years, reports on surgical treatment used serum GH concentrations of less than 10 μg/L as criteria for effective therapy. Using this cut-off, cure rates as high as 89% for microadenomas and 68% for macroadenomas were reported [2]. Based on this same cut-off, high "cure" rates using bromocriptine were also claimed [3]. As normal and abnormal GH secretion was more thoroughly studied, it became apparent that many, if not all of the patients with a random serum GH concentration below 10 μg/L were not cured and still had clinically active disease [3]. Accordingly, more recent surgical series have used a cut-off for random GH measurement of 5 μg/L as a definition of successful outcome. Surgical "cure" rates with this more stringent criterion were 70–83% for microadenomas and 35–69% for macroadenomas [4,5]. However, as discussed below, a patient with a serum GH of 5 μg/L is likely to still have active acromegaly. When the criteria of cure are based on a basal GH of less than 2.5 μg/L, the surgical cure rate dropped to 42% and 30% for micro- and macroadenomas respectively [5].

It would be reasonable to define "cure" as a post-treatment mean serum GH concentration that was certain to return an acromegalic patient's mortality to normal and to arrest the progression of GH-dependent morbidity. This would be the case even if GH secretory patterns were not identical to that of the normal population. Since the disease is rare and the morbidities studied take many years to develop, determining this

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cut-point is difficult. Retrospective analyses have suggested that longevity in acromegalic patients correlated with the last measured serum GH. The lower the value, the better the chances of survival [6,7]. Two recent analyses have attempted to define a GH cut-off for normalization of risk. Wrightson et al [8] used a regression logistic model to demonstrate increased chances for good clinical outcome and survival if the last known serum GH was below 2 μg/L rather than above 10 μg/L. Similarly, Bates et al [6] found that a mean serum GH in acromegalic patients of less than 2.5 μg/L reduced mortality to normal levels.

Although a basal serum GH below 2.5 μg/L in acromegaly is clearly preferable to a serum GH below 10 μg/L, the lower value does not necessarily insure against morbidity. In the study by Bates et al [6], there was a 40% increase in mortality over normal in subjects with basal GH below 2.5 μg/L. Although this difference did not reach statistical significance, this likely was a result of the relatively small number of subjects. It is probable that increased mortality would be demonstrated at this lower GH level if more subjects had been studied.

The poor reliability of an average GH below 2.5 μg/L to predict relative protection in individual acromegalic patients is demonstrated in the 24-h GH profiles in Figure 1. The profile in the upper panel was from a 40 year old man with newly-diagnosed and untreated gigantism. Despite the fact that his average daily plasma GH was 1.6 μg/L and all of his GH concentrations were below 2.5 μg/L, plasma IGF-I was twice the upper limit of normal. He had severe symptoms of active GH hypersecretion with hyperhidrosis, headache and progressive acral and mandibular enlargement. In contrast, the subject in lower panel was a healthy young man. His mean daily GH was 1.7 μg/L and serum IGF-I was within the normal range. Their profiles differ dramatically in that plasma GH concentrations in the normal subject were frequently below 0.2 μg/L. This suggests that simply lowering the mean GH without restoring the pattern of GH to normal, which includes periods of very low GH concentrations, may not be adequate.

This case illustrates the difficulty in defining an absolute serum GH that is safe in all patients. Although the epidemiological studies have suggested that a GH below 2.5 μg/L is adequate, this clearly was not the case for this patient. Perhaps this is because a serum GH concentration of less than 2.5 μg/L does not indicate restoration of normal pulsatile GH secretion. Until recently, serum GH concentration was measured by RIA using methods having a minimal detection limit of 0.3–0.5 μg/L. In contrast, newer immunochemiluminometric (ICMA) GH assays have minimum detection limits below 0.01 μg/L. Prior to the ICMA assays, interpulse GH concentrations were thought to be near the lower detection limit of the RIA. Repeat analysis of these same samples using ICMA has demonstrated that interpulse GH concentrations are actually much

