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ORIGINAL ARTICLE

Long-term follow-up of patients with surgical intractable acromegaly after linear accelerator radiosurgery

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Background/Purpose: Radiotherapy is a crucial treatment for acromegalic patients with growth hormone (GH)-secreting pituitary tumors. However, its effect takes time. We retrospectively reviewed the long-term outcome of linear accelerator stereotactic radiosurgery (LINAC SRS) for patients with acromegaly from the perspective of biochemical remission and associated factors.

Methods: Twenty-two patients presenting with residual or recurrent (GH)-secreting functional pituitary tumor between 1994 and 2004 who received LINAC SRS were enrolled and followed up for at least 3 years. Residual or recurrent tumor was defined as persistent elevated GH or insulin-like growth factor-1 (IGF-1) level and image-confirmed tumor after previous surgical treatment. Biochemical remission was defined as fasting GH less than 2.5 ng/mL with normal sex-and-age adjusted IGF-1.

Results: The mean follow-up period was 94.7 months (range 36–161 months). Overall mean biochemical remission time was 53 months (median 30 months). Biochemical control was achieved in 15 patients (68.2%) over the follow up period. One patient experienced recurrence

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after SRS and underwent another operation. Initial GH at diagnosis and pre-SRS GH correlated with biochemical control ($p = 0.005$ and $p < 0.0001$, respectively). Further evaluation demonstrated that biochemical control stabilized after 7.5 years. Overall post-SRS hormone deficit persisted in five patients (22.7%).

Conclusion: In comparison to other radiosurgery modalities, LINAC radiosurgery also provides a satisfactory outcome. SRS has maximum effect over the first 2 years and stabilizes after 7.5 years. Moreover, SRS elicits long-term biochemical effects and requires longer follow-up for better biochemical remission.

Introduction

Growth hormone (GH)-secreting pituitary tumors account for approximately 20% of pituitary tumors. Although most are benign, inadequate treatment may lead to clinical acromegaly, which increases mortality and morbidity.[1,2] Therefore, in order to achieve normal endocrine status, multiple methods have been established, including medication, operation, and radiosurgery. Surgery such as transsphenoidal adenomectomy has been used as a first-line treatment for the GH-secreting pituitary tumor with a good tumor control rate.[3] Somatostatin analog (SSA), dopamine analog, and GH receptor antagonist medications provide 44%, 10%,[4,5] and 60%[6] endocrine remission, respectively. Radiosurgery, first introduced in 1951 by Lars Leksell,[7] has been reported to have a 68–100% tumor control rate and nearly 96% endocrine remission rate.[8]

The long-term effects of radiosurgery on GH-secreting pituitary tumors have been investigated.[9,10] The slow-growing nature of the tumor leads to a longer effect of the radiation. The efficacy of radiosurgery on endocrine remission is thought to continue for more than 5 years, but the specific time of the radiosurgery effects remained unknown. Therefore, in the present study, we retrospectively reviewed the long-term outcome of linear accelerator radiosurgery for patients with acromegaly in our hospital with an emphasis on chronological biochemical remission. We further surveyed the possible risk factors and estimated the effective duration of radiosurgery.

Material and methods

Patient population

We retrospectively collected data from patients who underwent radiosurgery from July 1994 to July 2004. The inclusion criteria were GH-secreting pituitary adenoma and clinical presentation of acromegaly. Acromegaly was diagnosed by clinical observation according to the chart and fasting GH over 5 ng/mL or GH over 1 ng/mL in the oral glucose tolerance test (OGTT). In addition, magnetic resonance imaging (MRI) was used for imaging diagnosis.

