Fractionated radiotherapy and radiosurgery in acromegaly: analysis of 352 patients from the German Acromegaly Registry

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European Journal of Endocrinology

Abstract

Background: If biochemical control of acromegaly is not achieved by operation and medication, radiotherapy may be indicated.

Objective: To describe fractionated radiotherapy (FRT) and stereotactic radiosurgery (SRS) regarding excess of IGF-1 and pituitary function.

Design and methods: A retrospective analysis of 352 patients (4126 patient-years) from the German Acromegaly Registry was performed. Follow-up was 1.0–45.1 years after radiotherapy. Therapeutic success was defined by low or normal IGF-1 according to center-specific reference ranges without (= remission) or on (= controlled disease) suppressive medication.

Results: Time between radiotherapy and last follow-up was 13.0 ± 8.2 years for FRT (n = 233) and 8.9 ± 5.0 years for SRS (n = 119, $P < 0.001$). Median (IQR) basal growth hormone before radiotherapy was 6.3 (2.9–16.2) ng/mL for FRT and 3.5 (1.8–6.9) ng/mL for SRS ($P < 0.001$). Mean time in uncontrolled state was 3.0 years after FRT and 2.1 years after SRS (95% CI for the difference is 0.1 to 1.6 years, P = 0.021). The 10-year calculated remission rate was 48% for FRT and 52% for SRS (95% CI for the difference is −18 to 26% age points, P = 0.74) and the respective controlled disease rate was 23 and 26%. The odds ratio for adrenocorticotropic or thyreotropic insufficiency was 0.54 (95% CI: 0.30–1.00, P = 0.049) in SRS compared to FRT patients.

Conclusion: Both after FRT and SRS about 75% of patients with acromegaly are in remission or controlled after 10 years. A slightly faster achievement of target values was observed after SRS. The rate of pituitary insufficiency in FRT patients is significantly higher.

European Journal of Endocrinology (2020) **182**, 275–284

Introduction

For treatment of acromegaly, radiotherapy is usually applied as third-line therapy (1, 2) after surgical and pharmacological treatments, as suggested by current and previous guidelines (3, 4, 5).

Fractionated radiotherapy (FRT) was initially performed as 'conventional' two-field FRT (6, 7). Later on 'high precision' conformal FRT (8) and 'stereotactic' FRT (2) were introduced. The effects of conventional FRT have

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-19-0784

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been described in detail (6), with time-dependent positive effects on both growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) levels. The rates of pituitary hormone deficiencies varied per hormone axis between 44 and 58% after 10 years. With FRT, the remnants of the pituitary gland itself are usually within the radiation field.

Within the last three decades, much information had been published and reviewed regarding the use of single-fraction, stereotactic radiosurgery (SRS) for the treatment of acromegaly with follow-up periods between 0.5 and 10 years. Estimates of both remission rates and new pituitary insufficiencies can vary widely from 17 to 82% in the former and 0 to 47% in the latter case (9, 10, 11). Most publications have relied on relatively small patient numbers and the comparisons with FRT were lacking, except for fairly small cohorts (12).

A meta-analysis which compared FRT and SRS in the treatment of acromegaly suggested that SRS may result in both a better remission rate and a lower risk of hypopituitarism. However, the authors acknowledged that the evidence is weak for several reasons (13). To lessen the gap in the evidence, we analyzed the data of a large series of FRT and SRS collected in the German Acromegaly Registry and analyzed the side effects and endocrinological outcomes.

This is the first report containing data on the use of FRT and SRS for the treatment of acromegaly obtained from routine endocrinological practice.

Subjects and methods

The German Acromegaly Registry was established in 2003 by the Pituitary Disease Study Group on behalf of the German Endocrine Society (DGE). Descriptions of structure, database, and data collection have been given previously (1, 14, 15). Written informed consent was obtained from all individuals included in the present study. The protocol of the registry was approved by the Ethics Committee of the Charité, Universitätsmedizin, Berlin, Germany, and by the Berlin commissioner for data protection and freedom of information.

Patients who had radiotherapy and a follow-up of at least 1 year after radiotherapy were selected from the registry database which included a total of 2401 patients in July, 2017. Patients with operations after radiotherapy and patients with multiple radiotherapies were excluded from final analysis as were those with unspecified type of radiotherapy. To improve the quality of data, two dedicated case report forms were developed and sent to 55 centers, of which 31 responded and provided further data.