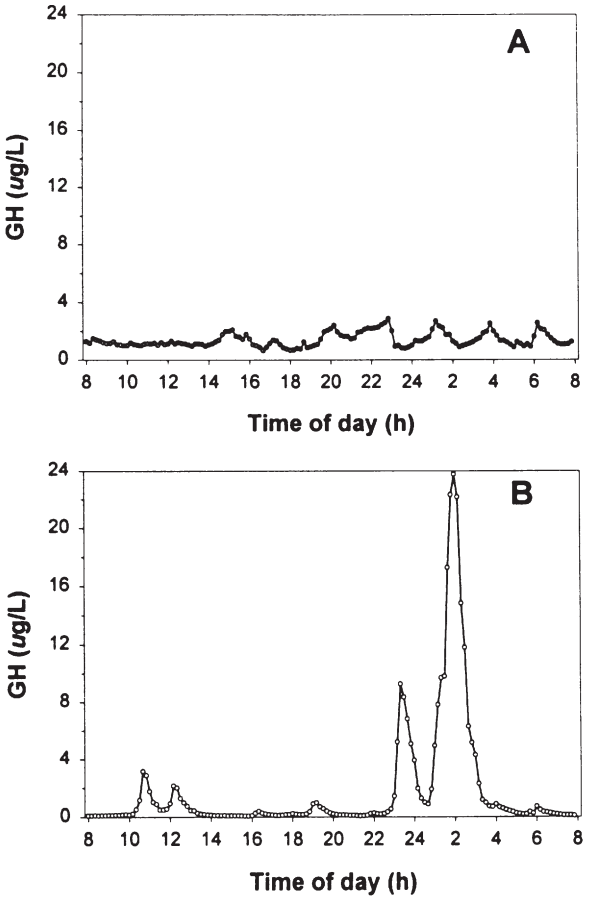

Fig. 1. *24 hour GH profiles of a patient with active acromegaly (top panel) and of a normal young man (lower panel). Mean plasma GH was 1.6 μg/L in the patient with acromegaly and 1.7 μg/L in the normal subject.*

lower and well below the detection limit of any GH RIA [9]. In normal young adults a random serum GH measurement during the day greater than 2 μg/L is infrequent whereas GH concentrations less than 0.5 μg/L occur approximately 50% of the time [10]. The parameters of GH secretion and exposure leading to acromegaly in the face of a normal mean daily serum GH are yet to defined.

There are similar qualifications regarding dynamic testing of the GH axis. Instead of repeated blood sampling to establish a reliable daily mean serum GH, some groups have used suppression of serum GH during an oral glucose tolerance test to define normal GH secretion. Jenkins et al [5] found a high correlation between mean GH following oral glucose and basal serum GH. Prior to the availability of supersensitive GH ICMA, cure was assumed if serum GH fell below 2 μg/L following oral glucose(11). As with basal interpulse GH measurements, the more sensitive GH assays showed that normal men and women suppress to below 0.03 and 0.25 pg/ml respectively [12]. Therefore,

data reporting "cure" based on GH suppression below 2 μg/L are suspect.

A better measure of the level of GH hypersecretion is serum IGF-I. In contrast to the pulsatile release of GH, serum IGF-I concentration is quite stable over the day and correlates with mean daily GH concentration in acromegalic subjects [13]. It is elevated even in patients with minimally active disease and "normal" serum GH concentrations [14,15]. Of interest, we observed that plasma GH was below 1.5 μg/L in nearly 90% of cases when IGF-I values were normal [16]. In contrast, over 60% of GH concentrations below 1.5 μg/L were accompanied by an elevated IGF-I.

Although GH has some metabolic and endocrine actions that are independent of IGF-I, most of the clinical manifestations of acromegaly are mediated through IGF-I [17]. Moreover, serum IGF-I is a surrogate for GH secretion and this single test readily separates acromegalic from normal patients [11]. Therefore normalization of IGF-I should be the goal of our therapies. As of yet, there are no mortality data in acromegaly stratified by serum IGF-I levels. However, it is likely that the IGF-I concentrations are more informative than mean GH concentration. In practice, most endocrinologists measure both parameters but tend to make treatment decisions based on the degree of elevation of serum IGF-I and the patients signs and symptoms.

Pituitary Irradiation Efficacy

Technical aspects of pituitary irradiation will not be discussed in this paper. For information on methods of conventional pituitary irradiation, the interested reader is directed to several excellent reviews [18,19].