In total, 1114 patients underwent stereotactic radiosurgery (SRS) from 1994 to 2004 at our neurosurgical institute. Among them, 117 were diagnosed with pituitary tumor, and GH-secreting pituitary adenoma was found in 28 patients. In our hospital, patients with GH-secreting pituitary adenoma received transsphenoidal adenectomy as standard primary treatment. Six patients were excluded due to incomplete data and follow-up less than 3 years. All patients who received SSA (n = 11; octreotide long-acting 20 mg intramuscular every month) stopped taking medication 4 months before SRS due to possible radioprotective effects.[11]

Radiosurgery

Patients' position and tumor localization were fixed with a Cosman-Roberts-Wells stereotactic frame system. A computed tomography scan with a slice thickness of 3 mm was used to localize both the target and the normal critical structures. The treatment target included the gross visible tumor in MRI images and was supplemented by pre-treatment MRI. The target volume ranged from 0.19 cm^3 to 4.86 cm^3 with a mean (±SD) of 1.38 cm^3 (±1.23). Linear accelerator SRS (LINAC SRS) was performed for the following indications: 1) primary, residual, or recurrent pituitary tumor; 2) tumor less than 3 cm in diameter; and 3) distance from tumor to the optic apparatus greater than 5 mm. Target localization was performed with MRI. The dosage depended mainly on target distance from optic apparatus; the dosage to the optic apparatus was kept less than 800 cGy. The mean tumor dosage was 2295 cGy (±561). The mean 80% isodose was 1455 cGy (±315).

Clinical evaluation and follow-up

All patients were followed up for more than 3 years. The criteria of biochemical remission were fasting GH less than 2.5 ng/mL with normal sex- and age-adjusted insulin growth factor-1 (IGF-1). Additional fasting GH less than 1 ng/mL was listed due to different criteria of biochemical remission in different studies.

Hormone activity was followed by measuring human Growth Hormone (hGH), IGF-1, Tri-iodothyronine (T3), Thyroxine (T4), Thyroid-Stimulating Hormone (TSH), Adrenocorticotropic hormone (ACTH), Luteinizing Hormone (LH), Follicle-stimulating hormone (FSH), testosterone (in men), and prolactin. During follow-up, GH and IGF-1 were the primary measures of tumor activity. Tumor size was followed using MRI or computed tomography scan. All patients underwent ophthalmologic examination to evaluate visual field and visual acuity.

Statistical analysis

Statistical analysis was performed with SPSS (SPSS Inc, Version 16, Chicago, UK, USA) and GraphPad Prism

(GraphPad Software, Inc. California, USA). Time to biochemical remission was calculated as a proportion using the Kaplan-Meier method. The dependent factor for correlation analysis was time to biochemical remission. Univariate analyses of variables including age, sex, pre-SRS GH, GH at diagnosis, radiation dosage, tumor volume, and use of SSA were performed using the log-rank test, and correlations were analyzed by Spearman's test. The percentage decrease in GH was calculated with an exponential regression curve to estimate the GH decrease plateau. The prescribed level of statistical significance (p value) was 0.05.

Results

General characteristics

General patient characteristics are summarized in Table 1. A total of 22 patients were included in this study. Fourteen patients (63.6%) were female, and eight were male. The mean age at diagnosis was 36.5 years. Twenty-one of the patients (95.5%) underwent transsphenoidal adenomectomy of the pituitary tumor as the primary treatment. One patient received SRS as the primary treatment due to poor nasal hygiene after consultation with the Ear Nose Throat doctor (ENT doctor).

Table 1 General characteristics of acromegalic patients.

