CLINICAL STUDY

Failure of radiotherapy in acromegaly

Renato Cozzi, Michela Barausse, Diego Asnaghi¹, Daniela Dallabonzana, Sandro Lodrini² and Roberto Attanasio

Divisions of Endocrinology and ¹Radiotherapy, Niguarda Hospital and ²Division of Neurosurgery, Neurological Institute Carlo Besta, Milan, Italy

(Correspondence should be addressed to R Cozzi, Via Bernina 43, I-20159 Milan, Italy; Email: renatocozzi@tiscalinet.it)

Abstract

Background: Recent data has raised skepticism regarding the long-term effectiveness of radiotherapy (RxT) in acromegaly and its role as an ancillary tool to neurosurgery (Tx).

Patients: We evaluated 72 acromegalic patients previously submitted to RxT. Data were discarded in 23 patients, who were lost to follow-up, operated on after RxT or irradiated with techniques different from external conventional fractionated RxT. Among the remaining 49 (five with mixed GH-prolactin adenoma), 34 were irradiated after surgical failure and 15 as primary treatment. A second cycle of RxT was administered in two.

Results: (i) GH/IGF-I. After a median follow-up of 14 years (range 3–41), normal age-matched IGF-I levels were reached in eight patients (16%) after 10 years, and GH levels <2.5 µg/l in six (12%) after 9 years. The rate of persistently pathological hormonal levels was still 90% at 25 years. All patients with GH/IGF-I normalization had undergone irradiation without any antiseecretory drug. Neither basal GH nor tumor size affected the outcome of RxT. In three patients (6%) a relapse/worsening occurred. (ii) Tumor size. Tumor shrank after 8.5 years in 24 patients (49%), in nine of whom during GH-suppressive treatment. Tumor shrinkage was not predictive of hormonal normalization. (iii) Side-effects. Hypopituitarism was diagnosed in four patients (selective in three and global in one) and GH deficiency in one. Three patients had neurological side-effects and meningioma was shown in two patients.

Conclusion: RxT is unable to cure acromegaly, because it seldom achieves hormonal normalization even after a very prolonged follow-up. Concomitant antiseecretory treatment seems to counteract its effects. RxT can still play a role in those patients with large tumor remnants, because of its capacity to shrink tumor size.

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Introduction

Radiotherapy (RxT) has been used for decades (1) in the treatment of acromegaly. Even though the role of RxT has become subsidiary since the development of microsurgery in the 1970s, the high rate of surgical failure with invasive macroadenoma and the need to treat definitively patients who either refused or could not undergo neurosurgery (Tx) still left room for the application of RxT. It is well known that the effects of RxT are delayed for many years and that they are often accompanied by the development of hypopituitarism; its long-term efficacy has not, however, been questioned until recent years. Recent epidemiological data show that the increased cardiovascular mortality of acromegalic patients (2, 3) can be reverted to normal by decreasing growth hormone (GH) levels below 2.5 µg/l and restoring age-matched insulin-like growth factor-I (IGF-I) levels (4–6). Long-term evaluation of the effectiveness of RxT in acromegaly by these updated criteria of cure, however, is still scanty and contradictory. We were thus prompted to evaluate retrospectively our

large series of acromegalic patients and address the following outcomes: hormonal normalization, tumor shrinkage and the occurrence of adverse events.

Patients and methods

Patients

A retrospective chart review was performed on all the acromegalic patients evaluated at our center during the past 40 years. The diagnosis of acromegaly had been made according to the clinical picture, elevated GH levels not suppressible after an oral glucose load (cut-offs differed according to the year of diagnosis) and high IGF-I levels (since available). Records of all patients submitted to RxT as part of their treatment were retrieved from the archives and pertinent data were extracted. Among the 72 patients thus obtained, 23 were discarded; because of incomplete data in nine patients, because of Tx post-irradiation in five, and because of irradiation by techniques different from external conventional fractionated RxT in nine (conformal

Table 1 Demographic and clinical data.