There is little doubt that external beam radiation is effective in lowering serum GH. Estimates for mean GH decline over time are plotted in Figure 2. From this graph, it is clear that there is a more rapid fall in GH during the first two years and the rate of fall subsequently slows. The few data available for follow-up for 10 years or greater has suggested that GH either continues to decline, albeit slowly [20], or else reaches a plateau at approximately 20% of the starting value [21,22]. As has been the case with pituitary surgery, criteria for successful pituitary irradiation have evolved over time. Early studies using the liberal criteria for "cure" of a GH less than 10 μg/L reported that irradiation cured acromegaly in over 70% of patients within 3 years [23]. A more recent study found that 77% of patients achieved a serum GH below 10 μg/L

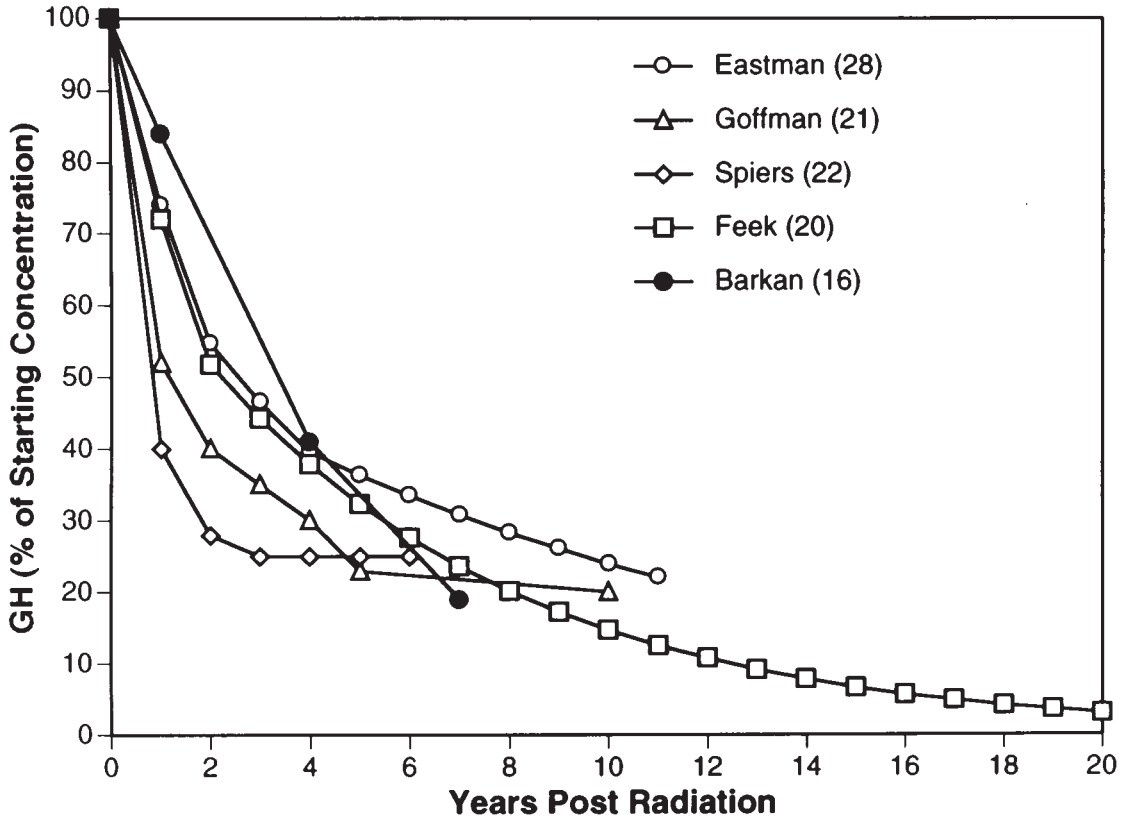

Fig. 2. *Post-radiation dynamics of serum GH concentrations from five separate studies. Authors and reference numbers are given in the legend.*

after 2–10 years but only 55% achieved a GH below 5 μg/L during the same time interval [21].

Various parameters have been suggested to predict which patients will respond to pituitary irradiation. Werner et al observed that patients with initial hyperprolactinemia responded better than did normoprolactinemic patients [24]. This however, has not been the case in three other studies [18,25,26]. Preoperative surgery did not alter the rate in decline of GH [18,22] nor was the response to therapy dependent on age or gender [26].

As suggested by Figure 2, the major determinant for normalization of serum GH is the pre-irradiation GH level. Based on the rates of GH fall found in various studies, if the starting GH is 10 μg/L, it will take between 1 and 4 years to achieve a serum GH of less than 5 μg/L. If the starting GH is 100 μg/L, this goal will not be realized for 10–20 years, if ever.