General characteristics	
Male, n (%)	8 (36.4%)
Female, n (%)	14 (63.6%)
Age at diagnosis (y), mean ± SD	36.5 ± 7.89
Age at diagnosis (y), median, range	35.5, 22—50
Follow-up (months), mean ± SD	94.68 ± 41.1
Follow-up (months), median, range	98, 36—161
Follow up >5 years, n (%)	17 (77.3%)
Previous operation, n (%)	21 (95.5%)
OP to SRS (months), mean ± SD	27.7 ± 30.03
OP to SRS (months), median, range	15, 1—98
Use of octreotide, n (%)	11 (50%)
SRS dose (cGy)	
80% isodose, mean ± SD	1455 ± 315
80% isodose, median, range	1500, 800—2000
Maximal dose, mean ± SD	2295 ± 561
Maximal dose, median, range	2290, 1370—3592
Tumor volume (cm^3), mean ± SD	1.38 ± 1.23
Tumor volume (cm^3), median, range	1.1, 0.19—4.86
Initial GH (ng/mL), mean ± SD	42.6 ± 30.2
Initial GH (ng/mL), median, range	46.9, 5.02—363.98
Pre-SRS GH (ng/mL), mean ± SD	21.3 ± 16.94
Pre-SRS GH (ng/mL), median, range	14.5, 3.46—59.1
Post-SRS GH (ng/mL), mean ± SD	2.25 ± 1.58
Post-SRS GH (ng/mL), median, range	1.85, 0.53—5.94
Biochemical remission[a]	
Group A, n (%)	6 (27.3%)
Group B, n (%)	15 (68.2%)
Biochemical remission (months)[a]	
Group A, mean ± SD	26 ± 20.01
Group A, median, range	23.5, 7—62
Group B, mean ± SD	53 ± 50.74
Group B, median, range	30, 7—157
Post-SRS visual change	0

[a] Group A: fasting GH < 1 ng/mL; Group B: fasting GH < 2.5 ng/mL. GH = growth hormone, OP = operation, SRS = stereotactic radiosurgery.

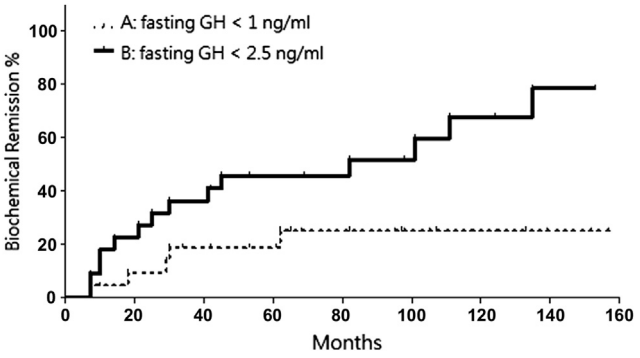

Figure 1 The proportion of patients in biochemical remission throughout the follow-up period. A significant difference was observed by using different criteria of biochemical remission ($p = 0.0008$). GH = growth hormone.

The mean time from operation to SRS was 27.7 months. The mean follow-up after SRS was 94.68 months (range 36—161 months), and 17 patients (77.3%) received follow-up for more than 5 years after radiosurgery. Eleven patients (50%) received SSA treatment. Mean tumor volume was 1.38 cm^3. Five patients required long-term hormone replacement after SRS; one presented with hypogonadism and the other four needed long-term cortisol replacement. No patients experienced visual field changes during post-SRS follow-up. No disease-related mortality was noted during follow-up.

Long-term effect of SRS on biochemical remission

Biochemical remission was achieved in 15 patients (68.2%) over the follow-up period. The mean duration from SRS to biochemical remission (GH < 2.5 ng/mL) was 53 months.

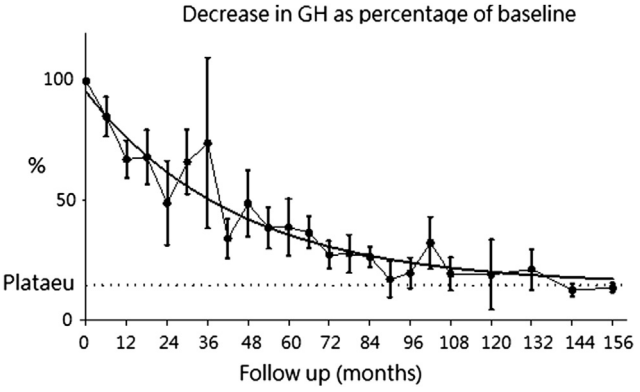

Figure 2 This figure shows the decrease in GH as a percentage of baseline. The plateau of regression curve is shown by the dotted line. The decrease in GH was stable at 7.5 years after stereotactic radiosurgery. GH = growth hormone.

