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Editorial: The Role of Radiotherapy in Acromegaly

The manuscript of Barkan *et al.* (1), in this issue of *JCEM* (see page 3187), in which they describe the inefficacy of pituitary irradiation in normalizing serum insulin-like growth factor I (IGF-I) concentrations in patients with acromegaly, is interesting because it is the first report that uses IGF-I instead of GH as the parameter for the efficacy of radiotherapy in acromegaly. Most previous reports use GH as the parameter in the long-term follow-up of acromegalic patients after radiotherapy (2–4). Roughly, these studies indicate that, after two yr, GH concentrations decrease by about 50% from baseline levels, and by five yr the GH concentrations are about 25% of the initial values. Speirs *et al.* (5) reported that radiotherapy is equally efficacious whether an earlier unsuccessful ablative procedure had been used or not. Acromegalic patients frequently do have abnormally large frontal air sinuses, which allow increased anterior beam transmission. This can cause an increased dose to the optic nerve and chiasm with potentially damaging effects. The resultant overdosage can be greater than 5% of the intended dose (6). These authors recommended therefore that acromegalic patients should be treated with a more acurately directed beam, which avoids the air sinuses altogether. Despite this, radiotherapy for acromegaly is a safe procedure in the long-term, with few reports of damage to the optic nerves (7, 8). The incidence of second brain tumors after pituitary irradiation is also low (9). Little is known, however, about the long-term effect of irradiation of the pituitary area on neuropsychological functions (9–11). The relationship between GH and IGF-I levels in patients with acromegaly does not follow a straight line. Only in GH concentrations up to 40–60 μg/L do GH and IGF-I demonstrate a close correlation, but higher GH concentrations do not lead to a further increase in IGF-I levels in most patients (12, 13). However, many patients demonstrate increased serum IGF-I levels in the follow-up, while GH concentrations are within the normal range and vice versa (13). After the introduction of somatostatin analogs in the treatment of acromegaly, the need for radiotherapy has decreased. The somatostatin analogs available (octreotide and lanreotide) decrease GH and IGF-I levels to normal levels in about 60% of patients (14). The recently developed long-acting somatostatin analogs will simplify therapy for these patients and will encourage their compliance, while the effectiveness of normalizing GH and IGF-I levels might be higher (15–20). With better medical treatment available, fewer acromegalic patients who fail surgical therapy will need radiotherapy. This is especially true for elderly patients, who are more sensitive to somatostatin analog therapy (13). One of the shortcomings of the study by Barkan and coworkers (1), as they themselves pointed out, is that no uniform radiotherapy technique was used in this retrospective study. Both proton beam radiotherapy and conventional radiation techniques were used, and patients were treated in several centers. The relatively low number of subjects in this study and the variability of the IGF-I assays used make it hard to draw final conclusions. In our own database, we looked for the course of serum IGF-I concentrations in acromegalic patients. In a group of 37 patients who were not cured after transsphenoidal surgery and radiotherapy and who could be followed for a period of 7 yr, we found that IGF-I concentrations had not normalized, even after a follow-up period of 7 yr. In the same group, anterior pituitary insufficiency had developed in about 40% (39% thyroidal insufficiency; 33% gonadal insufficiency; 42% adrenal insufficiency). This clearly demonstrates that pituitary damage frequently occurs after radiotherapy. The lowering of GH levels further supports the damaging effect of radiotherapy on the pituitary fossa. Why then do serum IGF-I concentrations not normalize, and what does this mean from a clinical viewpoint?

One of the major problems in assessing disease activity in acromegaly is the fact that neither serum GH nor IGF-I concentrations have been shown to be reliable parameters, although recently some investigators suggested a possible role for IGFBP-3 (21–24). There is consensus, however, that in patients with normal serum GH and IGF-I concentrations, disease activity is absent or low. It remains uncertain whether one or several GH samples or 24 hr GH profiles are necessary to obtain an impression of GH secretory reserve (21, 23). Why did serum IGF-I levels demonstrate such a disappointing decrease after radiotherapy?

One might speculate on a role of IGF-I modulating tissue repair after irradiation or ischemia. In acromegalics IGF-I levels are increased, which in theory might influence the outcome of radiotherapy. Several reports demonstrated that IGF-I can decrease cellular damage in cases of ischemia (25–27). IGF-I might be a potent neuronal rescue agent when injury is imminent in case of ischemia. When tissue damage is caused by irradiation, however, the role of IGF-I could be less beneficial (28). By inducing changes in chromatin confirmation IGF-I inhibits repair of irradiation-damaged DNA. Whether this plays a role where radiotherapy in acromegaly is concerned is not known. It would not explain why tumorous GH levels decrease after radiotherapy in these patients, while IGF-I concentrations do so to a much lesser extent. If these findings by Barkan and coworkers turn out to be correct, while we do not know the long-term adverse effect of radiotherapy on neuropsychiatric functions, we probably should reserve irradiation of the pituitary tumor (remnants) in acromegalic patients with active disease to those in whom other treatments like somatostatin analogs have failed to control disease activity.

However, more studies should be carried out to find the optimal biochemical parameters to be used in defining a

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"cure" of acromegaly. Also the high costs of long-term somatostatin analog therapy should be considered. In the meantime we reserve radiotherapy only for acromegalics with large, infiltrating pituitary tumors that cannot be cured surgically and that are also not controlled by somatostatin analog treatment with repeated long-acting depot preparations. This means that fewer patients will receive radiotherapy in future. Up till now, in many centers, including ours, patients who are not cured after neurosurgery are still treated with radiotherapy. With the report by Barkan et al. (1), however, the discussion about the role of radiotherapy is again intensified.

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