Yet, as discussed above, achievement of a serum GH of less than 5 μg/L does not indicate cure. Nor does serum GH below this level necessarily protect the patient from the morbidities associated with persistent GH hypersecretion. Improvements in clinical parameters of acromegaly such as arthralgias, hyperhidrosis and glucose metabolism do occur following irradiation, however the benefits are frequently not realized until many years following treatment. Failure of pituitary irradiation to effect a timely normalization of GH is exemplified by the progression of cardiovascular disease following radiation therapy [27]. In contrast, abrupt decreases in serum GH following pituitary apoplexy [28] or during octreotide treatment [29] have been reported to arrest or improve cardiac abnormalities. It is of interest to note that MacSweeney et al [30] concluded that heel pad thickness was an insensitive measure of biochemical "cure" after treatment with yttrium-90 implantation. Yet, soft tissue thickness is normal in acromegalics with inactive disease [31] and soft tissue swelling decreases in patients treated with octreotide who have normal serum IGF-I levels [32]. Cure in the yttrium-90 treated patients was defined as a GH below 5 μg/L and these patients undoubtedly had elevated serum IGF-I.

Although the effects of pituitary irradiation on serum GH are well documented, the effects of this treatment on IGF-I are not as well studied. Ciccarelli et al [33] reported that pituitary irradiation normalized serum IGF-I in 13/19 patients within 2–4 years of treatment. Another study found normal or low IGF-I in 23/40 irradiated patients 3–12 years post irradiation [34]. However, the validity of the IGF-I assays in these reports is in question. In the former study, normal serum IGF-I was associated with frankly elevated mean daily serum GH. In the latter report, a third of patients with reportedly normal IGF-I had clinically active acromegaly.

In contrast to these two studies, we [16] and others [35] have recently reported on the ineffectiveness of pituitary irradiation to normalize serum IGF-I. Data from our study are presented in Figure 3. Of 38 patients followed for a maximum of 10 years, only two patients receiving pituitary irradiation had a serum IGF-I that was persistently within the age-and gender-adjusted normal range. In contrast, serum GH rapidly declined following irradiation and 65% of the patients had a random GH of less than 5 μg/L within 5 yr. Consistent with our results, Thalassinos et al [35] also found that pituitary irradiation seldom resulted in "safe" GH levels. In that study, serum GH fell below 2.5 μg/L in only 20% of their patients by 10 yr. Of a total of 21 patients who were followed for at least 10 year, serum IGF-I data was available on 14 subjects. Of these, only 4 had normal IGF-I levels. It was not stated whether their IGF-I normal ranges were corrected for age and gender so that is conceivable that the number of patients with a truly normal serum IGF-I was even

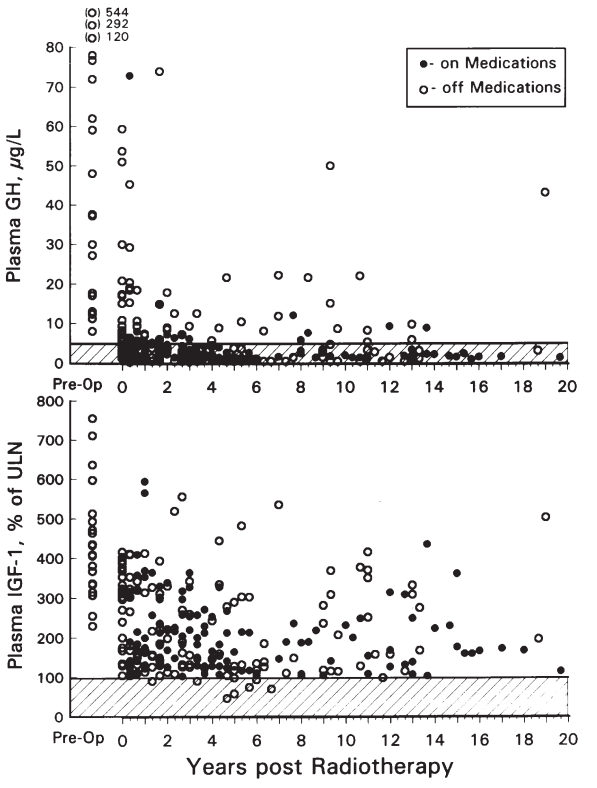

Fig. 3. *Preoperative, postoperative and post-irradiation GH and IGF-I values in 38 patients with acromegaly who were treated with pituitary irradiation. Many values were obtained while the patients were treated with medications (bromocriptine or octreotide, open circles). Off medication values are shown by the closed circles. Plasma IGF-I is expressed as a percent of the age-and gender-specific upper limit of normal. (From Barkan AL, Halasz I, Dornfeld KJ, Jaffe CA, DeMott Friberg R, Chandler WF, et al. Pituitary irradiation is ineffective in normalizing plasma insulin-like growth factor I in patients with acromegaly. J Clin Endocrinol Metab 1997;82:3187–3191. © The Endocrine Society)*