No.	Sex	Year of RxT	Age at RxT	Interval between Tx and RxT (years)	Dose (Gy)	Follow-up (years)
1	M	1990	20	1	46	10
2	F	1979	56	1	40	21
3	F	1990	55	14	46	10
4	F	1980	48	1	42	18
5	M	1976	29	1	46	24
6	M	1984	52	1	54	16
7	F	1987	56	1	40	11
8	F	1992	42	7	46	7
9	F	1993	33	4	46	5
10	F	1986	24	0	46	14
11	M	1990	44	11	46	6
12	M	1979	18	0	19	14
13	F	1990	46	4	48	10
14	F	1992	15	4	44	8
15	F	1974	39	0	46	25
16	M	1989	27	1	60	11
17	F	1977	37	0	46	23
18	F	1974	41	0	28	18
19	F	1993	55	1	46	3
20	M	1990	42	5	47	3
21	F	1990	52	1	46	6
22	F	1974	27	0	46	26
23	F	1990	15	0	46	9
24	F	1985	52	10	46	13
25	F	1989	41	0	45	11
26	F	1991	33	6	46	8
27	F	1993	27	3	46	7
28	F	1984	41	1	46	11
29	M	1986	31	1	46	14
30	F	1990	41	10	46	10
31	F	1993	30	0	46	6
32	F	1986	41	1	46	5
33	F	1990	36	4	45	9
34	F	1977	33	0	42	23
35	F	1977	47	—	46	23
36	M	1990	64	—	46	10
37	F	1977	55	—	46	23
38	F	1991	70	—	40	5
39	F	1971	25	—	46	28
40	F	1976	43	—	42	24
41	M	1981	57	—	46	17
42	F	1972	31	—	42	27
43	F	1959	42	—	46	41
44	M	1983	57	—	44	17
45	F	1982	57	—	42	18
46	F	1963	35	—	75	29
47	M	1983	37	—	45	17
48	M	1974	46	—	46	26
49	F	1972	41	—	46	26

stereotactic and radiosurgery in three and six respectively). One patient (no. 46) was included regardless of inadequate baseline assessment, because long-term follow-up confirmed the diagnosis.

Forty-nine patients (36 females and 13 males) were assessed (Table 1). In five patients (nos 7, 12, 14, 23, 47) there was a mixed hypersecretion of GH and prolactin (PRL).

Irradiation had been performed at the age of 41 years (median, range 15–70 years). In two female patients (nos 18, 46) a second cycle of RxT had

been administered, after 8 and 5 years respectively, due to persistence of the disease, as determined by no significant change in GH levels. In these patients the date of the second cycle was considered as time zero for follow-up.

In 34 patients (26 females and 8 males) RxT had been administered as adjuvant after Tx, when the disease was persistent postoperatively. Tx had been performed (by the transsphenoidal route in 28 patients and by the transcranial approach in six, nos 12, 15, 18, 22, 27, 31) 1 year (median, range three months to 14 years)

before RxT. Five patients (nos 6, 14, 23, 27, 31) had undergone a second operation before irradiation. In 15 patients (nos 35–49, ten females and five males) RxT had been performed as primary treatment (in one patient, no. 46, it had been performed twice, 5 years apart).

In the patients with persistence of the disease, GH-suppressive treatment, either dopamine agonists (DA) or somatostatin analogs (SA), had been started and controls had been performed regularly. While ongoing treatment had been continued in the patients with persistently high GH/IGF-I levels, GH-suppressive drugs had been periodically withdrawn in those with normalized hormonal values on medical treatment to evaluate the effects of RxT. In 21 patients, mainly in those treated in the last few years, RxT had been administered while on DA or SA.

Procedures

Data regarding GH and IGF-I levels, concomitant anti-GH treatments (if applicable), neuroradiological evaluations, pituitary function, and complications, both before and after treatment, were obtained from each hospital record. The end-points were the attainment of age-matched IGF-I normalization and of GH levels below $2.5 \mu\text{g/l}$, tumor shrinkage (if applicable), and the onset of hypopituitarism.