Table 2 Factors associated with biochemical remission.

Factors	P value	Hazard ratio
Age	0.929	
Sex	0.908	
GH at diagnosis	0.001	4.409
Pre-SRS GH	0.027	3.239
Time from OP to SRS	0.382	
Radiosurgery dosage	0.56[a], 0.629[b]	
Tumor volume	0.18	
Use of octreotide	0.544	

Initial and pre-SRS GH levels are significantly related to the duration of biochemical remission. GH = growth hormone, OP = operation, SRS = stereotactic radiosurgery.
[a] Maximal SRS dosage.
[b] 80% SRS isodose.

Overall biochemical remission in the two categories is shown in Fig. 1. Approximately 50% patients achieved biochemical remission at the 82nd month. One patient had recurrence during follow-up and underwent a second operation for tumor excision.

The decrease in GH as a percentage of the baseline value is shown in Fig. 2. The maximal percentage decrease in GH occurred during the first 2 years after SRS. An exponential regression curve of percentage decrease in GH was calculated to estimate the plateau of the decrease, which was found to be 14.6% of baseline. The plateau indicates no change in GH after 90 months, indicating the decrease in GH becomes stable at 90 months after radiosurgery. The increase in GH at month 36 may be due to the recurrent patient, who had a fourfold GH increase compared with baseline.

Factors associated with biochemical remission

Factors associated with biochemical remission are shown in Table 2. Univariate analysis showed both GH at diagnosis and pre-SRS GH levels to be highly associated with the time to biochemical remission ($p < 0.05$). In addition, Spearman's correlation test demonstrated these factors to positively correlate with hazard ratio (4.409 and 3.239, respectively), indicating higher GH levels at diagnosis and before SRS necessitate more time to reach biochemical remission. In contrast, age, sex, time from operation to SRS, radiosurgery dosage, tumor volume, and use of sandostatin do not have significant effects to the biochemical remission.

Discussion

SRS is currently a widely used modality for treatment of pituitary tumors. However, the biochemical effects of radiosurgery usually take time. Pollock et al.[10] suggested that patients with GH-producing pituitary adenomas should not undergo further radiation therapy or surgery for at least 5 years after radiosurgery because GH levels continue to normalize over that period. However, the time required for GH to reach a stabilized level after radiosurgery still remained unknown. In our study, we followed the decrease