Besides demographic data and initial tumor size (microadenoma vs macroadenoma) the following data were collected: level of random GH, endocrinological assessment of IGF-1 level (as low/normal/elevated) according to center specific, age-, and gender-adjusted reference ranges, any specific therapy (including date), and assessment of other pituitary functions/substitution (adrenocorticotropic, thyreotropic, and gonadotropic axis). The type of radiotherapy could be specified upon entering the data. For fractionated radiotherapy (FRT), three options were available (conventional, conformal, and stereotactic). For stereotactic, single-session radiosurgery (SRS), three options were available as well (gamma-knife, LINAC, and cyber-knife).

The endocrinological data sets selected for this analysis were the first visit, the last visit prior to radiation therapy, the last visit in the database, and the last visit in each of the time intervals defined by the boundaries 2, 4, 6, 8, 10, 15, 20, and 25 years after radiotherapy.

Endocrine remission was defined by normal or low IGF-1 without suppressive medication, whereas a controlled state was defined by normal or low IGF-1 under suppressive medication. Elevated IGF-1 levels were defined as an uncontrolled state. If information on IGF-1 was unavailable at a given visit, then the state from the previous visit was carried forward.

Regular nation-wide inter-laboratory comparisons are mandatory in Germany for clinical laboratories participating in patient care.

Statistical analysis

All analyses were performed and graphics produced using the software R (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/), version 3.4.2. The null hypothesis between groups was tested with a chi-squared test without continuity correction for count data unless expected counts were below five in which case Fisher's test was used. Continuous variables were tested with a *t*-test using Welch's approximation and a logarithmic scale for GH values. Multi-state models were calculated for the time-dependent models of uncontrolled, controlled, and remission states using the package 'msm' (Christopher H. Jackson (2011). Multi-State Models for Panel Data: The msm Package for R. Journal of Statistical Software, 38(8), 1–29. URL http://www.jstatsoft.org/v38/i08/). Transitions

were permitted between all non-absorbing states and GH values on a logarithmic scale before radiation therapy was used as a covariate and a model including sex was used as a sensitivity analysis. If GH prior to radiation therapy was unavailable, then multiple imputation with 50 sets was used for the multi-state models, where age, sex, and year of radiotherapy were used as imputation variables. As a further sensitivity analysis, a model was analyzed in which the first 2 years were left out to test robustness with respect to the Monte Carlo assumption that the probabilities of transitions between states depend only on the current state. Sojourn times and prevalence of states were estimated for both groups given the same median GH concentration prior to radiation therapy.

Pituitary function was analyzed with logistic regression. Adrenocorticotropic and thyreotropic insufficiencies were modeled together taking the baseline state, sex, age, time after radiotherapy, and type of radiotherapy as covariates. Because of anticipated bias in the reporting of gonadotropic insufficiency in women post menopause, this was modeled separately for males only.

The significance level was set at $\alpha=0.05$.

Results

There were 352 patients in our registry with a single radiotherapy and without a subsequent operation, where primary data were available (Fig. 1). Analyses of particular excluded subgroups such as patients with operations after radiotherapy can be found in the supplementary material. Fractionated therapy was administered to 233 (66%) and stereotactic radiosurgery to 119 (34%) of them. At the time of radiotherapy, only 33 patients (9%) were documented as being on acromegaly medication. Population characteristics are presented in Table 1. In total, 4126 person-years were observed, whereby the mean observation time of 13.0 years for the FRT group was 4 years longer than for the SRS group. The difference in mean observation time is a result of the median date for SRS being about 4 years later than FRT (Supplementary Fig. 1, see section on supplementary materials given at the end of this article). Only five patients were observed for less than 1.5 years and 12 others for less than 2.5 years. There were 182 patients observed for more than 10 years. GH levels prior to radiotherapy were a factor 1.9 greater in FRT than in SRS patients (95% CI: 1.3–2.8, $P<0.001$). Since laboratory testing methods for GH have changed over time, we corrected for the date of radiation and found