All but two patients (nos 38, 46) had been irradiated at the same center near our hospital. After computed tomography (CT) evaluation, since available, to define the pituitary border or computer-aided three-dimensional treatment planning, the mean ($\pm$ S.E.) dose delivered had been $45.08 \pm 0.98 \text{ Gy}$, the mean number of fractions had been 22.4 and the mean dose for each fraction 200 Gy. The three-field technique using an opposed pair of lateral beams with a third anterior or vertex beam had been used in seven patients; the opposed lateral fields only had been used in 41 patients. Beam energies had been derived from a cobalt source in 24 patients, a cesium source in one patient, a betatron in 16 patients (nos 1, 2, 5, 12, 15, 17, 22, 34, 37, 39, 41, 44, 45, 47–49) (with 30 MV and 35 MV photons in 11 and 5 patients respectively), and a linear accelerator with 15 MV photons in seven patients (nos 8, 9, 14, 19, 26, 27, 31). Technical details were not fully available in three patients (nos 38, 43, 46).

Patients had been followed-up at regular intervals (at least every 12 months for clinical and hormonal evaluation and at least every 5 years for neuroradiological evaluation) up to the last control. Hormonal data at each control were recorded in two categories, according to whether or not anti-GH treatment was still ongoing or had been withdrawn (for at least 2 months). In the Results section data obtained at each follow-up evaluation are detailed only for patients off medical treatment, namely at 2, 5 and every 5 years since RxT, up to the most recent evaluation.

GH levels had been assayed on three blood samples; IGF-I levels, assayed on a single morning sample, were considered normal if below the age-matched upper limit of the normal range (ULNR).

In the patients with previously normal pituitary function, assessment of urinary free cortisol, plasma free thyroid hormones and testosterone (in males) had been performed at yearly intervals. Pituitary failure was considered with assays of peripheral hormones showing values below normal range. Gonadal failure in females was considered only if menstrual cycles had terminated before 45 years of age.

GH deficiency (GHD) had been diagnosed when undetected basal GH levels did not increase after stimuli (arginine plus GH-releasing hormone (GHRH) and/or insulin tolerance test).

Methods

GH and IGF-I had been assayed in duplicate by various assays over the years. In the last 10 years GH had been assayed by DELFIA with commercial kits purchased from Sorin (Saluggia, Italy), with standards calibrated against the 1st IS 80/505 ($1 \text{ ng} = 2 \mu\text{IU}$), a detection limit of $0.1 \mu\text{g/l}$ and intra- and inter-assay coefficients of variation of 3.5 and 5.5% respectively. IGF-I had been assayed throughout the same period by RIA after acid–ethanol extraction, with kits purchased from Nichols (San Juan de Capistrano, CA, USA), with standards calibrated against WHO 87/518, and intra- and inter-assay coefficients of variation of 3.7 and 7.2% respectively. In our laboratory current normal values for IGF-I are $114\text{--}492 \mu\text{g/l}$ in patients 25–39 years old, $90\text{--}360 \mu\text{g/l}$ in patients 40–54 years old and $71\text{--}290 \mu\text{g/l}$ in patients older than 55 years.

CT and thereafter magnetic resonance imaging (MRI) had been performed with a Siemens Somatom HiQ and a Philips Gyroscan (ACS-NT) at 1.5 T respectively, since their introduction into routine practice. In images evaluated by CT, shrinkage was diagnosed if two neuroradiologists agreed on its occurrence or if a neuroradiological picture of empty sella (ES) not previously apparent was shown. For MRI, on each scan the largest diameter of the tumor was measured on coronal and axial sections and the shrinkage of the tumor was arbitrarily considered significant when such a diameter was reduced by at least 25%. The shrinkage is reported in the Results section if the comparison of tumor size could be performed by the same neuroradiological technique in each patient.

Statistical analysis

Values are expressed as median and interquartile range (25–75%), unless otherwise stated.

Due to the changes in assays of IGF-I throughout the follow-up period, absolute values have been regarded as

misleading and values are thus expressed only as percentage of the ULNR (%ULNR) for each assay.

Analyses have been performed on raw data, or after transformation of hormonal data as a percentage of the baseline.

Data have been analyzed by parametric or non-parametric tests, depending on whether or not they passed preliminary tests of normality and of equal variance respectively. Continuous data with normal distribution have been analyzed by a *t*-test for paired or unpaired data, ANOVA followed by a Student–Newman–Keuls test, and a Pearson correlation test. Continuous data with uneven distribution have been analyzed by a Wilcoxon test, a Mann–Whitney test, a Kruskal–Wallis test followed by a Dunn test, and a Spearman correlation test. Multiple regression analysis has been performed by stepwise regression. Categorical data have been analyzed by a Chi-square test or a Fisher exact test, as appropriate. Longitudinal evaluations (on GH/IGF-I values and on the occurrence of tumor shrinkage and the onset of hypopituitarism) have been performed by a Kaplan–Meyer test and differences between subgroups have been evaluated by a log-rank test.