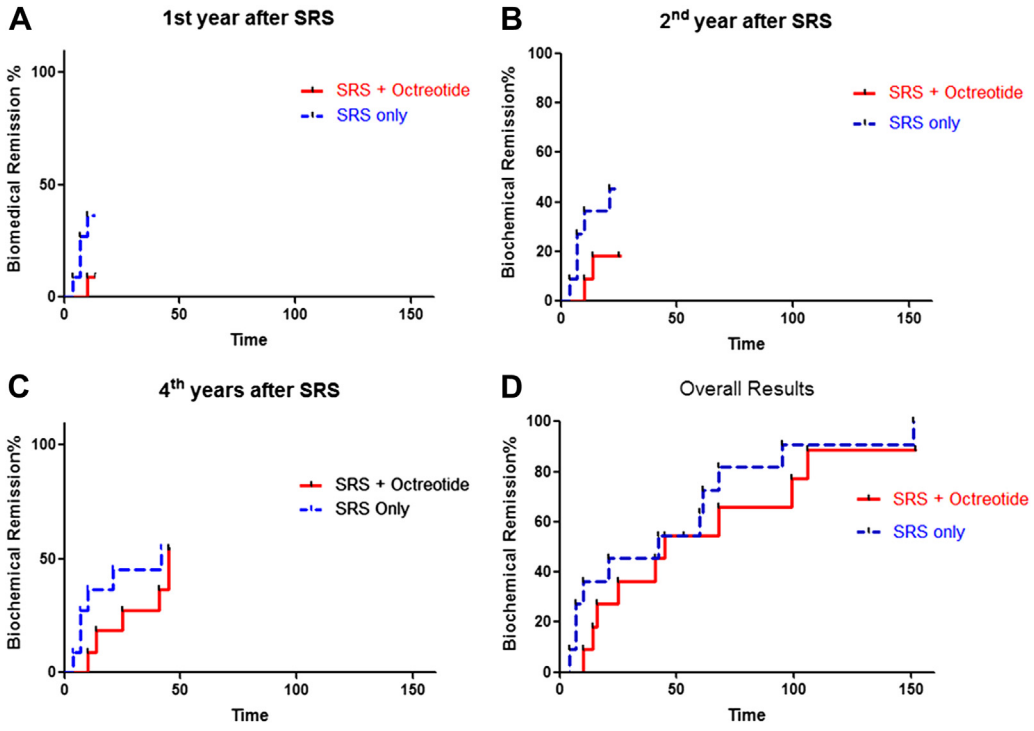

Figure 3 There was significant difference of biochemical remission in the first and second years (A, B). The difference diminished after year 4 (C). Although patients who needed octreotide after SRS may have fair biochemical outcome in the overall follow-up (D), it might take years to achieve the effect. SRS = stereotactic radiosurgery.

in GH over a 13-year follow-up period and observed an estimated plateau at the 90th month after SRS. This finding may provide helpful information for post-SRS clinical follow-up.

A question remains regarding how to proceed if GH dose not normalize within 90 months after radiosurgery. Should we go further with other management options or just wait for the long-term effect?

In our study, we observed the greatest effect within the first 2 years, which is comparable with most previous studies.[12–16] We found GH declined by approximately 50% in the first 2 years. In addition, 40% of patients had GH levels less than 2.5 ng/mL within 2 years. Therefore, it is worthy to wait for the SRS effects in the first 2 years. After the first 2 years, other treatment modalities may be used individually on different patients.

In our hospital, most patients who received octreotide were administrated the drug after radiosurgery followed by unsatisfactory clinical outcome. Further study on the difference between patients who did or did not use octreotide showed there was no difference on the overall biochemical outcome (Fig. 3D). The result may be due to a significant variation in GH levels at diagnosis (31.47 ng/mL and 53.73 ng/mL respectively in patients without and with octreotide after SRS). This may imply that patients with higher initial GH levels can have fair biochemical control by using octreotide after SRS. On analysis of the chronological effect, we found a slower biochemical remission in patients who needed to receive additional octreotide. These patients have worse biochemical control on the first 1 and 2 years and have equal biochemical results 4 years after (Fig. 3A–D).

In our study, we concluded that GH at diagnosis and pre-SRS GH status may have a significant influence on biochemical remission. Higher GH levels necessitate a longer time to reach biochemical remission. The same result has been shown in many studies.[10,17] No significant association between biochemical remission and age, sex, or radiation dosage was observed. However, other studies have reported a positive relationship between radiation dosage and GH outcome.

The diagnosis of acromegaly has now been more strictly defined using basal GH, GH after OGTT, and IGF-1. The consensus statement of the European Society of Endocrinology suggests the post-operative criteria for biochemical remission are nadir GH less than 0.4 ng/mL, post-OGTT GH less than 1 ng/mL, and normal age- and sex-adjusted IGF-1.[18] However, many recent studies used normal age-and-sex adjusted IGF-1 accompanied by basal GH less than 2–2.5 ng/mL as the biochemical remission criteria.[10,17,19,20] Few centers use OGTT as a standard criterion for post-radiosurgery biochemical remission. Pollock et al.[10] suggested that OGTT may be impractical in daily practice, and Peacey et al.[21] suggested that radiation therapy may alter GH feedback regulation.

Our study has some limitations. It was not a prospective trial, and the treatment policy slightly differed in some patients due to the different period of clinical course. This difference might contribute some bias to our conclusions, but the long investigation period of the study remains valuable.

We believe that SRS is a safe and effective modality to treat GH-producing pituitary tumor. SRS had maximum effect in the first 2 years and stabilized after 7.5 years.

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