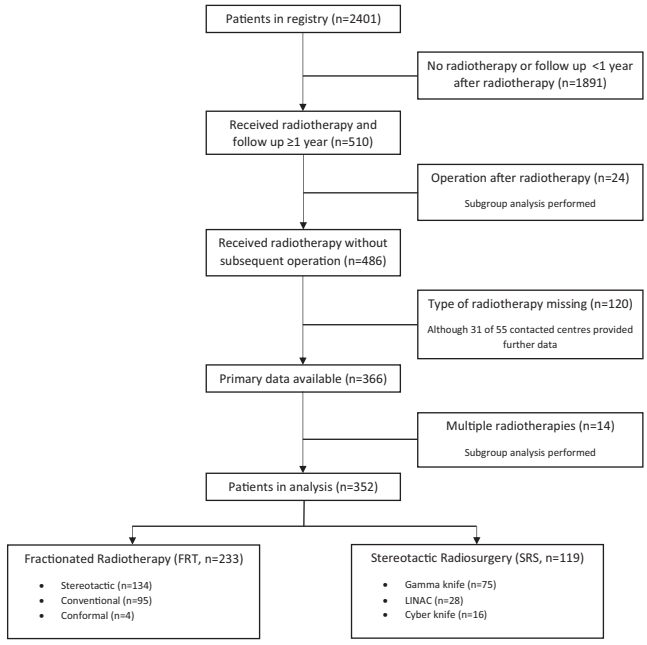

Figure 1
Flow chart of patient selection.

that GH levels before radiotherapy were only a factor 1.6 greater in FRT patients (95% CI: 1.1–2.3, $P=0.024$).

In the analysis of disease progression, seven patients were not included since little or no information was available on IGF-1. A total of 1428 transitions were observed that included transitions between all three states (uncontrolled, controlled, and remission) and 12 deaths (Table 2). IGF-1 was unavailable for 192 of the 1428 (13%) post-radiotherapy states. The first transition took place at a median of 1.9 years (IQR 1.4–3.3 years) after radiotherapy after which 60, 7, and 33% of the FRT group were in the uncontrolled, controlled, and remission states respectively compared to 50, 13, and 37% in the SRS group ($P=0.14$).

The multi-state models show that the mean time in the uncontrolled state is 3.0 years for FRT and 2.1 for SRS (95% CI for the difference is 0.1–1.6 years, $P=0.021$) (Fig. 2).

The calculated proportion of patients in remission after 10 years is 48% for FRT and 52% for SRS (95% CI for the difference is −18 to 26% age points, $P=0.74$). However, about 75% of patients were in remission at some point in time, and the lower long-term average arises due to transitions from the remission to the controlled or uncontrolled state. Such transitions occurred in 42/119 (35%) SRS and 96/227 (42%) FRT patients, for a difference of 7% age points (95% CI: −4 to 18% age points, $P=0.21$). The GH levels prior to radiotherapy did not have significant

Table 1 Baseline demographic and clinical characteristics. Entries are mean ± S.D., median (interquartile range), or *n* (%).

	FRT (*n* = 233)	**SRS** (*n* = 119)	***P*-value**
Number of females	126 (54%)	60 (50%)	0.52
Age at first diagnosis	40.7 ± 11.7	39.4 ± 11.6	0.30
Radiotherapy			**<0.001**
Before 1990	23 (10%)	0 (0%)	
1990–2005	136 (58%)	53 (45%)	
After 2005	74 (32%)	66 (55%)	
Time between first diagnosis and radiotherapy (years)	4.5 ± 5.2	5.5 ± 6.3	0.12
Time between radiotherapy and last follow-up (years)	13.1 ± 8.1	9.1 ± 5.1	**<0.001**
Basal GH at first diagnosis (ng/mL)	33.0 (9.0, 66.0)	20.9 (9.5, 40.0)	0.15
Basal GH before radiotherapy (ng/mL)	6.3 (2.9, 16.2)	3.5 (1.8, 6.9)	**<0.001**
Basal GH at last visit (ng/mL)	0.8 (0.4, 2.0)	0.8 (0.3, 1.7)	0.31
IGF-1 at last visit			0.11
Low	5 (2%)	9 (8%)	
Normal	157 (67%)	74 (62%)	
Elevated	51 (22%)	27 (23%)	
Unavailable	20 (9%)	9 (8%)	
On medication at last visit	145 (62%)	67 (56%)	0.28

The *P*-values for growth hormone (GH) are based on a *t*-test using a logarithmic scale for the variable. Statistically significant values are presented in boldface.