All statistical tests have been two-tailed and values of *P* less than 0.05 have been considered significant.

Results

Follow-up

Of the total 51 cycles of RxT administered in our 49 patients, one had been performed during the 1950s, two during the 1960s, 15 during the 1970s, 15 during the 1980s, and 18 between 1990 and 1994.

Follow-up had been prolonged for a median period of 14 years (range 3–41 years) and in 15 patients lasted more than 20 years.

Five patients (nos 12, 20, 28, 32, 38) had been lost to follow-up, i.e. the last evaluation had been performed more than 3 years ago. In all the other patients the last evaluation had been performed within the last 3 years (in the present year in 26 cases).

Hormonal values

In the group submitted to RxT as primary treatment the patients were older, irradiated earlier and followed-up longer than in the group of those treated after surgical failure, but all the other evaluated parameters were superimposable (Table 2), allowing the pooling of data for analysis in the following sections.

Thirty patients still had pathological GH/IGF-I levels at their last evaluation, notwithstanding ongoing anti-GH treatment (ON group).

In the remaining 19 patients, evaluated after withdrawal of anti-GH treatment (OFF group), IGF-I values had remained normal in eight patients (16% of the series, nos 1, 10, 13, 16, 27, 33, 37, 46), irradiated 10 (8–13) years before. In this group IGF-I levels had fallen from 432 (209–522)%ULNR to 116 (55–195)%ULNR ($P < 0.0001$). Normal age-matched IGF-I levels had been obtained after 2 years from irradiation in one patients (no. 27), after 5 years in one (no. 2), after 10 years in four (nos 1, 10, 13, 25), after 20 years in two (nos 17, 37) and after 25 years in one (no. 39). A recurrence had occurred later in one of the patients who had initially been considered normalized (no. 2, vide infra).

GH levels had remained below 2.5 µg/l in six patients (12% of the series, nos 1, 10, 13, 27, 39, 46), between 2.6 and 5 µg/l in eight and between 5.1 and 10 µg/l in three. GH levels had decreased from 18 (7–26) µg/l to 4 (1.3–5.2) µg/l ($P < 0.0001$). 'Safe' GH levels had been obtained at 9 (4.7–22) years since treatment, namely after 2 years from irradiation in one patients (no. 27), after 5 years in one patient (no. 1), after 10 years in three patients (nos 2, 10, 13) and after 25 years in another patient (no. 39).

Both 'safe' GH and normalized IGF-I levels had been achieved by five patients (10.2%, nos 1, 10, 13, 27, 46). In all but two patients (nos 16, 33) GH normalization had forerun IGF-I normalization by 1–3 years.

Hormonal levels before treatment, date, dose of radiation and length of follow-up of the OFF group were not different from those of the ON group.

Table 2 Results of RxT in patients treated after Tx or not.

	Post-surgical	Primary	<i>P</i>
<i>n</i>	34	15	—
Sex (M/F)	8/26	5/10	N.S.
Age (years)	38±2	47±3	0.014
Date	1986±1	1977±2	<0.0001
Dose (Gy)	46 (46–46)	46 (42–46)	N.S.
Pre-irradiation GH (µg/l)	22 (11–40)	20 (18–20)	N.S.
Pre-irradiation IGF-I (%ULNR)	318 (203–500)	432 (364–541)	N.S.
Follow-up (years)	10 (7–15)	23 (17–27)	<0.0001
Final GH <2.5 µg/l (%)	4 (12)	2 (13)	N.S.
Normalized final IGF-I (%)	7 (21)	2 (13)	N.S.
Shrinkage (%)	12 (35)	9 (60)	N.S.
GH decrease (%) at 10 years	29 (8–64)	39 (22–86)	N.S.

Figure 1 Percent decrease (median and interquartile) of GH and IGF-I after RxT (baseline normalized to 100%).

The longitudinal evaluation showed that 2 years after RxT, GH and IGF-I levels were 75 (53–97)% and 82 (51–101)% of basal levels respectively. The following percent decreases were similar between the two hormones (Fig. 1).