lower. Subsequent to the publication by Barkan et al [16] on the poor efficacy of pituitary irradiation to normalize serum IGF-I in acromegaly, a preliminary report claimed a 44% serum IGF-I normalization rate with conventional therapy [36]. Further investigation into this question is needed.

In summary, it can be safely concluded that pituitary radiation rapidly lowers GH. Yet, GH secretion is infrequently brought down to a level that results in normalization of serum IGF-I, even after 10 years of follow-up. This persistently elevated IGF-I is likely to put irradiated patients at risk for further morbidity associated with acromegaly. Whether other modalities of radiotherapy will be found to be more effective is unknown. Proton beam does not appear to have any advantage over conventional external beam irradiation and it may have more adverse effects [37]. Whether gamma-knife radiation is more successful remains to be seen. An early study on gamma-knife radiation in 21 patients with GH-secreting macroadenomas reported a more rapid decline in GH with this therapy than is seen with conventional irradiation [38]. Plasma GH concentrations fell below 2 μg/L in 5/21 of the patients who underwent radiosurgery, however few IGF-I data were given. Preliminary data demonstrating 20% normalization of IGF-I by 6 years after gamma-knife treatment is encouraging [39].

This high failure rate of conventional pituitary irradiation is not unexpected. The experience with this therapy for the treatment of other types of pituitary tumors would predict this. In the case of adult Cushing's disease, irradiation as a primary therapy results in long term cure in at best 50–60% of patients [40,41], although irradiation as a secondary treatment appears to be efficacious [42]. Similar to the decline in GH in acromegaly, irradiation of prolactinomas results in an impressive initial fall in prolactin yet only 50% of patients achieved a normal prolactin after a mean follow-up of 8.5 yr [43].

Although pituitary irradiation is not very effective in normalizing serum IGF-I it might play a role in preventing further growth or in shrinking GH secreting adenomas. Early studies observed a reduction in fossa size by lateral skull film or improvement in visual-field defects [25]. In addition, irradiation increases recurrence-free rates post resection of large macroadenomas [19]. Eastman et al [18] reported that none of their 86 patients had clinical symptoms that would suggest progression of tumor size and, in a review of the literature, they found evidence for tumor progression in only 3/1027 acromegalic patients treated with radiotherapy. Similarly, Tsang et al [44] reported that follow-up computer tomography or magnetic imaging scans indicated a 96% progression-free rate at 10 years in a group of 145 patients with secretory pituitary tumors. Of this group, 1/3 were acromegalics. Unfortunately, the authors gave no further information on change in tumor size or concomitant medical treatments. More conclusive radiologic evidence for the benefit of pituitary irradiation in acromegaly was provided by Ciccarelli et al [33]. They found that 3/19 GH secreting tumors completely disappeared after 6 months and another 4/19 decreased 20–55% in size within 36 months of treatment.

Side Effects

In general, external beam pituitary irradiation is well tolerated. The major risks are the development of hypopituitarism, visual loss or brain damage. Hypopituitarism is common, and after exclusion of patients with pre-irradiation hormonal deficiency, the incidence of secondary gonadal, adrenal or thyroid deficiencies is as high as 50, 37 and 37% respectively in acromegalic patients [45,46]. The risk of hypopituitarism is dose dependent and Littley et al [47] have suggested that 20 Gy and the standard dose of 50 Gy are equally effective in suppressing serum GH. Others (48), however have reported less efficacy in decreasing GH with lower doses and hypopituitarism can occur even after treatment with 20 Gy [49].

Visual loss is a rare side effect of conventional pituitary radiation. It is estimated that the risk for this complication in acromegalic patients is approximately 2% [18]. This number is probably an overestimation as it includes patients who received dose fractions or total irradiation in excess of current recommendation. However, visual loss due to radiation damage can occur even when "safe" doses of are administered [50]. If the total dose is limited to 45 Gy and the daily dose does not exceed 2 Gy, it is likely that the risk of radiation damage to the optic nerve or chiasm will be much lower than the 2% estimate [23].