effects on the hazard ratios for the primary transition probabilities (i.e. from uncontrolled to controlled or uncontrolled to remission states). However, those who were in remission within 2 years of radiotherapy had pre-therapy GH levels that were a factor 2.9 (95% CI: 1.2–6.8, $P=0.014$) lower than for those in a controlled state within those 2 years. The pre-therapy GH levels between those in an uncontrolled state was almost identical to those in a controlled state (a factor 1.3, $P=0.54$). In sensitivity analyses, the remission rate at 10 years was also 49% for non-imputed data and for models disregarding the first 2 years. If only patients with radiotherapy after 2005 are considered, then the curves remain similar to those of Fig. 2, but estimates are inaccurate due to smaller patient numbers. There were 245/352 (70%) patients with normal or low IGF-1 at their final visit, that is, controlled or in remission.

At the final visit, data on pituitary function were available from 254 patients. These patients did not differ from the remainder regarding sex, age, proportion receiving FRT/SRS, or year of receiving radiotherapy. In the FRT group 132/165 (80%) had at least one insufficiency compared to 56/89 (63%) in the SRS group. The respective proportions of documented cases at radiotherapy were 61% (FRT) and 57% (SRS). In a logistic model for adrenocorticotropic or thyreotropic insufficiencies, a prior insufficiency and the length of time since the radiotherapy had strong effects (Table 3A). The odds ratio for insufficiency was 0.54 (0.30–1.00, $P=0.049$) in SRS compared to FRT patients. Exemplary curves showing the probabilities of these pituitary dysfunctions can be found in Fig. 3. Estimated effects for gonadotropic insufficiencies among males are similar, but confidence intervals are wider because of the smaller sample size, meaning power is lower (Table 3B).

In our cohort undergoing different modes of FRT, insufficiency rates (determined by hormone substitution) were 39.2% for adrenocorticotropic, 32.1% for thyreotropic, and 56.2% for gonadotropic insufficiencies prior to radiation and rose to 60.8, 59.8, and 71.9% at last follow-up after a mean of 13.0 years. In the cohort of patients undergoing different modes of SRS, insufficiency rates were almost equal compared to the FRT group (39% for adrenocorticotropic, 35% for thyreotropic, and 51% for gonadotropic) prior to radiation, which rose to 45, 40, and 55% at last follow-up (after a mean of 8.9 years).

Table 2 Transition table.

	To			
	Uncontrolled	Controlled	Remission	Death
From				
Uncontrolled	402	91	261	6
Controlled	20	88	11	2
Remission	66	73	404	4

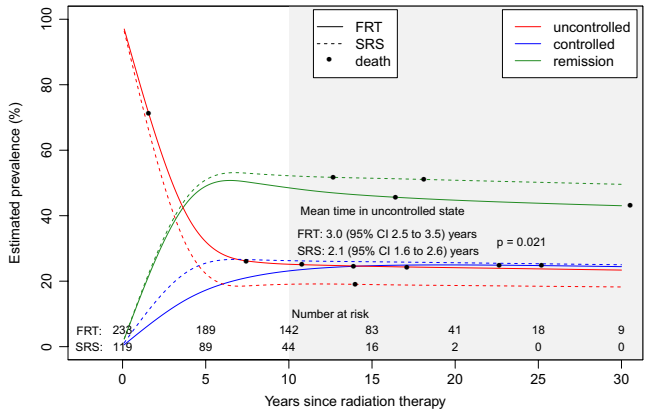

Figure 2

Estimated prevalence of disease state as a function of time for patients who received FRT or SRS. FRT, fractionated radiotherapy; SRS, stereotactic radiosurgery. The gray shading indicates that estimates become unreliable as the data grow sparse.

Discussion

For the first time, we provide a description of the effects of either FRT or SRS from a single registry on a large cohort of patients with acromegaly derived from routine endocrinological data. In our analysis of 352 patients covering 4126 patient-years from the German Acromegaly Registry, we found that the mean time in the uncontrolled state after radiotherapy was about 2 years and that long-term stable remission rates of 50% were reached. Patients transited out of the uncontrolled state about 1 year earlier in the SRS group than in the FRT group. Pituitary dysfunction was extremely common and the elapsed time after radiotherapy was the primary risk factor, but FRT was additionally a significant risk factor compared to SRS for adrenocorticotropic or thyreotropic insufficiency.