Preirradiation GH levels and the length of follow-up did not influence the outcome of irradiation. In particular, there was no correlation between basal and final GH values and superimposable results were achieved in the patients whose preirradiation GH levels were above or below 20 µg/l, that is the median value of this series. Moreover, patients with a longer follow-up did not show a higher prevalence of hormonal normalization.

By Kaplan–Meyer analysis the rate of pathological GH/IGF-I levels had fallen from 98% at 2 and 5 years, to 90% at 10 years and later on (Fig. 2).

All eight patients who had attained IGF-I normalization had withdrawn SA/DA treatment throughout the irradiation period. In contrast, IGF-I normalization had not been reached by all the patients who had maintained GH-suppressive drugs during treatment ($P = 0.011179$ by log-rank). The respective figures for 'safe' GH levels were six and nil ($P = 0.038162$). Neither basal hormonal levels before RxT nor length of follow-up were different between the two subgroups.

Sex and age did not influence the outcome of treatment. As for year of irradiation, an earlier hormonal normalization had been observed in the patients irradiated more recently ($P = 0.001233$ and 0.0165 for IGF-I and GH respectively).

A recurrence or worsening of disease, with a full-blown clinical picture, high hormonal levels, and/or tumor regrowth, had been observed 15–25 years after RxT in three patients (nos 2, 5, 49); one patient (no. 2) had initially been considered cured.

Tumor size

In two patients (nos 2, 5) progression of tumor growth had been observed during follow-up.

Tumor size reduction had occurred in 24 (nos 1, 2, 5–7, 11, 16, 18, 23–25, 27, 28, 31, 35, 37, 39, 40, 42–47) out of the 42 (57%) patients bearing pituitary adenoma, 8.5 (4.5–20) years after irradiation; ten (nos 1, 16, 24, 35, 37, 39, 40, 42, 45, 46) of them (24%) had reached a picture of ES. Tumor had shrunk in all the four patients bearing mixed GH-PRL adenoma.

Tumor shrinkage had preceded hormonal normalization by a couple of years in all the three patients who had achieved both these end-points (nos 1, 27, 46).

Tumor size influenced significantly the rate of post-irradiation shrinkage. Namely, tumor had shrunk in 20 out of 27 patients bearing macroadenoma (74%), as compared with three out of 13 (23%) bearing post-surgical remnant ($P = 0.0031$).

Follow-up in the patients showing tumor shrinkage had been longer (17 (11–23) years vs 10 (7–18) years), even though the difference did not reach significance ($P = 0.055$). In contrast, there was no difference in basal hormonal levels, dose of radiation or figure of

Figure 2 Percentage of patients still pathological for GH and IGF-I after RxT, evaluated by Kaplan–Meyer analysis.

hormonal normalization between patients who had obtained shrinkage or not.

At the longitudinal evaluation, tumor size reduction had occurred within 2 years after RxT in three patients, within 2 and 5 years in six patients, within 5 and 10 years in four patients and after 10 years in 11 patients.

The rate of unchanged tumor volume had fallen from 94% at 2 years, to 81% at 5 years, to 71% at 10 years, to 48% at 20 years, and to 33% at 25 years (Fig. 3).

Nine out of the 24 patients who had obtained tumor shrinkage had also been effectively treated after RxT with GH-suppressing drugs, namely SA (nos 2, 5, 6, 18, 43, 44) or DA (nos 7, 23, 47), i.e. with suppression of GH/IGF-I levels greater than 50% of basal levels. In contrast, in the other 15 patients GH-suppressing treatment had not been administered or had been poorly effective. The prevalence of tumor shrinkage in these two subgroups was superimposable, i.e. tumor shrank in 53% (9 out of 17) of the former group, as compared with 60% (15 out of 25) of the latter group.

Hypopituitarism

Seventeen patients were already hypopituitary before RxT. In two (nos 25, 27) of these patients hypoadrenalism had reverted after RxT.

Panhypopituitarism had developed in one patient (no. 26) 3 years after treatment and thyroid failure in another (no. 7) after 4 years. Worsening of preexisting

partial hypopituitarism had been observed in two patients (nos 4, 16), 7 and 18 years after RxT.