Potential brain damage resulting from pituitary irradiation has been extensively reviewed by several authors [18,51,52]. A variety of anatomical changes, including cerebral atrophy, hypothalamic gliosis, temporal lobe changes, and radiation necrosis have been described. Cases of Kluver-Bucy syndrome [53] and necrotizing brainstem leukoencephalopathy [54] following pituitary irradiation have occurred. al-Mefty et al [51]. observed that abnormalities of brain parenchyma were present in 30% of patients with pituitary tumors at a mean follow-up of 8 years. The clinical significance of these changes was uncertain. Grattan-Smith et al [52] described four cases of radiation necrosis out of 11 patients with Cushing's disease who received pituitary irradiation. None of the 11 acromegalics and 1 of 17 patients with chromophobe adenoma developed this complication. Brain necrosis, however is a rare event. Pooling data from a large number of studies Sheline et al [55] concluded that the risk of this occurring is 0.04–0.4%, depending on the radiation dose and method of delivery.

The risk of development of second brain tumors following pituitary irradiation is uncertain. A retrospective analysis by Bliss et al [56] found only one

malignant brain tumor in 296 patients irradiated for pituitary adenoma in Edinburgh between 1962 and 1990 and a compilation of data from 37 studies that included 1027 acromegalic patients found only two cases of a secondary brain malignancy resulting from the irradiation [18]. Jones [56a] similarly observed that secondary brain tumors were rare in a series of 332 consecutive cases of pituitary adenoma irradiated. He cautioned that few of the previous reports warning against this potential side effect had adequately defined denominator groups and therefore could not define relative risk.

Several recent studies, however suggest that the risk of secondary malignancy may be greater than that reported earlier. Tsang et al [57], found 4 cases of glioma in 305 patients with pituitary adenoma treated with pituitary irradiation the tumors developed with a latency of 8–15 yr. The patients had a relative risk of malignant brain tumor of 16 times greater than the general population and the cumulative actuarial risk of secondary glioma was 2.7% at 15 yr post pituitary irradiation. Similarly, Brada et al [57a] concluded that the relative risk for development of a second brain tumor compared with the incidence in the normal population was approximately 9. Simmons and Laws [58] recently reported the diagnosis of gliomas in two patients with acromegaly who had received pituitary irradiation. They reviewed the literature and concluded that conventional pituitary radiotherapy clearly increased the risk for development of aggressive gliomas. Moreover, they noted that a large proportion of these secondary gliomas were associated with GH-secreting pituitary adenomas. Although glioma appear to be the most frequent secondary brain malignancy following pituitary irradiation, development of meningioma [59] and astrocytoma [60] have also been reported.

An important question is whether pituitary irradiation compromises intellectual function. It is the impression of may clinicians that this is the case. There are, however no conclusive data on this question. Information on intellectual development in children who have received brain or pituitary irradiation is conflicting and is confounded by the concomitant use of chemotherapeutic agents in many of the children.

Conclusions

Until recently, pituitary irradiation was recommended in acromegaly as a primary therapy or after failed attempts at surgical cure. Although GH predictably falls post-pituitary irradiation, several recent studies suggest that this treatment infrequently results in normalization of serum IGF-I. Hence, conventional irradiation is unlikely to protect patients from the morbidities of acromegaly. It may therefore be necessary to rethink the role of pituitary irradiation in this disease. Since pituitary surgery has the potential to rapidly cure some patients and, at the least, results in a substantial fall in serum GH, most patients should undergo adenomectomy as a first step. Even if not cured by surgery, the lower GH will allow subsequent treatments to more likely normalize IGF-I. In most patients who are not cured by surgery, the addition of a long acting somatostatin agonist should be the next step since octreotide normalizes serum IGF-I and reduces tumor size in approximately 50% and 35% of patients respectively [61]. For those acromegalics who are not cured by surgery but who have low enough GH and IGF-I concentrations such that normalization can be expected in a few years, treatment with either pituitary irradiation or a somatostatin analog should be offered. The risks from pituitary irradiation are low, however data on potential adverse effects on cognitive function is lacking. Irradiated patients should receive subsequent medical treatment with a long acting somatostatin agonist until serum IGF-I normalizes. Pituitary irradiation should also be considered if the post surgical tumor residual grows in spite of medical treatment and for those patients in whom somatostatin analogs do not completely normalize serum IGF-I.

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