It is crucial to keep in mind that significant differences between FRT and SRS demonstrate that the observed difference cannot easily be attributed to chance. They cannot be interpreted to mean that FRT or SRS caused this difference, since the indications for SRS are not identical to those of FRT nor are other aspects of treatment.

Endocrinological efficiency of FRT and SRS

For our registry-based evaluation, we defined normal or subnormal IGF-1 levels without medication to be remission of acromegaly, since in daily endocrinological practice this is the most commonly used parameter. Therefore, remission rates in our study may be overestimated compared to studies incorporating GH levels as well. Although a 90% control of tumor size was reported after SRS for secreting pituitary adenomas involving 35 peer-reviewed studies with 1621 patients, comparison of endocrinological effects turned out to be difficult due to different criteria defining endocrinological remission or control (16), which is particularly true in acromegaly (17). Currently accepted criteria for remission of acromegaly are a random GH level less than 1 ng/mL and/or GH level less than 0.4 ng/mL after glucose load and a normal serum level of IGF-1 accounting for sex and age (5, 18, 19, 20). The latter is considered to be the more relevant since elevated IGF-1 correlates to persistent acromegalic states (17, 21). When those criteria were used in a retrospective study of only 36 acromegalic patients who underwent conformal

Table 3 Results of logistic regression for secondary hypopituitarism.

	Odds ratio (95% CI)	***P*-value**
(a) Adrenocorticotropic or thyreotropic insufficiency		
Insufficiency before radiotherapy		**<0.001**
Yes vs no	8.00 (3.14 vs 22.36)	
Unknown vs no	1.42 (0.70–2.89)	
Time after radiotherapy (per year)	1.10 (1.05–1.16)	**<0.001**
Sex (female vs male)	0.57 (0.31–1.02)	0.061
Type of radiotherapy (SRS vs FRT)	0.54 (0.30–1.00)	0.049
Age at radiotherapy (per year)	0.98 (0.96–1.01)	0.22
(b) Gonadotropic insufficiency (males only)		
Insufficiency before radiotherapy		**<0.001**
Yes vs no	10.74 (2.30 vs 63.61)	
Time after radiotherapy (per year)	1.07 (0.92–1.28)	0.44
Type of radiotherapy (SRS vs FRT)	0.37 (0.06–1.90)	0.24
Age at radiotherapy (per year)	0.99 (0.89–1.09)	0.78

Statistically significant values are presented in boldface.

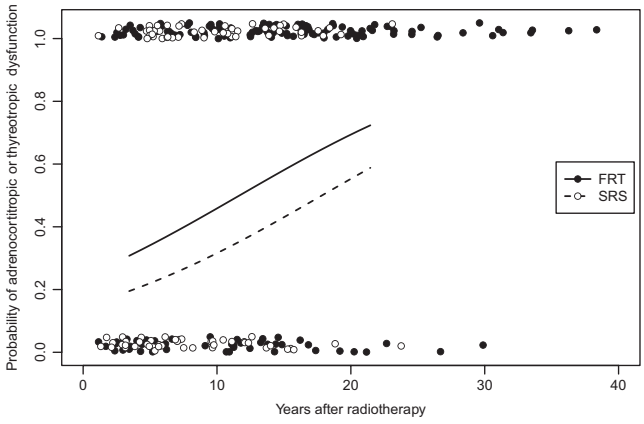

Figure 3

Illustrative probability curves derived from a logistic regression model of adrenocorticotropic or thyreotropic dysfunction are shown for FRT and SRS as a function of time. In this example, a 45-year-old female patient without dysfunction prior to radiotherapy is modeled. Curves extend from the tenth to the ninetieth percentiles of 'years after radiotherapy'. The dots at the bottom of the plot represent data points for patients without any insufficiencies at the last visit and those at the top with at least one insufficiency. Data were available for 254 patients (165 FRT and 89 SRS). FRT, fractionated radiotherapy; SRS, stereotactic radiosurgery.

FRT, a remission rate of 55% after 63 (±33) months was reported (8), which is comparable to our results.