Over more than 20 years the rate of hypopituitarism had an increase of 12, 2 and 3% for hypothyroidism, hypoadrenalism and hypogonadism respectively (Fig. 4).

No demographic data had any bearing on the development of pituitary failure.

Criteria for GHD had been fulfilled by one patient only (no. 13) 9 years after RxT, when already panhypopituitary after Tx.

Side-effects

In patient no. 4, transient palsy of cranial nerves had developed 6 months after RxT; patient no. 24 had developed radionecrosis with bilateral optic atrophy after 9 months; and patient no. 26, irradiated with high doses, had developed partial cavernous sinus syndrome after 3 years, with palsy of the third and sixth cranial nerves.

In patients nos 46 and 48, meningioma had been shown 27 and 30 years after RxT respectively. Cerebral atrophy also had developed in patient no. 46.

Discussion

Tx is generally considered the first-choice treatment for acromegaly. If the disease persists, 'RxT can effectively

Figure 3 Prevalence of tumor shrinkage after RxT. On the vertical axis is shown the percentage of patients without tumor shrinkage, evaluated by Kaplan–Meyer analysis. In the right insert is the ratio of patients achieving (hatched) or not achieving (empty) shrinkage, according to drug treatment during follow-up; in the lower pie are depicted patients sensitive to drug treatment, in the upper those untreated or non-responders.

Figure 4 Percentage of patients developing hypoadrenalism, hypothyroidism and hypogonadism after RxT, evaluated by Kaplan–Meyer analysis.

reduce the size of residual tumor, prevent its regrowth and usually cause lowering of hormonal levels'.

This concept (7) has not been questioned for many years. Most reports agreed on normalization of GH levels in the majority of patients, even if the effects could have been delayed for up to 20 years (8–10). Other series reported GH normalization in a lower figure, although greater than 30–40% (11–14). GH levels were shown to decrease consistently by after 1 year from irradiation (15), down to 50% of baseline at 2 years, 20% at 5 years and 10% at 10 years (16, 17). In more recent years, criteria for the cure of acromegaly have become more stringent (18), in agreement with epidemiological indicators (4–6), such as the normalization of life expectancy following the lowering of GH levels below 2.5 µg/l and the normalization of age-matched IGF-I levels. Only a few papers addressed the topic of RxT results in acromegaly using these criteria, stressing the normalization of IGF-I as well as lowering of GH levels. While some reports showed a good reduction of IGF-I, with RxT success rate ranging from 47 to 96% (15, 17), others reported more disappointing results, showing IGF-I normalization in less than 20% of their series (19, 20).

Our results are in keeping with those of the investigators who showed little effect of RxT on IGF-I levels. We found that up to 84% of the patients in our series (41/49) still had abnormally high hormone levels and required GH-suppressive medical treatment, regardless of a very prolonged follow-up and technical modalities of irradiation that were comparable with other series. In our series, median follow-up was 14 years, whereas many authors who reported better results had a shorter follow-up (9, 21, 22). This low figure of cure did not improve even after the exclusion from the analysis of both the patients with the shortest follow-up, and the patients with other putative biases, such as double irradiation or attendance at our center only many years after irradiation (data not shown), ruling out the theoretical possibility that we had selected a population resistant to treatment.

Basal hormonal levels were not different from those of the other reported series and did not influence final results, in contrast with data reported by others (23, 24).

The fact that RxT was performed with varying techniques is a limitation of this study as well as of other series; however, it is noteworthy that the great majority of irradiation procedures were performed in the same medical center. Despite the evolution of technical modalities of irradiation throughout the years, RxT obtained a poor outcome also in the patients treated in more recent years. We found no difference in the results between recently irradiated patients and the group of patients who had been irradiated at an earlier date (after the same follow-up). The real technical improvement introduced in recent years has been radiosurgery, but results obtained in acromegalics by the use of this new tool are still inconsistent (25–27).

The evaluation of RxT outcome according to the maintenance of GH-suppressive treatment during irradiation showed that only patients who had undergone RxT without any regimen showed the best results, i.e. IGF-I normalization, as compared with the group of patients who had maintained either SA or DA during the period of irradiation. These data point to a putative interference of GH-suppressive treatments on the effectiveness of RxT, and support strongly the preliminary results reported by Landolt and colleagues (28), showing a radioprotective effect of octreotide treatment on RxT outcome. The hypothesis that the reduction of metabolic activity of the tumoral cells caused by the drug could actually lessen the effects of RxT needs to be addressed by prospective studies.