Our data suggest that about half the population is in remission within about 5 years both after FRT and SRS, but SRS patients leave the uncontrolled state almost a year sooner. Remission rates remain stable at about 50% after 10 years suggesting that the numbers going into remission and those leaving it are roughly in balance. At the final visit, IGF-1 was low or normal in 69% of patients after FRT and in 70% after SRS (with or without additional medication: control rate at last visit). This is slightly lower than the 77% of 1344 unselected patients from the German acromegaly registry previously reported (1). Relapse of disease was common in our data set and did not differ between FRT and SRS.

Gamma-knife SRS in functioning pituitary adenomas revealed that tumor margin dose and time to endocrine remission were inversely correlated to each other and that the median time to remission was 48.9 months (22). Previously, the same group showed that, besides age and cavernous sinus invasion, acromegaly was associated with longer time to endocrine remission in a retrospective study with 121 cases of acromegaly and matched patients with Cushing's disease (23). In a retrospective multicenter study including 317 patients with acromegaly undergoing gamma-knife SRS, the mean time to durable remission was 38 months (24).

GH level prior to radiation therapy

In our analysis, GH levels before radiotherapy had no significant effect on the hazard ratio for the primary transition probability. However, if remission was achieved within 2 years after radiotherapy, GH levels prior to radiotherapy were a factor 2.9 lower than in patients who were in a controlled state. This suggests that GH levels prior to radiation therapy are not predictive for the probability of remission but for the time course of its development. However, we need to emphasize that GH was not involved in our definition of the outcome states. This was also described by others: the time course of GH and normalization of IGF-1 after FRT was dependent on the GH level prior to radiation (6).

GH levels prior to radiation correlated inversely with endocrinological effect of gamma-knife SRS in a series of 40 acromegaly cases (25). In a large registry-based study from the UK, the rate of 'safe' GH (<2.5 ng/mL) depended on the GH level prior to radiation at any time point of follow-up after FRT (e.g. 73% after 10 years, when GH before FRT was <10 ng/mL; and about 50% otherwise) (6).

Secondary hypopituitarism after FRT and after SRS

The development of new hypopituitarism after irradiation is time dependent (6), which is supported by our data. In our cohort of patients undergoing different modes of SRS, insufficiency rates (determined by hormone substitution) were almost equal compared to the FRT group (39% for ACTH, 35% for TSH, and 51% for LH/FSH) prior to radiation, which rose to 45, 40, and 55% at last follow-up (after a mean of 9.1 years). Moreover, a multivariate analysis of adrenocorticotropic or gonadotropic insufficiencies in our data suggests that the odds for development of secondary insufficiency of axis was twice as high after FRT compared to SRS after taking relevant covariates into account.

For stereotactic FRT applied to 68 large and infiltrative non-functioning pituitary adenomas, one study found new pituitary dysfunction in 40% of irradiated patients after 5 years and in 72% after 10 years (26). According to the analysis of the British Acromegaly Registry, the rates of new pituitary hormone deficits 10 years after conventional FRT varied per hormone axis (18% for LH/FSH, 15% for ACTH, and 27% for TSH) resulting in an increase of total insufficiency rates before radiation between 17 and 40%

to rates between 44 and 58% after 10 years, with further increase in the following years (6). The latter is supported by our observations.

With a median follow-up of 31 months in 418 cases with different pituitary adenomas, gamma-knife SRS was followed by new hypopituitarism in 24% of the patients (22). This proportion increased with longer follow-up and reached 29% in a later study by the same group (23). A review of literature reported an incidence of new pituitary deficits of 24% 5 years after SRS for any pituitary adenoma (range from 10 to 40%), with no difference between secreting and non-functional tumors (27). In 40 cases of acromegaly treated by gamma-knife SRS (including four cases with second SRS), a new deficit of pituitary axis deficiency occurred in 40% after a median onset of 36 months (25). In 60 patients with acromegaly and a follow-up of at least 5 years (median 159.5 months) after SRS with gamma-knife, new pituitary deficiency occurred in 58.3% after a median time of 61 months (28). In 20 cases undergoing gamma-knife SRS for acromegaly as the first treatment at a median follow-up of 146 months 53% developed hypopituitarism and in some cases as late as 20 years after treatment (29). For preservation of gonadotropic function, a safe mean radiation dose to the pituitary of 15 Gy was calculated (18 Gy for the adrenocorticotropic function) for gamma-knife SRS in 63 patients with pituitary adenomas (30).

Bias in selection of radiation mode

In their review on the effect and side effects of stereotactic FRT and SRS for pituitary adenomas, Minitti *et al.* recommended SRS for small and medium-sized tumor remnants with a distance to the optic nerve(s) of at least 2 mm and stereotactic FRT for tumors larger than 2.5–3 cm and/or involvement of the anterior optic pathway (31). In a two-center study of 35 patients with acromegaly, a risk-adapted radiotherapy was introduced with LINAC-based SRS when the planning target volume was less than 4 cm^3 and the distance to the optic pathways at least 2 mm (21 cases) and FRT when the tumor volume was larger and the distance to the optic pathway smaller than 2 mm. Two patients received both kinds of irradiation consecutively and 11 patients received no operation before irradiation. The remission rate of the whole cohort was 23%, and the endocrinological control rate was 63%, with slightly better results for the FRT group (32). In a large series of 242 cases with secreting pituitary adenomas (each 121 acromegaly and Cushing's disease) undergoing SRS in one institution, only 10% of the tumors had suprasellar extension (23). However, 75% of those had cavernous sinus infiltration, indicating that (unilateral) parasellar infiltration is the domain of SRS. Therefore, the combination of surgery and postoperative SRS has been proposed for GH-secreting pituitary adenomas, which infiltrate either cavernous sinus (12), improving the remission rate of these tumors from 28% after surgery alone to 82% after both treatments (33). On the other hand, in 40 acromegaly cases treated with SRS involvement of the cavernous sinus was correlated to worse endocrinological response (34).

Beside personal preferences and availability of different techniques, it seems that FRT is mainly used in larger, bilateral tumor remnants, indicating a bias toward more infiltrative and aggressive tumors (35), where the pituitary itself is always within the radiation field. The latter will explain the higher rate of secondary hypopituitarism after FRT compared to SRS as also shown by our data. Whether this advantage of SRS will remain with the concept of whole-sellar SRS in the long run is questionable (36). In a multicenter matched cohort study, new pituitary hormone deficits have been observed in 40.6% after whole-sellar SRS vs 29.7% after targeted SRS, but showed no statistical difference (37). SRS, however, is restricted to smaller tumor remnants with a longer distance to the optic pathways showing a correlation between higher marginal doses and endocrinological effect (32). The pituitary gland itself may be spared by SRS in many cases. On the other hand, our data suggest that, with longer follow-up periods after SRS, the rate of secondary pituitary insufficiency may also increase to the range found many years after FRT.

Radiation therapy as primary treatment for acromegaly

In our subgroup analysis of 24 patients (Supplementary data) who were operated after radiation therapy (FRT or SRS), radiation was performed as the first treatment in nine of them. In eight of these patients, acromegaly was controlled immediately after surgery, seven were even in remission. Therefore, from our data we cannot recommend radiation therapy as first-line treatment in acromegaly.

Typically, radiation therapy is supposed to be a third-line therapy in acromegaly after surgery and any kind of suppressive medication (1, 2, 20). A multicenter trial using SRS for acromegaly (n=25) or Cushing's disease (n=21) without prior operation revealed a 5-year remission rate of 28% in acromegalic patients and 82% in Cushing's disease (38). Out of a series of 20 acromegaly cases, who

underwent primary SRS after 20 years of follow-up, 12 out of 19 were under control, three in remission, three had subsequent transsphenoidal surgery, and one was uncontrolled (29).

Limitations

In the German Acromegaly Registry, no data on the total radiation dose, the doses of single fractions in FRT, or the tumor margin dose in SRS are given. Therefore, an analysis of these parameters was not feasible with our data. For the same reason, a subgroup analysis of particular forms of FRT (conventional, conformal, and stereotactic) or SRS (gamma-knife, LINAC, and cyberknife) was not meaningful. Medication may also differ between FRT and SRS and over time, which was not taken into account in this analysis.

We had to exclude 120 cases from final analysis, where the mode of radiation was not identifiable. Radiation in most of these cases was performed earlier than those in the final group and also earlier in the individual treatment courses. Both facts reflect the development of new pharmacotherapies for acromegaly in between.