As for the control of tumor size, RxT was very effective. It obtained the stability of tumoral remnant in 38% of patients and decreased its volume markedly in 57%. However, tumor recurred in two patients. Tumor shrinkage was more impressive in patients bearing large tumors. In some cases the shrinkage was observed only after starting a medical treatment (SA or DA) effective in suppressing GH or GH/PRL levels. These observations, coupled to the reversible tumoral expansion observed in a few patients after the transient withdrawal of GH-suppressive treatment, suggest that in some cases tumor size reduction can be confidently ascribed to the effects of pharmacological agents. However, the figure of shrinkage remained well above 50% even after the exclusion of these patients from the analysis. Other authors have already reported shrinkage with different figures, ranging from 45% (29) to 60% (30). In our study the cumulative percentage of patients whose tumor shrank increased steadily over the years without reaching an apparent plateau, in agreement with Zhang and colleagues (31). In conclusion, RxT can thus be regarded as effective in controlling the neoplastic growth in the majority of patients with tumoral remnant.

However, only in a few cases was tumor size reduction observed concomitantly with hormonal normalization, as previously reported (26). The hypothetical sequence of events following irradiation – preliminary tumor size reduction, followed by hormonal reduction and by normalization – occurred only rarely in our series. In contrast, some patients showed tumor shrinkage and persistence of disease activity, whereas others showed hormonal normalization without tumor size reduction. RxT works even at the suprapituitary level, mainly on the hypothalamus and the pituitary stalk. It may be hypothesized that in patients with tumor shrinkage and persistence of disease activity, RxT might lead to an impairment of the GHRH/somatostatin drive, thus leading to a lessening on GH-secreting cells both of the GHRH trophic effect (causing tumor shrinkage), and of somatostatin inhibitory tone, present in some acromegalic patients (32), explaining the high hormone levels. On the contrary, in the patients with hormonal

normalization without tumor shrinkage, irradiation should exert its effect only at the pituitary level, without impairing GHRH–somatostatin inflow.

Hypopituitarism was an uncommon event in our series, occurring as either partial or global pituitary failure only in a few patients. On the contrary, preexisting hypopituitarism reverted in 2 out of 17 patients, in whom glucocorticoid replacement therapy could be withdrawn. Our low figure of hypopituitarism is in agreement with others (21), but contrasts sharply with the data from most authors (8, 11, 15, 24, 33–37), ranging between 15 and 70%. The low occurrence of this side-effect in our series may be speculatively attributed to a GH protective effect on pituitary function due to the persistence of GH hypersecretion, whereas the improvement in adrenal function observed in two of our patients might be regarded as a clinical proof for the existence of the still elusive corticotropin-release inhibitory factor (38).

In one patient, GHD was diagnosed after RxT. Only a few other similar cases have been previously reported in acromegaly (39).

As for neurological side-effects (40), we observed problems in only four patients. In three out of these four patients the procedure had been performed many years before, when measures used to reduce side-effects were still not well developed; in the last patient it could be attributed to a high dose of radiation. Meningioma was diagnosed many years after RxT only in two patients. The occurrence of a second neoplasm in the field of irradiation has been already described as a rare event (41–43). In our opinion the causal relationship between the two events needs to be demonstrated, with the use of a proper control group (non-irradiated acromegals), because we have observed the occurrence of meningioma even in some acromegalic patients not irradiated and an increase of tumor prevalence has been already shown in this population (3). Neurocognitive dysfunction was not formally evaluated in this series.

In conclusion, RxT should be regarded as a failure in acromegaly, at least by the conventional fractionated technique, inasmuch as the evaluation of its effects with modern criteria of cure (i.e. the normalization of IGF-I levels) shows that most patients still have active disease and need medical GH-suppressive treatment, even many years after irradiation. Concomitant GH-suppressive treatment seems to counteract the effects of irradiation. RxT maintains its effectiveness in controlling neoplastic growth, since it obtains stabilization of tumor size or shrinkage in most patients; thus it can still play a role only in the patients with large post-surgical tumor remnants.

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