The literature suggests that smaller tumor remnants before SRS of functioning pituitary adenomas with gamma-knife are associated with better endocrine outcome (22), probably due to the fact that larger tumor margin doses can be applied in smaller tumor remnants. In the present study, an analysis of tumor size prior to radiation was not possible, since this parameter was only coded as a binary variable (microadenoma vs macroadenoma). It can be assumed, however, that tumor mass correlates with GH prior to radiation, which was accounted for. Since cavernous sinus infiltration, which may also influence the endocrinological outcome after radiation therapy, is also not documented in our registry, no conclusion concerning this issue can be drawn from our data (23, 25, 32, 34, 39).

We did not evaluate absolute IGF-1 levels prior to radiation nor for follow-up, because methods of detection and age- and gender-adjusted reference ranges were different between the centers of the registry and sometimes changed over time. Instead, we relied on the assessment of the attending endocrinologist resulting in the categories low, normal, and elevated. Moreover, a certain imprecision of our data is given due to the fact that IGF-1 levels were unavailable in 192 of 1428 time points (13.4%) and therefore carried forward. Thus, the selection of the last visit of the defined time intervals, respectively, and the fact that the endocrinologists may have ceased the medication rather late may have prolonged the time point to transitions in our investigation. On the other hand, the time in the uncontrolled state after radiation therapy may be influenced not only by radiation itself, but also by intensified medication and new pharmacological developments over the years. At the latest, 20 years after radiation therapy, our data are too few to be meaningful. Nevertheless, they suggest that both FRT and SRS are potent to treat the hypersecretion syndrome in acromegalic patients.

Side effects like visual impairment and disturbance of extraocular motor function (27, 39), neurocognitive disorders (7, 40), or appearance of secondary intracranial tumors (35, 41) are not recorded consistently enough in the input mask of the German Acromegaly Registry to be analyzed.

Future developments

Recently, hypofractionated stereotactic radiosurgery, which is supposed to combine the advantages of SRS and FRT, has been introduced in the treatment of acromegaly with promising results (42). However, long-term results in larger series are still missing. We will introduce this modality of radiation therapy to the input masks of the German Acromegaly Registry. Proton therapy revealed a complete remission in 26% of 50 acromegalic patients after 3 years, and a median time to remission of 62 months (43), but for better estimates, will have to wait for results from larger patient cohorts.

Conclusions

For patients treated with FRT and SRS, about 75% of patients with acromegaly are controlled according to their IGF-1 status after 10 years. The rate of pituitary insufficiency is higher after FRT than after SRS.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-19-0784.

Declaration of interest

U J Knappe reports receiving personal honoraria from Novartis. S M Schmid reports grants and personal honoraria from Novartis, grants and personal honoraria from Ipsen, and grants and personal honoraria from Pfizer outside the submitted work. C Schöfl reports speaker's honoraria (Sanofi Aventis) and is member of a steering committee (Novartis) and an advisory board (NovoNordisk). J Schopohl reports grants and personal fees from Novartis, grants and personal fees from Ipsen, grants and personal fees from Pfizer, grants from OPKO, grants from Chiasma, and grants from

Aeterna Zentaris, outside the submitted work. M R Stieg reports grants from Pfizer and personal honoraria from Shire outside the submitted work. The other authors have nothing to disclose.

Funding

The German Acromegaly Registry is supported by grants from Novartis Pharma GmbH, Nuremberg, Germany; Ipsen Pharma GmbH, Ettlingen, Germany, and from Pfizer Deutschland GmbH, Berlin, Germany.

Acknowledgements

The authors thank all participants of the German Acromegaly Registry, namely K Bacher, K Badenhoop, K Cissewski, F Demtröder, S Diederich, J W Dietrich, M Droste, M Engelbach, M Fassnacht, J Feldkamp, R Finke, D Führer-Sakel, B Gallwitz, A Gerhardt, M Gruber, D Haaser, S Hering, J Honegger, O EJanßen, C Jaursch-Hancke, U Kajdan, P Kann, W Karges, C Kasperk, D Klingmüller, A Knauerhase, E Kornely, N Krause, F Lammert, H Lehnert, A Lößner, W A Mann, J Meuser, A Meyer, H Mönig, U A Müller, M Müller-Schilling, J Pichl, U Plöckinger, P Pohlmeyer, K Reschke, M Schott, J Seufert, C Sieber, H Siggelkow, G K Stalla, A Steveling, C J Strasburger, N Uksul, and M M Weber.

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Received 1 October 2019
Revised version received 6 January 2020
Accepted 9 January 2020